Using hierarchical dimensional models to investigate the genomic and neural correlates of transdiagnostic psychiatric phenotypes across the lifespan

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Abstract

Hierarchical dimensional models have recently gained popularity as a data-driven alternative to traditional psychiatric classification systems. The transdiagnostic phenotypes derived from these models demonstrate greater reliability and validity than traditional diagnostic categories and hold the promise of facilitating new discoveries regarding the biological underpinnings of mental illness. No studies have attempted to systematically examine evidence regarding the biological correlates of transdiagnostic dimensions across the lifespan and research examining the latent structure and biological correlates of these phenotypes specifically in ageing populations is notably lacking. **Chapter 1** presents a broad overview of hierarchical dimensional models of psychopathology, focusing in particular on important methodological considerations, the advantages of hierarchical models in identifying biological associations, and emphasizing the need to adopt a lifespan approach to this research. **Chapter 2** is the first systematic review to investigate the genetic and neural correlates of transdiagnostic dimensions of psychopathology across the lifespan. The review identified a range of biological correlates that have been reported across multiple studies and age groups; however, there were no included studies that investigated these relationships specifically in older adulthood. **Chapter 3** presents the first study to investigate the latent hierarchical structure of psychopathology in older adults, examines whether a lower-order dimension capturing cognitive dysfunction can be incorporated into this structure, and examines whether this structure is invariant across four age groups throughout later life. **Chapter 4** presents the first study to investigate whether transdiagnostic dimensions of psychopathology are associated with brain structure in older adulthood. **Chapter 5** presents the first study to investigate the genomic correlates of transdiagnostic dimensions specifically in older adulthood. **Chapters 4-5** additionally examine the utility of hierarchical dimensional models of psychopathology in investigating the relationships between psychopathology and all-cause incident dementia in later life. Together,

the empirical studies presented in this thesis provide a significant contribution to our understanding of the latent structure, biological correlates, and clinical consequences of psychopathology across the lifespan and address important gaps in the existing literature with respect to ageing populations.

Thesis statement of originality

I certify that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged.

This thesis has not been submitted for any other degree or purposes.

Nicholas Hoy

23 June 2025

Artificial Intelligence statement

During the preparation of the thesis the author used OpenAI for assisting with editing and refining text (e.g., sentence structure, paraphrasing, improving clarity of expression). The author confirms that where text was modified by generative AI, the content was carefully reviewed for possible errors, inaccuracies, and bias. The author takes full responsibility for the submitted thesis and ensures their work is their own and has used generative AI in accordance with University guidelines and policies.

Author attribution statement

The chapters of this thesis contain three published papers, one manuscript that is currently under review for publication, and one manuscript in preparation for submission to a journal. I am the lead author on all of these publications and the corresponding author on all but one (i.e., the protocol paper for **Chapter 2**). Permission to include this protocol paper in the appendices has been granted by the corresponding author. Citations are provided on page xv.

Study 1 / Chapter 2 reports on the content published in two journals: a protocol for a systematic review published in *Frontiers in Psychiatry* and the results of that review published in *Neuroscience and Biobehavioral Reviews*. For the former, the authors are Nicholas **Hoy** (NH), Samantha Lynch (SL), Monika Waszczuk (MW), Simone Reppermund (SR), and Louise Mewton (LM). NH conceptualized the study with support from LM, SR, and MW. All authors critically reviewed the manuscript and approved the final version. For the latter, the authors are Nicholas **Hoy** (NH), Samantha Lynch (SL), Monika Waszczuk (MW), Simone Reppermund (SR), and Louise Mewton (LM). NH conceptualized the study with support from LM, SR, and MW. NH screened 100% of the titles and abstracts identified by the search strategy and SL screened 25% of the titles and abstracts. NH and SL screened 100% of the full texts identified via title and abstract screening. NH completed 100% of data extraction and quality assessments, completed the narrative synthesis and drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

Study 2 / Chapter 3 is published on a preprint server and is currently under review with the *Journal of Psychopathology and Clinical Science*. The authors are Nicholas **Hoy** (NH), Miriam K. Forbes (MF), Monika Waszczuk (MW), Matthew Sunderland (MS), Simone Reppermund (SR), and Louise Mewton (LM). NH conceptualized the study with support from LM, SR, MW, MF, and MS. NH conducted all analyses and drafted the manuscript. NH conducted all analyses and drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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As supervisors for the candidate upon which this thesis is based, we confirm that the author attribution statement above is correct.

Louise Mewton	**Simone Reppermund**	**Monika Waszczuk**	**Matthew Sunderland**
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This thesis is dedicated to my mother, Tanya Maree Hoy (1960-2022).

Any accomplishment in my life is made in complete awareness of the fact that none of it would have been possible without your love, support, and unwavering belief in me. A part of you is quietly woven into every page.

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Dissemination and funding awarded during candidature

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Chapter 1

General Introduction

1.1 Hierarchical dimensional models of psychopathology as an alternative to traditional psychiatric classification systems

1.1.1 The categorical model of psychopathology and its limitations

The categorical model of psychopathology is a consensus-based classification system that organizes psychiatric symptoms into a set of diagnostic categories that are treated as distinct from one another and from normal functioning. This model forms the foundation of most widely used diagnostic instruments, endorsed by the American Psychiatric Association since the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 1980) and by the World Health Organization (WHO) since the tenth edition of the *International Classification of Diseases* (ICD; (World Health Organization, 1992). Historically, the categorical approach to psychiatric classification played a critical role in unifying the field of psychiatry, improving diagnostic practices, and facilitating psychiatric research (Fischer, 2012; Surís et al., 2016).

In recent years, a growing body of research indicates that this approach to classification fails to accurately capture the underlying structure of mental illness and thus provides a suboptimal framework for clinical diagnosis and research. Within a strict categorical framework, disorders and their corresponding symptoms are typically defined dichotomously as either present or absent and diagnoses are determined on the basis of whether a particular threshold of polythetic symptom criteria has been met. However, research has consistently demonstrated that symptom severity and liability towards disorder varies along a graded continuum, ranging from normal functioning to more severe expressions of psychopathology (Haslam et al., 2020; Kotov et al., 2021; Krueger et al., 2018; Markon et al., 2011). A dichotomous approach to classification thus results in critical loss of information both in clinical and research contexts, particularly with respect to individuals who present with clinically meaningful symptoms that are below diagnostic thresholds (i.e., subclinical cases).

In addition, a substantial body of research indicates that comorbidity among putatively distinct psychiatric disorders is ubiquitous. Multiple disorders are frequently reported to co-occur within the same individual (Caspi et al., 2020; McGrath et al., 2020) and longitudinal research further reports widespread patterns of homotypic (i.e., the same disorder predicts itself over time) and heterotypic (i.e., one disorder predicts other disorders over time) continuity in the expression of mental illness (Cohen et al., 2018; Helgeland et al., 2005; Lahey et al., 2014; Woodward & Fergusson, 2001). Widespread patterns of comorbidity among psychiatric disorders challenges the assumption that psychopathology should be demarcated into a set of distinct categorical entities.

Finally, research also indicates significant heterogeneity within psychiatric disorders, such that two individuals diagnosed with the same disorder can present with vastly different and even non-overlapping symptoms (Allsopp et al., 2019). For example, one study determined that major depressive disorder according to the DSM-5 criteria (American Psychiatric Association, 2013) has 1,030 possible symptom profiles, 501 of which were reported by only one individual, while the most common profile occurred in just 1.8% of cases (Fried & Nesse, 2015). Heterogeneous symptom presentation within psychiatric disorders highlights the imprecision of traditional diagnostic frameworks and further challenges the validity of categorically-defined psychiatric phenotypes. The empirical evidence outlined above indicates that, despite its prominence in clinical and research settings, the categorical model does not accurately describe the structure of psychopathology. In light of these limitations, research has more recently shifted focus toward transdiagnostic and dimensional conceptualizations of mental illness.

1.1.2 Transdiagnostic and dimensional approaches to conceptualizing psychopathology

Empirical research investigating the structure of psychopathology typically relies on a range of statistical techniques that estimate latent (i.e., unobserved) constructs from patterns of covariation across a broad set of observed indicators (e.g., psychiatric symptoms or disorders). Generally speaking, latent variable models of psychopathology posit that associations among psychiatric indicators measured (i.e., observed) in a given dataset can be explained by the presence of one or more unobserved (i.e., latent) psychiatric phenotypes. The phenotypes derived from these models are typically continuous latent variables and are described as 'transdiagnostic' because they tend to capture psychiatric indicators that cut across traditional diagnostic categories.

Early research identified two transdiagnostic dimensions of internalizing and externalizing in children (Achenbach, 1966; Achenbach & Edelbrock, 1984), which were subsequently found to emerge across different cultures, nationalities, and ethnicities (Eaton et al., 2013; Krueger et al., 2003) and to be invariant across age groups (Eaton et al., 2011; Hoertel et al., 2015) and gender (Eaton et al., 2012). The internalizing dimension captures a broad range of emotionally-focused psychiatric indicators, including those related to depression and anxiety, self-harm and suicidality, trauma and stress, obsessive-compulsiveness, eating pathology, and sexual dysfunction (Watson et al., 2022). This phenotype has also been found to bifurcate into two notable subdimensions, labelled distress (defined by pervasive negative emotionality e.g., major depressive, dysthymic, general anxiety, and post-traumatic symptoms) and fear (defined by context-specific distress and avoidance e.g., specific phobias, social phobia, panic disorder; Watson et al., 2022). Importantly, dimensional measures of internalizing demonstrate greater reliability compared to discrete measures of internalizing-related psychiatric disorders (Watson et al., 2022). For example, meta-analytic evidence indicates that continuous measures of internalizing psychopathology demonstrate significantly greater test-retest reliability compared to discrete measures (Markon et al., 2011). In addition, field trials of the DSM-5 found that several common diagnoses along the internalizing spectrum (e.g., major depressive disorder and generalized anxiety disorder) demonstrated poor interrater reliability that improved with dimensional assessments (Regier et al., 2013) and symptom composite scores (Narrow et al., 2013).

The externalizing dimension captures a broad range of behaviorally-focused psychiatric indicators, including those related to attention-deficit hyperactivity disorder, alcohol, cannabis, nicotine, and other substance use disorders, intermittent explosive disorder, conduct disorder, oppositional defiant disorder, and a range of personality pathologies (e.g., antisocial personality disorder, borderline personality disorder, histrionic personality disorder; Krueger et al., 2021). Externalizing has also been found to bifurcate into several widely studied subdimensions, including disinhibited-externalizing (defined by indicators of behavioral disinhibition e.g., substance use, hyperactivity, inattention, impulsivity, risk taking) and antagonistic-externalizing (defined by antagonistic behaviors e.g., hostility, callousness, manipulativeness, deceitfulness; Krueger et al., 2021). Consistent with the internalizing dimension, meta-analytic evidence indicates that externalizing demonstrates superior test-retest reliability compared to categorical diagnoses (Markon et al., 2011). Field trials of the DSM-5 also indicate that dimensional measures of externalizing-related psychopathology show greater interrater reliability compared to discrete measures (Narrow et al., 2013; Regier et al., 2013).

Several other transdiagnostic dimensions have been identified as more large-scale datasets with broader measurement of psychopathology became available. The psychosis spectrum is one of the more prominent and tends to capture a range of psychotic- and detachment-like psychiatric indicators, including those related to schizophrenia, bipolar, mania, dissociative and other psychotic disorders, schizoaffective disorder, schizophreniform disorder, and various personality disorders (e.g., paranoid personality disorder, schizotypal personality disorder, schizoid personality disorder; Kotov et al., 2020). This dimension has been found to bifurcate into two subdimensions labelled thought disorder (capturing positive psychotic symptoms e.g., delusions, hallucinations, disorganization) and detachment (capturing negative psychotic symptoms e.g., inexpressivity, avolition, emotional detachment, anhedonia, social withdrawal; Kotov et al., 2020). Dimensional measures of psychosis spectrum phenotypes have likewise demonstrated superior reliability when compared to categorical measures (Kotov et al., 2020). Dimensional assessments of psychoticism and detachment show substantial test-retest reliability in both patients (Quilty et al., 2013) and general population samples (Al-Dajani et al., 2016). Field trials of the DSM-5 also indicated only modest interrater reliability for categorically-defined psychosis-spectrum conditions (e.g., schizophrenia, schizoaffective disorder and bipolar disorder) and greater reliability for dimensional assessments (Narrow et al., 2013; Regier et al., 2013). Other transdiagnostic phenotypes have been identified but have not yet been as widely studied, most notably including somatoform (Krueger et al., 2018) and neurodevelopmental (Michelini et al., 2019) dimensions. Importantly, empirical evidence indicates that in addition to accounting for the covariance among observed psychiatric indicators, transdiagnostic dimensional phenotypes also tend to be positively correlated with one another (Caspi et al., 2014; Lahey et al., 2012). This suggests that there may be broader transdiagnostic constructs that account for these associations, pointing to a general liability towards all forms of psychopathology and highlighting the need for more comprehensive modeling approaches.

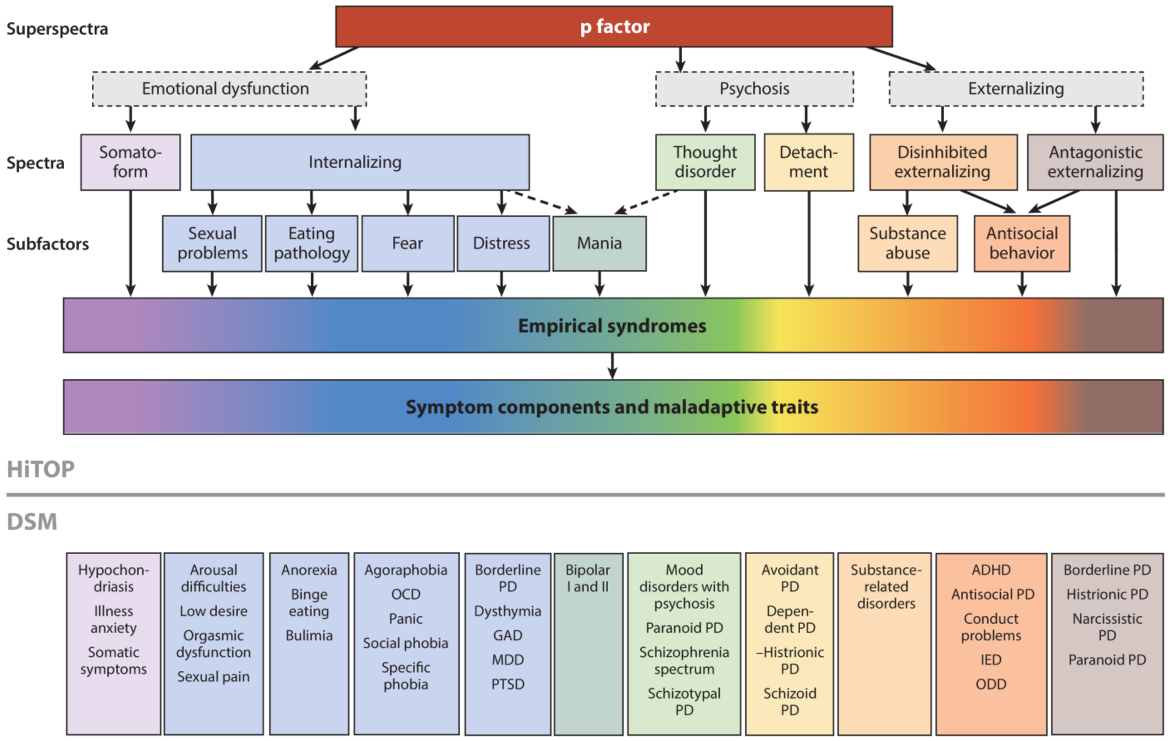
1.1.3 Hierarchical dimensional models of psychopathology

Seminal factor-analytic studies identified a broad overarching dimension of mental illness, often referred to as the p-factor or general psychopathology (Caspi et al., 2014; Lahey et al., 2012). As a construct, general psychopathology is analogous to the general factor of intelligence (or g-factor), which similarly accounts for positive correlations among dissociable dimensions of cognitive function (e.g., processing speed, working memory, verbal reasoning, visuospatial abilities; Deary, 2001; Spearman, 1904). Proponents of general psychopathology argue that it reflects the presence of shared causes across different expressions of mental illness and an underlying liability towards the full spectrum of psychopathology (Caspi & Moffitt, 2018; Lahey et al., 2017a, 2017b). The identification of this general dimension led to a proliferation of research examining the latent hierarchical structure of mental illness. The most prominent model to emerge from this research is the Hierarchical Taxonomy of Psychopathology or HiTOP model (Figure 1.1; Kotov et al., 2017, 2021).[2] Within the HiTOP framework, a general dimension of psychopathology is positioned at the apex of a structural hierarchy and increasingly specific dimensions and subdimensions are positioned at lower-levels. The general dimension is defined by patterns of covariation among these lower-order dimensions, which are themselves defined by patterns of covariation among individual psychiatric indicators (e.g., signs, symptoms, and maladaptive traits).

[2] This model is subject to a continuous process of revision on the basis of newly emerging evidence pertaining to its overall structure, the placement of psychiatric indicators within a given dimension of psychopathology, and the identification of novel phenotypes that fit within the hierarchical structure.

Figure 1.1

The Hierarchical Taxonomy of Psychopathology (HiTOP) model



Note. ADHD, attention-deficit/hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAD, generalized anxiety disorder; HiTOP, Hierarchical Taxonomy of Psychopathology; IED, intermittent explosive disorder; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; ODD, oppositional defiant disorder; PD, personality disorder; PTSD, posttraumatic stress disorder. DSM diagnoses are not included in the HiTOP model, but symptoms and signs that constitute them are in HiTOP. Dashed lines indicate dimensions included on a provisional basis. Emotional dysfunction, psychosis, and externalizing superspectra are hypothesized but not formally part of HiTOP at present. Symptom components and maladaptive traits are listed in Kotov et al. (2021, figure 3). Source: "The Hierarchical Taxonomy of Psychopathology (HiTOP): A Quantitative Nosology Based on Consensus of Evidence", Kotov et al., 2021, p. 87.

Hierarchical dimensional models of psychopathology offer several advantages in psychiatric research, overcoming many of the aforementioned limitations of the categorical approach (Kotov et al., 2017, 2021). In modeling the correlational structure of psychopathology, they directly account for widespread patterns of comorbidity among disorders, providing a more valid and parsimonious approach than models which organize psychopathology into a vast set of distinct diagnostic categories prone to multimorbidity. These models also account for the dimensionality of psychiatric expression, offering greater precision and reliability than categorical diagnoses (Kotov et al., 2020, 2021; Krueger et al., 2021; Markon et al., 2011; Watson et al., 2022) and removing arbitrarily defined thresholds that fail to capture subthreshold but clinically-meaningful symptom presentations. In addition, by grouping psychiatric indicators together into a coherent set of dimensions based on their statistical associations with one another, these models reduce heterogeneous symptom presentation among same-disorder cases as is prevalent within traditional diagnostic frameworks (Clark & Watson, 2006; Kotov et al., 2017).

Finally, hierarchical dimensional models allow researchers to examine associations with psychopathology at multiple levels of analysis and across the full spectrum of mental illness. That is, researchers can examine broad non-specific associations at the highest level of the structural hierarchy (e.g., associations with general psychopathology), as well as associations with specific/lower-order dimensions (e.g., psychosis-spectrum), subdimensions (e.g., thought disorder, detachment), and individual symptoms and traits. This has the advantage of facilitating research aiming to distinguish between shared and unique associations with different expressions of psychopathology in a way that is difficult to achieve when relying upon categorically-defined psychiatric phenotypes.

1.1.4 The validity and utility of hierarchical dimensional models of psychopathology

The validity and utility of hierarchical dimensional models of psychopathology has been detailed extensively through previous reviews (Kotov et al., 2017, 2020, 2021; Krueger et al., 2021; Lynch et al., 2021; Watson et al., 2022). Arguments supporting the validity of transdiagnostic dimensions and their hierarchical organization typically center on demonstrating that different etiological influences, neurocognitive mechanisms, developmental antecedents, illness trajectories, and treatment response patterns are not distinctly associated with specific diagnostic categories. Instead, they tend to align with a range of disorders or symptoms that correspond to higher- and lower-order transdiagnostic dimensions identified through phenotypic research.

For example, several environmental risk factors have shown associations common across internalizing- (e.g., childhood maltreatment, adolescent stressors, racial discrimination, relationship satisfaction; Watson et al., 2022) and externalizing-related conditions (e.g., neighborhood risk factors, peer interactions, childhood maltreatment; Krueger et al., 2021). Many environmental factors also extend across the psychosis spectrum (e.g., ethnic minority status, heavy cannabis use) and conditions related to thought disorder specifically (e.g., living in an urban environment, childhood adversity; Kotov et al., 2020). Research also indicates that there are common antecedents associated with internalizing- (e.g., high negative affectivity, low approach-sociability), externalizing- (e.g., high negative affectivity, low effortful control), and psychosis-related psychopathology (e.g., indicators of detachment in childhood and adolescence; Kotov et al., 2020; Krueger et al., 2021; Watson et al., 2022). Finally, studies investigating treatment response likewise indicate shared mechanisms that cut across internalizing- (e.g., response to cognitive behavioral therapy, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors), externalizing- (e.g., psychosocial interventions) and psychosis-related conditions (e.g., response to antipsychotics, cognitive behavioral therapy; Kotov et al., 2020; Krueger et al., 2021; Watson et al., 2022).

Support for the validity of hierarchical dimensional models also comes from research directly examining associations with transdiagnostic dimensional phenotypes. For example, a systematic literature review in participants aged 10 to 24 years old identified seven risk factors that showed replicable associations with internalizing dimensions (i.e., being female, earlier pubertal timing, deficits in executive function, maternal depression, high neuroticism, low extraversion, and high behavioral inhibition) and six that showed replicable associations with externalizing dimensions (i.e., executive functioning deficits, earlier pubertal timing, being male, stressful life events, high neuroticism, and low effortful control; Lynch et al., 2021). Importantly, the findings reviewed above reveal mechanisms that are associated with multiple transdiagnostic dimensions and subdimensions, supporting the presence of higher-order constructs (e.g., general psychopathology). However, there are also mechanisms that appear distinctly associated with specific/lower-order dimensions or subdimensions, supporting the coherence of phenotypes at lower levels of the structural hierarchy.[3]

Despite strong empirical support for the validity of hierarchical dimensional models, the validity of general psychopathology is the subject of ongoing debate in the literature. The identification of general psychopathology was not driven by theory but by observations that a commonly studied model (i.e., the bi-factor model) tended to provide better fit to the data than models without a general factor. Theoretical explanations of general psychopathology were thus developed post-hoc and no clear consensus has been reached regarding its substantive meaning (Watts et al., 2023). Indeed, researchers have offered a range of competing interpretations, including that that general psychopathology indexes deficits in cognitive function (Caspi & Moffitt, 2018), disordered thought processes (Caspi & Moffitt, 2018; Lahey et al., 2012), negative emotionality (Brandes et al., 2019), deficits in emotional and behavioral control (Carver et al., 2017), severity of psychopathology (Caspi et al., 2014; Caspi & Moffitt, 2018), functional impairment (Smith et al., 2020), and unspecified causal mechanisms (Lahey et al., 2012, 2017a). Alternative explanations have been proposed that suggest the general factor of psychopathology is not a substantive construct and reflects nothing more than a statistical

[3] There is also a substantial body of evidence supporting the biological validity of hierarchical dimensional models, which is detailed in subsequent sections.

artifact (e.g., that it arises simply due to a positive manifold among the observed indicators included in structural models; Caspi & Moffitt, 2018; van Bork et al., 2017).

These criticisms notwithstanding, several studies have demonstrated support for the criterion validity of general psychopathology (Smith et al., 2020). For example, the general factor of psychopathology has been found to be strongly linked to suicide risk and non-suicidal self-harm (Conway et al., 2019a). Longitudinal research also indicates that general psychopathology predicts various important outcomes (e.g., future diagnoses of psychiatric disorders, prescriptions of anxiolytic and antidepressant medication, wellbeing, academic achievement, criminality, and court convictions) when controlling for specific/lower-order dimensions (e.g., internalizing, externalizing; Pettersson et al., 2018; Sallis et al., 2019). Finally, the systematic review described above found that general psychopathology was associated with several risk factors that replicated across multiple studies (i.e., executive functioning deficits, genetic risk for attention-deficit hyperactivity disorder, genetic risk for schizophrenia, earlier pubertal timing, stressful life events, maternal depression, high negative affectivity, high neuroticism, low effortful control, high rumination, and low extraversion; Lynch et al., 2021). These findings provide support for substantive interpretations of general psychopathology; however, critics caution that there is a tendency to interpret any significant correlation with a criterion variable as evidence of the validity of general psychopathology without adequately considering certain important limitations. Specifically, concerns have been raised about the magnitude of associations with external criteria and issues surrounding discriminant validity and falsifiability (i.e., the absence of theoretical assertions regarding what general factors *should not* be associated with; Watts et al., 2023).

Another important issue in the literature is that arguments supporting the utility of hierarchical dimensional models apply primarily to their advantages in research contexts, whilst their utility in clinical settings has yet to be realized. A recent survey of clinicians found that transdiagnostic dimensional phenotypes were preferred over diagnostic categories in terms of overall clinical utility, formulation of effective interventions, communicating clinical information to the client, and describing global functioning (Balling et al., 2023). However, few studies have empirically tested whether hierarchical dimensional models outperform current approaches to diagnosis and treatment and there are several important unanswered questions regarding their suitability to clinical practice. For instance, applying a dimensional model in clinical settings would require decisions to be made according to continuums of severity (i.e., patient levels on different dimensions of psychopathology) rather than the current dichotomous approach (i.e., whether a disorder is present or absent). However, at present there are no validated cut-offs that clinicians can apply in determining severity or the need for intervention according to hierarchical dimensional models (e.g., HiTOP; Ruggero et al., 2019). There is also no clinical assessment that captures the entire system of symptoms and corresponding transdiagnostic dimensions captured by hierarchical dimensional models like HiTOP (Ruggero et al., 2019). The HiTOP consortium is currently developing these measures; however, there are concerns that such a comprehensive assessment process would be cumbersome, time-consuming, and potentially impractical in acute settings (Ruggero et al., 2019). That being said, proponents argue that hierarchical models would allow for clinical decision making to follow a step-wise approach in which higher-order constructs (e.g., internalizing, externalizing, psychosis-spectrum) are assessed first and patients could then receive additional assessments at lower levels of the hierarchy as required and when there was sufficient time to do so (e.g., in outpatient clinical settings; Ruggero et al., 2019). Finally, for any model to have utility in clinical settings it is necessary to validate that model in different populations and across the lifespan. Hierarchical dimensional models have primarily been validated in samples of adults, with more recent research extending to childhood and adolescence. However, studies examining their validity in older adults are notably lacking (Kotov et al., 2017). There is a clear need for validation studies in older adulthood to ensure that hierarchical dimensional models have the potential to offer a clinically useful framework across all stages of life.

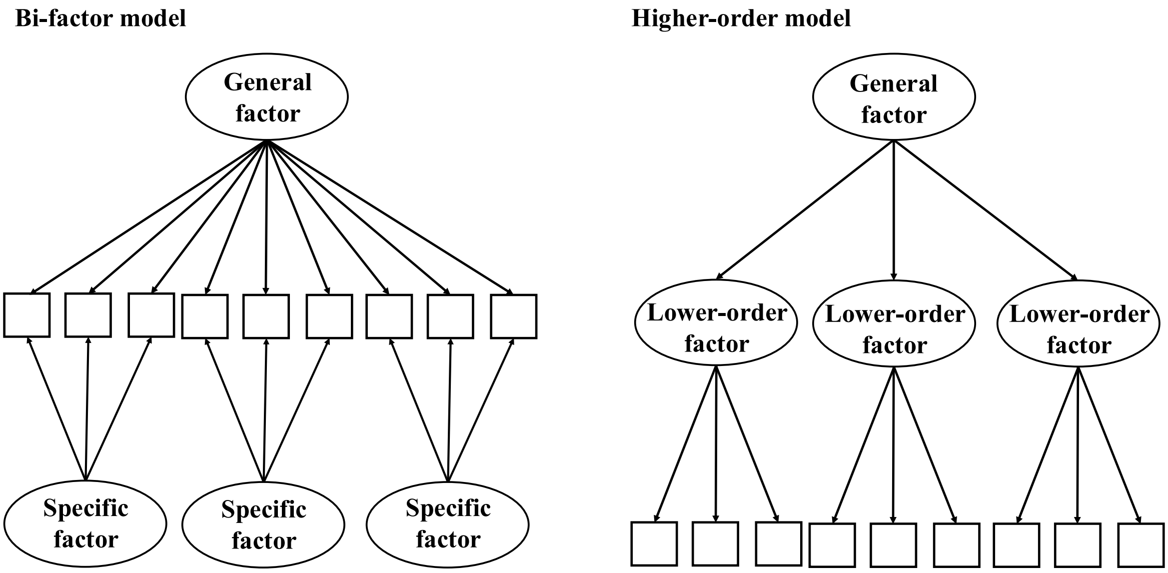
1.2 Methodological considerations in modeling the latent structure of psychopathology

1.2.1 Methodological considerations in the interpretation of general and specific/lower-order dimensions across modeling approaches

Although hierarchical dimensional models of psychopathology offer many advantages over traditional classification systems, their use in psychiatric research requires careful consideration of several important methodological issues. Firstly, the structure of psychopathology can be estimated through a variety of competing latent variable models (e.g., one-factor, correlated-factors, higher-order, and bi-factor models) that have implications for the interpretation of general and specific/lower-order dimensions. There are two primary models that are used for estimating the latent *hierarchical* structure of psychopathology, referred to as bi-factor and higher-order models (Figure 1.2). In a bi-factor model, all observed indicators are specified to load onto both a general factor (e.g., general psychopathology) and one of several specific factors (e.g., internalizing, externalizing, thought disorder) that are specified to be orthogonal to (i.e., uncorrelated with) one another. Therefore, the general factor captures shared variance across all observed indicators and each specific factor captures residual variance that is not accounted for by the general factor but unique to specific domain of psychopathology (Markon, 2019; van Bork et al., 2017). In contrast, the higher-order model is specified such that all observed indicators load onto one of several *correlated* lower-order dimensions (e.g., internalizing, externalizing, thought disorder) and the shared variance of these dimensions defines the general factor (i.e., correlated lower-order dimensions are specified to load onto a general higher-order dimension; Markon, 2019; van Bork et al., 2017). These structural differences have important implications for the interpretation of general and specific/lower-order dimensions. In a bi-factor model, the general factor reflects common variance across observed indicators that is unique to the general factor and independent from the residualized domain-specific variance of the specific factors. In a higher-order model, the general factor reflects shared variance among a set of lower-order dimensions that are themselves correlated and that contribute directly to defining the general factor, rather than being statistically independent from it.

Figure 1.2

Simplified path diagram depicting bi-factor and higher-order models commonly applied in studies investigating the hierarchical structure of psychopathology



Note. This figure represents two commonly applied confirmatory factor analysis models used to examine the latent hierarchical structure of psychopathology (i.e., bi-factor and higher-order models). Latent factors are depicted using ellipses and observed indicators are depicted using squares. For the bi-factor model, all indicators are specified to load onto the general factor and one of the specific factors included in the model and all factors are orthogonal to one another. For the higher-order model, all indicators are specified to load onto one of the correlated lower-order factors included in the model and the lower-order factors are specified to load onto a general higher-order factor.

1.2.2 Methodological considerations in evaluating and adjudicating between competing models of psychopathology

Studies typically fit multiple factor analytic models to the same set of observed psychiatric indicators and then adjudicate between them on the basis of model-fit statistics. Commonly applied model-fit statistics include the Comparative Fit Index (CFI), Tucker Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA; Hu & Bentler, 1999; Marsh et al., 2004). These and other traditional model-fit indices provide information regarding the degree to which a hypothesized model reproduces the observed covariance structure in a given dataset, thereby offering a quantitative index of how well the model captures underlying relationships among observed variables. Model-fit indices have conventionally accepted thresholds (e.g., CFI ≥ 0.90, TLI ≥ 0.90, and RMSEA ≤ 0.06), which are used to determine whether a given model provides acceptable fit to the observed data (Hu & Bentler, 1999; Marsh et al., 2004). When a variety of competing models are evaluated, the 'best-fitting' model is typically determined based on superior model-fit values and is assumed to provide most accurate representation of the structure of psychopathology based on the models tested in a particular sample. However, research investigating the latent hierarchical structure of psychopathology has been criticized for falsely equating model-fit with model validity, with opponents arguing that a well-fitting latent variable model does not necessarily capture the 'true' underlying structure of psychopathology (Watts et al., 2020).

Early research investigating the hierarchical structure of psychopathology consistently identified the bi-factor model as providing the best overall fit to the data (Kotov et al., 2017). As a consequence, much of the literature investigating hierarchical dimensional models of psychopathology and associations between transdiagnostic dimensions and external criteria has been conducted using this model. An important limitation of bi-factor models is that they have a relatively high fitting propensity because they include a greater number of model parameters (i.e., parametric complexity) and follow a more complex approach to configuring those parameters (i.e., configural complexity) compared to other commonly studied models (Bader & Moshagen, 2022). As a consequence, these models have a tendency to 'overfit' the data and also to produce unstable parameter estimates (Bonifay et al., 2017; Bonifay & Cai, 2017). Indeed, bi-factor models tend to produce specific factors with inconsistent patterns of factor loadings (i.e., low and even negative loadings) that complicate interpretation and do not align with theoretical assumptions (e.g., that all indicators of a given factor will load substantially and positively on that factor). Simulation studies also demonstrate that they tend to fit even invalid or random response patterns (Bonifay & Cai, 2017; Reise et al., 2016) and show superior fit over competing (e.g., higher-order) models when the true underlying structure does not conform to a bi-factor structure (Greene et al., 2019; Morgan et al., 2015). The high fitting propensity of the bi-factor model indicates that researchers should not adjudicate between competing models (e.g., bi-factor and higher-order models) based solely on traditional model-fit indices (Watts et al., 2020).

A number of recommendations have been put forward to strengthen the empirical basis upon which models are evaluated and selected over competing alternatives. For instance, increasing attention has been given to the importance of considering model-based estimates of reliability and replicability in addition to traditional model-fit indices (Forbes et al., 2021b; Rodriguez et al., 2016a, 2016b; Watts 2019). In the context of bi-factor models, several specific indices have been proposed to evaluate the strength and reliability of general and specific factors. Examples include the explained common variance (ECV), percent uncontaminated correlations (PUC), omega hierarchical (ωH), and the omega hierarchical subscale (ωHS).

ECV values quantify the proportion of shared variance among observed indicators that is attributable to the general factor compared to the specific factors included in a given model, providing an index of the relative strength of the general factor (Reise et al., 2013). ECV values range from 0 to 1, with values > 0.7 typically interpreted as indicating a reasonably strong general factor and values > 0.85 indicating 'unidimensionality' in the data (Rodriguez et al., 2016b). Relatedly, PUC values provide an index of the proportion of correlations among indicators that solely reflect variance from the general factor (i.e., without influence from specific factors; Reise et al., 2013). These values serve as an index of potential bias introduced by applying a unidimensional model to data with an underlying multidimensional structure, with values > 0.7 considered to indicate unidimensionality (Reise et al., 2013; Rodriguez et al., 2016a). Taken together, ECV and PUC values help to determine whether common variance in a bi-factor model can be considered essentially unidimensional, in which case specific factors may represent nuisance variance rather than conceptually meaningful constructs (Forbes et al., 2021b; Reise et al., 2013). ωH quantifies the proportion of variance in raw total scores attributable to the general factor after accounting for the specific factors, with values > 0.8 indicating sufficient reliability of the general factor (Reise et al., 2013). In contrast, ωHS indicates the reliability of each specific factor after controlling for variance attributable to the general factor, with values > 0.75 indicating sufficient reliability (Reise et al., 2013; Rodriguez et al., 2016a).

In addition to these indices, researchers have also recommended examining the H coefficient, a measure of construct reliability and replicability that can be applied to both bifactor and higher-order models (Forbes et al., 2021b). The H coefficient assesses the extent to which variance in a given factor is explained by its specific indicators, as well as the likelihood that the factor will replicate across independent samples (Hancock & Mueller, 2001; Rodriguez et al., 2016a). H can be calculated for the general and specific factors of a bi-factor model and for the lower-order factors of a higher-order model (Forbes et al., 2021b). Values range from 0-1, with higher values reflecting a factor that is more replicable and well-defined by its respective indicators (Forbes et al., 2021b; Rodriguez et al., 2016a). Values > 0.7 are typically interpreted as evidence that a factor is reliably represented by the indicators used to define it (Hancock & Mueller, 2001).

In addition to evaluating model-based reliability, researchers have also emphasized the importance of closely examining the interpretability of model parameters (Forbes et al., 2021b; Watts et al., 2019). This includes consideration of the significance, direction, and magnitude of factor loadings, as well as their precision (e.g., the size of their standard errors). When applied together, these complimentary methods (i.e., evaluation of traditional model-fit indices, model-based reliability, and the interpretability of model parameters) offer a more optimal approach to determining the best-fitting model of psychopathology.

1.2.3 Methodological considerations regarding indicator selection and sample characteristics in modeling psychopathology

Finally, there is increasing recognition of the importance of indicator selection and sample characteristics in modeling the structure of psychopathology. An important limitation in the extant literature has been its reliance on dichotomized psychiatric disorders as observed indicators of psychopathology (Forbes et al., 2021a; Kotov et al., 2017). Disorder-level dichotomous indicators lose information about within-disorder heterogeneity and severity. In addition, some symptoms are shared across different disorders and may make those disorders more likely to covary with one another, potentially inflating associations between disorder-level indicators (Forbes et al., 2021a). Reliance on disorder-level indicators also means that models are capturing variance associated with more severe psychopathology, despite knowledge that psychiatric expression exists on a continuum in the general population. These limitations are addressed by using symptom-level indicators in general population samples, which allow for more detailed examination of the latent dimensional structure of psychopathology in a way that is less dependent on the structure of diagnostic manuals (Forbes et al., 2021a). Importantly, the methodological issues outlined in this section have important implications not only for research aiming to investigate the latent structure of psychopathology but also for studies aiming to identify associations with the phenotypes that are derived from these models.

1.3 Hierarchical dimensional models as a novel framework for investigating the biological underpinnings of psychopathology

1.3.1 Challenges in identifying the biological correlates of psychopathology

A comprehensive model of psychopathology requires an understanding of how biological factors interact with the expression of maladaptive behaviors and mental processes. Of particular importance is the identification of valid biological markers, which would improve our understanding of the etiology and consequences of mental illness, facilitate early identification and intervention, and provide targets for evaluating and monitoring the efficacy of different treatment strategies. There have been significant advances in genetic sequencing and neuroimaging techniques over the past three decades, which brought hope of facilitating new discoveries in biological psychiatry (Hyman, 2007; Venkatasubramanian & Keshavan, 2016). However, these technological advances have so far failed to produce consistent findings regarding biological markers that are clinically meaningful and sufficient to improve psychiatric diagnostic practice or treatment. Indeed, studies investigating the biological correlates of psychiatric disorders have been plagued by small effect sizes (Marek et al., 2022) and frequent failures to replicate biological associations (Burmeister et al., 2008; Poldrack et al., 2017). Attempts to address these limitations have primarily focused on the utilization of increasingly larger sample sizes (Marek et al., 2022; Poldrack et al., 2017; Sullivan et al., 2018), facilitated by the proliferation of large-scale population-based datasets such as the Adolescent Brain and Cognitive Development (ABCD) study (Karcher & Barch, 2021) and the UK Biobank (Bycroft et al., 2018). However, it is widely acknowledged that progress in identifying the biological correlates of psychopathology will be impeded by continued reliance on imprecise psychiatric phenotypes, regardless of larger sample sizes, further technological advancements, and improved analytic approaches (Tiego et al., 2023).

1.3.2 The advantages of using phenotypes derived from hierarchical dimensional models in biological psychiatry

In order to detect meaningful associations between psychopathology and biology, it is critical that the psychiatric phenotypes included in a given analysis are valid and reliable constructs. Analyses involving psychiatric phenotypes that lack validity will necessarily fail to identify valid relationships between psychopathology and biology because they are searching for associations with non-meaningful constructs; however, such analyses may also identify spurious relationships that complicate or otherwise hinder scientific discovery. Measures with limited reliability introduce greater measurement error, leading to noisier estimates that may weaken observed relationships between psychopathology and biology (Tiego et al., 2023). This increased error also reduces statistical power, making it more difficult to detect meaningful associations between psychiatric and biological variables (Tiego et al., 2023). Recent research has proposed several recommendations to ensure more precise psychiatric phenotyping and greater ability to detect biological associations, including detailed symptom-level measurement across a broad spectrum of psychopathology, assessment of measurement invariance, sampling across the full spectrum of psychopathology (i.e., using general population rather than clinical samples), and the use of hierarchical dimensional models (Tiego et al., 2023).

Historically, studies in psychiatric neuroscience and genetics have aimed to identify biological markers that are uniquely associated with a given categorically-defined psychiatric disorder. These studies typically utilize a case-control design in which researchers investigate whether participants who meet the diagnostic criteria for a given disorder differ from healthy controls on certain biological variables of interest (e.g., genetic, structural neuroimaging, and functional neuroimaging variables). This approach assumes that the psychiatric disorders captured by traditional classification systems represent valid and reliable constructs that are distinct from one another both phenotypically and biologically. However, as previously mentioned, transdiagnostic dimensional phenotypes have demonstrated significantly greater validity and reliability compared to categorically-defined and highly comorbid psychiatric disorders (Kotov et al., 2020, 2021; Krueger et al., 2021; Markon et al., 2011; Watson et al., 2022). The greater precision of these phenotypes and associated improvements in their validity and reliability improves both the power to detect associations with biological variables and the strength of those associations (Tiego et al., 2023).

Indeed, dimensional psychiatric phenotypes have shown stronger associations with biological measures when compared to categorical phenotypes (DeYoung et al., 2024). The established dimensionality of psychiatric expression also suggests that reliance on diagnostic categories may arbitrarily reduce statistical power to detect associations with biological correlates (Markon et al., 2011; Tiego et al., 2023) and simultaneously obscure biological associations with subthreshold but clinically meaningful symptom expression. Importantly, evidence from genetic and neuroscientific research supports the dimensionality of psychiatric expression. For example, subclinical symptom expression is associated with similar impacts on brain structure compared to corresponding clinical disorders (Besteher et al., 2020). Likewise, polygenetic liability towards psychopathology ranges on a continuum from trait-like variation in the general population to clinical symptom expression (Martin et al., 2018).

Another advantage of hierarchical dimensional models is that they allow for examining biological associations across varying levels of breadth. Case-control studies of categorical psychiatric disorders often assume that evidence of biological differences implies evidence of a disorder-specific association; however, identified associations may actually be present across a range of disorders that were simply not included in the analysis. Within a hierarchical dimensional framework, researchers are able to examine associations with broad nonspecific dimensions of psychopathology (e.g., general psychopathology), identifying common mechanisms that may show utility in transdiagnostic prevention and intervention strategies (DeYoung et al., 2024; Waszczuk et al., 2020). Importantly, evidence from genetic and neuroscientific research consistently supports the presence of common biological mechanisms across different diagnostic categories. For example, a meta-analysis of 193 studies examining the relationship between whole-brain gray matter volume and psychopathology across six psychiatric disorders (i.e., schizophrenia, bipolar, depression, anxiety, addiction, and obsessive-compulsive disorder) found that lower gray matter volume in the dorsal anterior cingulate, as well as the left and right insula, was common across each diagnostic category (Goodkind et al., 2015). Similarly, a meta-analysis of functional neuroimaging studies found evidence of abnormal neural activity in the anterior insula, right ventromedial cortex, right intraparietal sulcus, midcingulate/presupplementary motor area and the anterior cingulate cortex across a range of psychiatric disorders (i.e., schizophrenia, bipolar or unipolar depression, anxiety, and substance use disorders; McTeague et al., 2017). In molecular genetic research, studies have recently shifted focus from aiming to identifying disorder-specific associations with one or more ‘candidate genes’ to examining the polygenetic effect of many different genetic variants (e.g., single nucleotide polymorphisms or SNPs) on the expression of psychopathology (Duncan et al., 2019). Many of these genetic variants are found to act pleiotropically, such that multiple genetic variants influence the expression of multiple psychiatric phenotypes (Smoller et al., 2019). As with the neuroimaging literature, these findings indicate common biological influences on the expression of mental illness and support the presence of broader transdiagnostic constructs over distinct diagnostic categories.

Hierarchical models also facilitate research aimed at identifying dissociable biological mechanisms across different levels of the structural hierarchy (i.e., from general psychopathology to specific/lower-order dimensions and subdimensions to individual symptoms and traits). Whereas traditional case-control designs primarily compare one disordered group to healthy controls, hierarchical approaches provide a unique profile of scores for each participant across all psychopathology dimensions included in a given model. Therefore, they allow for explicitly testing whether there are biological associations that are common across the full spectrum of mental illness (i.e., associations with general psychopathology) and more specific associations at lower structural levels (e.g., distinct associations with internalizing, externalizing, thought disorder). This approach has already identified several distinct associations between transdiagnostic dimensions in genomic (Chen et al., 2022; Lahey et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021), structural neuroimaging (Kaczkurkin et al., 2018; Parkes et al., 2021; Romer et al., 2021; Romer et al., 2023; Snyder et al., 2017), and functional neuroimaging (Lees et al., 2021) studies. In providing more valid and reliable phenotypes and allowing a more nuanced examination of biological associations across multiple levels of analysis, hierarchical dimensional models provide a powerful framework for investigating the biological basis of mental illness and uncovering both shared and distinct mechanisms that underpin differential psychiatric expression.

1.4 Importance of investigating the latent structure and biological correlates of psychopathology across the lifespan

An additional and highly important aspect of establishing a comprehensive and useful model of psychopathology is to understand how biology and psychiatric expression interact across different age groups and developmental periods. Epidemiological research indicates that the majority of psychiatric disorders emerge between childhood and early adulthood (McGrath et al., 2023) and that within this period there are age-specific patterns in the onset of different psychiatric disorders (Solmi et al., 2022; Wilson & Olino, 2021). Research further indicates that the development of psychopathology in this period is driven by a range of genetic, environmental, and neurobiological influences. For example, the onset of most psychiatric disorders coincides with a critical period of neurodevelopment, characterized by increases in white matter volumes and an inverted U-shape trajectory of cortical and subcortical gray matter volume driven in part by synaptic proliferation and pruning (Giedd et al., 2015). Disruptions to normative neurodevelopmental process (e.g., delays in the age of cortical maturation, differences in the time taken for maturation to occur) are driven by genetic and environmental factors and are thought to contribute to the onset of various psychiatric disorders (Giedd et al., 2015; Shaw et al., 2010).

For these reasons, most research aiming to identify the biological basis of mental illness has focused on studies of youth (i.e., childhood to young adulthood). However, it is widely-established that the expression of psychopathology changes across the lifespan and includes differences in both the prevalence of psychiatric disorders (Caspi et al., 2020) and in the presentation of symptoms within specific diagnostic categories (Mohlman et al., 2012; Schaakxs et al., 2017; Thompson et al., 2021). For example, longitudinal research in the general population indicates that the proportion of individuals meeting the criteria for a given disorder or set of disorders increases from adolescence to a peak in early adulthood and then begins to decrease by midlife (Caspi et al., 2020). The prevalence of common psychiatric disorders is further found to be lower in older adults compared to younger age groups (Gum et al., 2009;

Kessler et al., 2005; Sunderland et al., 2015) and continues to decrease with increasing age throughout later life (Reynolds et al., 2015; Streiner et al., 2006). Early genetic and environmental influences on neurodevelopment may have downstream effects on the expression of mental illness in adulthood and older adulthood; however, biological changes (e.g., in gene expression, brain structure) are also known to occur across the lifespan and have been found to have distinct influences on mental illness both in early development and ageing (Brouwer et al., 2022). Therefore, it is critical to investigate biological associations with psychopathology across different age groups and developmental periods.

The aforementioned advantages of hierarchical dimensional models suggests that this approach may offer new insights into the structure and biological correlates of psychopathology across the lifespan. Importantly, age-related differences in prevalence and symptom presentation may impact the comorbidity structure of mental illness across the lifespan, as well as the constructs and dimensions that make up that structure, highlighting the importance of investigating whether hierarchical dimensional models of psychopathology emerge and/or differ across different age groups and developmental periods. However, the latent hierarchical structure of psychopathology has predominately been investigated in samples ranging from childhood to adulthood (Kotov et al., 2017, 2021). Furthermore, despite the advantages of hierarchical dimensional models in investigating the biological correlates of psychopathology, no research has systematically examined age-specific differences in associations with transdiagnostic dimensions across the lifespan.

1.5 Thesis aims and overview

The foundation of this thesis is a systematic review aiming to identify the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan. The review identified older adults as an understudied population in the current literature and the following empirical chapters were designed to address this gap by investigating: 1) the latent hierarchical structure of psychopathology in older adulthood and its invariance across different age groups in later life; 2) the neurobiological correlates of transdiagnostic symptom dimensions in older adulthood; and 3) the genomic correlates of transdiagnostic symptom dimensions in older adulthood. Given the specific focus of later chapters on older adults, additional aims were to examine whether a dimension capturing cognitive dysfunction could be incorporated into the latent hierarchical structure of psychopathology in later life and whether transdiagnostic psychiatric and cognitive phenotypes could be used to predict all-cause incident dementia in this population.[4]

Four studies were designed to address eight key research questions:

1) What are the biological correlates (i.e., genomic, brain structural, and brain functional) of general and specific/lower-order dimensions of psychopathology in general population samples across the lifespan? **[Chapter 2]**
2) What is the symptom-level latent hierarchical structure of psychopathology in the general population of older adults? **[Chapters 3-5]**
3) Is there evidence that a dimension capturing cognitive dysfunction can be incorporated into the latent hierarchical structure of psychopathology in older adulthood? **[Chapters 3 and 5]**
4) Is the latent hierarchical structure of psychopathology invariant across different age groups throughout older adulthood? **[Chapters 3 and 5]**

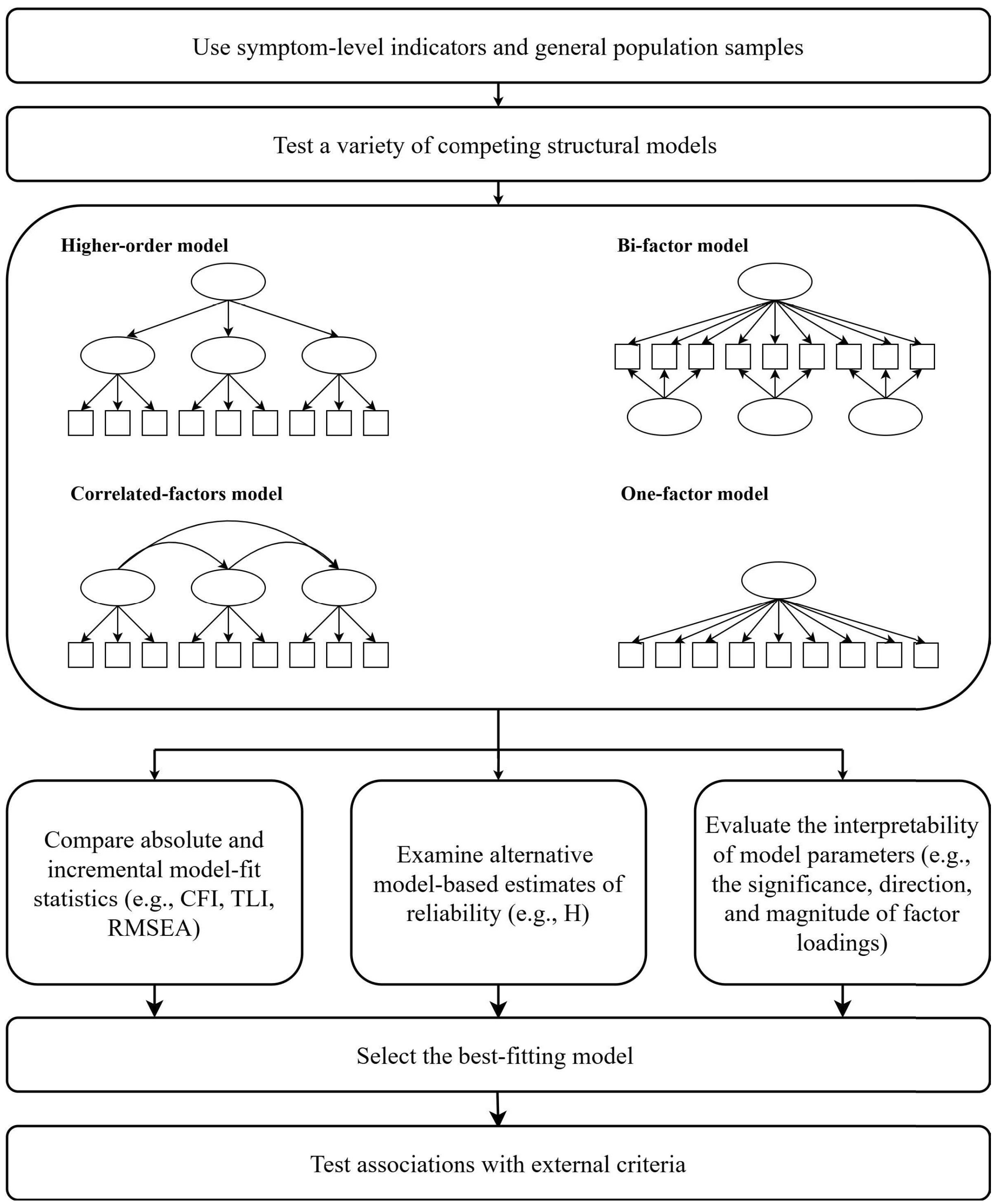
[4] Dementia represents one of the largest burdens of disease among older adults (Nichols et al., 2022) and is known to be associated with a range of putatively distinct psychiatric disorders (Richmond-Rakerd et al., 2022), as well as impairment in cognitive functioning (Belleville et al., 2017; Hayat et al., 2021).

5) Are general and specific/lower-order transdiagnostic symptom dimensions associated with global and regional measures of gray matter structure in older adults? **[Chapter 4]**
6) Does polygenetic risk for Alzheimer's disease predict variations in higher- and lower-order transdiagnostic dimensions in older adulthood? **[Chapter 5]**
7) Are general and specific/lower-order transdiagnostic dimensions associated with all-cause incident dementia in older adulthood? **[Chapters 4-5]**
8) Do biological predictors mediate the relationship between transdiagnostic dimensions and all-cause incident dementia in older adults? **[Chapter 5]**

The preceding sections of this introduction outline several clear steps researchers should take in modeling the latent structure of psychopathology prior to investigating associations between transdiagnostic dimensions and external criteria (e.g., biological associations; Figure 1.3).

Figure 1.3

Schematic representation of recommended steps for examining the latent structure of psychopathology



Note. CFI, Confirmatory Fit Index, TLI, Tucker Lewis Index; RMSEA, Root Mean Square Error of Approximation; H, H coefficient.

Firstly, researchers should include symptom-level indicators over dichotomous disorder-level diagnoses where possible to avoid biases and loss of information that occur when collapsing symptom sets into binary indicators derived from traditional diagnostic categories. Studies should also aim to examine the symptom-level structure of psychopathology in general population samples so as to properly capture the dimensionality of mental illness and the full spectrum of symptom severity. Most importantly, researchers should take a rigorous approach to model-selection prior to testing associations with external criteria. This includes testing and adjudicating between multiple viable models of psychopathology, consideration of absolute and incremental model-fit statistics (e.g., CFI, TLI, RMSEA values), model-based estimates of reliability (e.g., the H coefficient), and thorough evaluation of model parameters and interpretability (e.g., the significance, direction, and magnitude of factor loadings, as well as the magnitude of standard errors). Each of these recommendations are carefully followed throughout the empirical chapters of this thesis.

Chapter 2 presents the first systematic literature review examining the biological correlates of transdiagnostic dimensions of psychopathology and the first study to examine these associations across the lifespan. The review produced several novel findings regarding the biological correlates of these phenotypes and identified that no studies to date have investigated biological associations specifically in older adulthood.

Chapter 3 presents the largest study of the latent hierarchical structure of psychopathology in older adulthood. It is also the first study to examine whether a dimension capturing cognitive dysfunction can be incorporated into this structure in older adults and to examine the invariance of hierarchical dimensional models across different age groups throughout later life.

Chapter 4 presents the first study to investigate the neurobiological correlates of transdiagnostic symptom dimensions specifically in older adulthood and the first study to investigate whether transdiagnostic dimensions are associated with incident dementia in later life.

Chapter 5 presents the first study to investigate the genomic correlates of transdiagnostic symptom dimensions specifically in older adulthood and the largest study to explore whether these phenotypes can be used to predict incident dementia in older adults. This is also the first study to investigate whether the relationship between transdiagnostic dimensions and incident dementia are mediated by biological (i.e., genomic) predictors.

Finally, **Chapter 6** synthesizes the findings from **Chapters 2-5**, discusses the strengths and limitations of this research, outlines implications for research and clinical practice, presents suggested directions for future research, and offers final conclusions.

Chapters 2 and **4** have been peer-reviewed and published in high-impact international journals. **Chapter 3** has been submitted for publication and is currently under review. These chapters are based on the original manuscripts but have been adapted slightly for inclusion in the thesis. Revisions were made to enhance overall coherence, streamline the presentation of recurring concepts and definitions, and ensure consistency in formatting, terminology, referencing style, and the numbering of figures, tables, and appendices.

Chapter 2

Transdiagnostic biomarkers of mental illness across the lifespan: a systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population

Preface

As detailed in **Chapter 1**, recent decades have seen a proliferation of research investigating transdiagnostic dimensional models of psychopathology as an alternative to traditional psychiatric classification systems. These models offer several advantages over categorically-defined psychiatric phenotypes and appear to be more closely aligned with the genetic and neural architecture underlying psychiatric expression. For these reasons, it is thought that research investigating the genetic and neural correlates of transdiagnostic dimensional phenotypes will generate more valid and reliable findings with respect to the underlying biology of mental illness. There have been several narrative reviews that broadly outline the validity of these models and their utility across various fields of psychiatric research (Conway et al., 2019b; Kotov et al., 2017, 2021; Latzman & DeYoung, 2020; Perkins et al., 2020; Waszczuk et al., 2020). Some of these reviews focused specifically on the validity and utility of transdiagnostic dimensional models in genetic (Waszczuk et al., 2020) and neuroscientific (Latzman & DeYoung, 2020; Perkins et al., 2020) research. However, no studies have attempted to comprehensively and *systematically* review existing evidence regarding the biological correlates of transdiagnostic dimensions or to characterize these associations in a lifespan developmental context.[5]

As a consequence, the field lacks: 1) a comprehensive and cohesive understanding of the extant literature; 2) an understanding of how biological associations with transdiagnostic dimensions evolve across different stages of life (e.g., from developmental to ageing contexts); and 3) a clear picture of what gaps exist in the current evidence-base. To address this, **Chapter 2** presents the first systematic review to examine the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan. The review synthesizes associations across a broad array of transdiagnostic phenotypes (i.e., general and specific/lower-order dimensions of psychopathology) and biological domains (i.e., genomic, structural neuroimaging, and functional neuroimaging correlates). Findings are characterized by age group to highlight potential developmental patterns and identify important gaps in the current literature with respect to our understanding of these associations across the lifespan. One of the most striking findings to emerge from the review was that not a single included study had examined the biological correlates of transdiagnostic dimensions in older adulthood. This finding informed the remaining empirical chapters of the thesis, which were dedicated towards examining the latent structure and biological correlates of transdiagnostic psychopathology specifically in this population.

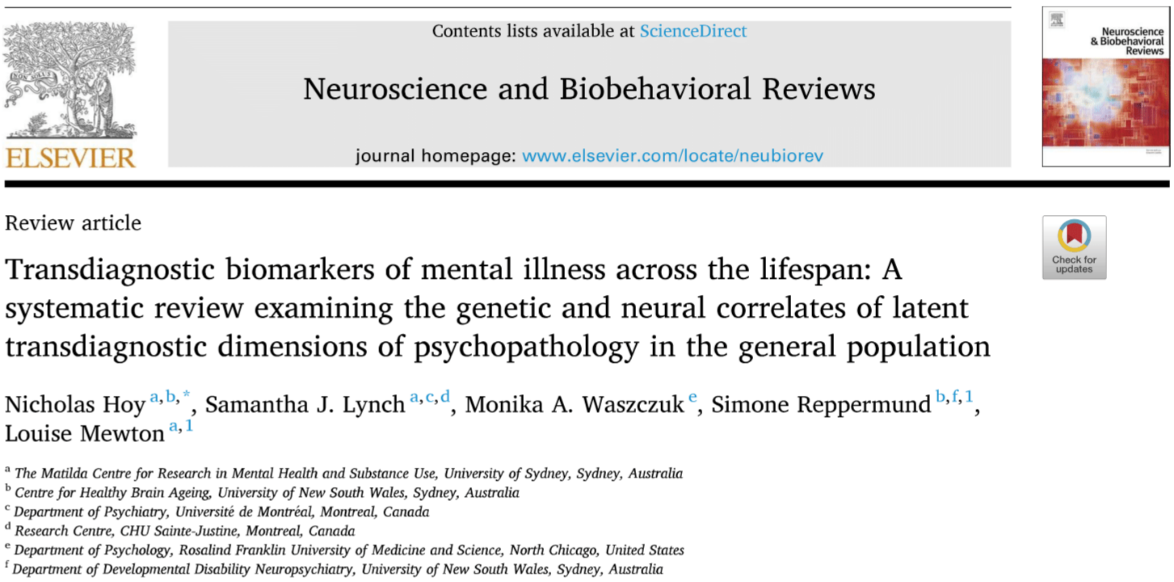
[5] It is noted that a systematic review of neuroimaging studies investigating associations with dimensions of psychopathology classified within the Hierarchical Taxonomy of Psychopathology (HiTOP) has since been published (DeYoung et al., 2024); however, this review was released after the current study was accepted for publication.

This study was published as:

Hoy, N., Lynch, S.J., Waszczuk, M.A., Reppermund, S., & Mewton, L. Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population. *Neuroscience and Biobehavioural Reviews*, 155, 105431.

Figure 2.1

Screenshot of "Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population" by Hoy et al. (2023) published in Neuroscience and Biobehavioural Reviews



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Review article

Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population

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The published manuscript for this study is included in **Appendix A**. The published protocol and supplementary material for the protocol are provided in **Appendices B** and **C**, respectively. Supplementary materials for **Chapter 2** are provided online and in **Appendix E**.

2.1 Abstract

Aims This systematic review aimed to synthesize evidence from research investigating the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology (e.g., general psychopathology, internalizing, externalizing) across the lifespan. **Methods** Eligibility criteria captured genomic and neuroimaging studies investigating general and specific/lower-order transdiagnostic dimensions of psychopathology in general population samples across all age groups. MEDLINE, Embase, and PsycINFO were searched for relevant studies published up to March 2023. **Results** There were 46 studies selected for inclusion in the review. Results revealed several biological correlates consistently associated with transdiagnostic dimensions of psychopathology, including polygenic scores for attention-deficit hyperactivity disorder and neuroticism, global surface area and global gray matter volume. Shared and unique associations between transdiagnostic dimensions are highlighted, as are potential age-specific differences in biological associations. Findings are interpreted with reference to key methodological differences across studies. **Conclusions** The included studies provide compelling evidence that the general dimension of psychopathology reflects common underlying genetic and neurobiological vulnerabilities that are shared across diverse manifestations of mental illness. Substantive interpretations of general psychopathology in the context of genetic and neurobiological evidence are discussed.

2.2 Introduction

Mental illness is a leading contributor to the global burden of disease (GBD 2019 Mental Disorders Collaborators, 2022). The most recent estimates indicate that mental illness affects approximately 970 million people worldwide, corresponding to a 48.1% increase in the prevalence of psychiatric disorders since 1990 (GBD 2019 Mental Disorders Collaborators, 2022). Effective strategies for the prevention, diagnosis, and treatment of psychopathology are needed to reduce the global burden of mental illness. Biological research plays a critical role in the development of these strategies by informing our understanding of the etiology, course, and consequences of psychopathology (Cuthbert, 2014; Glannon, 2022; Wilson & Olino, 2021). This research broadly aims to identify valid and reliable biological markers of mental illness, in order to facilitate the development of effective preventative interventions (e.g., identifying at-risk individuals) and treatment approaches (e.g., predicting illness course, informing decision-making, pharmacological interventions). Importantly, identifying the biological underpinnings of mental illness also helps to validate and distinguish between different psychiatric phenotypes, which is critical to improving diagnostic accuracy and disentangling the inherent heterogeneity of psychiatric expression (Cuthbert & Insel, 2013; Michelini et al., 2021; Smoller et al., 2019).

2.2.1 The categorical model of psychopathology

Despite decades of research and significant advances in genetic and neuroimaging methods, little progress has been made in identifying disorder-specific biomarkers with demonstrated clinical significance (Venkatasubramanian & Keshavan, 2016). A growing number of researchers argue that this lack of progress is in part driven by reliance on the categorical model of psychopathology (Cuthbert & Insel, 2013; Latzman & DeYoung, 2020; Waszczuk et al., 2020), endorsed by both the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 2013) and the *International Classification of Diseases* (ICD; World Health Organization, 2019). As outlined in **Chapter 1**, the categorical model organizes psychiatric symptoms into a set of discrete diagnostic categories, distinct from other forms of psychopathology and from normal functioning. However, research has consistently demonstrated that liability towards disorder follows a continuum, ranging from normal functioning to more severe expressions of mental illness (Kotov et al., 2017; Krueger et al., 2018; Markon et al., 2011). Psychiatric disorders also frequently co-occur within the same individual (i.e., comorbidity; Caspi et al., 2020; Kessler, 1994) and show marked heterogeneity in symptom presentation and severity between individuals diagnosed with the same disorder (Caspi et al., 2020; Feczko et al., 2019). Overall, this research suggests that the structure of psychopathology is poorly aligned with the discrete categorical boundaries imposed by traditional classification systems.

2.2.2 Hierarchical dimensional models of psychopathology

Chapter 1 introduced hierarchical dimensional models of psychopathology as a data-driven alternative to traditional psychiatric classification systems. Briefly, these models are typically estimated using latent variable techniques (e.g., confirmatory factor analysis) that group individual psychiatric symptoms, traits, and/or disorders into broader dimensional phenotypes (e.g., internalizing, externalizing, thought disorder) based on their patterns of covariation with one another (Kotov et al., 2017, 2021). The phenotypes derived from these models are described as transdiagnostic because they tend to capture patterns of covariation that cut across traditional diagnostic categories. A growing body of evidence also supports the presence of a superordinate general dimension (i.e., general psychopathology) that is posited to account for positive associations among specific/lower-order transdiagnostic dimensional phenotypes and to reflect an underlying liability towards the full spectrum of mental illness (Kotov et al., 2017, 2021).

Recent decades have seen a proliferation of research investigating the hierarchical structure and underlying biology of psychopathology. This research is supported by the collection of large-scale datasets, primarily involving general population samples. Prominent examples include the Adolescent Brain and Cognitive Development (ABCD) Study (Karcher & Barch, 2021) and the Philadelphia Neurodevelopmental Cohort (PNC; Satterthwaite et al., 2016). These studies involve extensive multidimensional data collection, often including detailed psychiatric assessments, as well as both neuroimaging and genomic measures. They also recruit significantly large sample sizes, providing the necessary statistical power for analyses of high-dimensional (e.g., genomic, neuroimaging) data and increasing the generalizability of research findings.

2.2.3 Advantages of using transdiagnostic dimensional phenotypes in genetic and neuroscientific research

Transdiagnostic dimensional phenotypes offer several advantages over categorically-defined psychiatric disorders in investigating the biological basis of mental illness. As detailed in **Chapter 1**, these phenotypes demonstrate greater validity and reliability compared to discrete categorical phenotypes (Kotov et al., 2020; Krueger et al., 2021; Markon et al., 2011; Watson et al., 2022) and offer greater precision and statistical power (Tiego et al., 2023). Moreover, they allow for examining biological associations at varying levels of specificity (e.g., associations with general and specific/lower-order dimensions) and across the full spectrum of mental illness (Latzman & DeYoung, 2020; Waszczuk et al., 2020; Zald & Lahey, 2017). The use of these phenotypes in neuroscientific and genetic research may thus facilitate new discoveries regarding the underlying biology of psychiatric expression.

2.2.4 Evidence from genetic and neuroscientific research that aligns with the hierarchical dimensional structure of psychopathology

Evidence reviewed in **Chapter 1** indicates that the biological architecture underlying mental illness aligns with the transdiagnostic and dimensional nature of psychiatric expression identified through research investigating the latent structure of psychopathology. For instance, genetic research investigating associations with PGSs capture polygenetic influences on psychiatric phenotypes (i.e., the contribution of multiple genetic variants to a given disorder) and have consistently demonstrated evidence of widespread pleiotropy across different forms of mental illness (Lee et al., 2021; Lewis & Vassos, 2022; Smoller et al., 2019). That is, genetic variants influencing the expression of psychopathology are largely shared across putatively distinct diagnostic categories (Waszczuk et al., 2020). Alterations in brain structure and function have also been implicated across a range of psychiatric disorders and evidence from meta-analytic research suggests that these associations are primarily shared across different diagnostic categories (Goodkind et al., 2015; McTeague et al., 2017; Sha et al., 2019). Both genomic and neuroimaging studies also indicate that the biological mechanisms underlying different manifestations of psychopathology are associated with subclinical expressions of mental illness in the general population, which is further consistent with the observed dimensionality of psychiatric expression (Besteher et al., 2020; Martin et al., 2018). These findings highlight the potential utility of transdiagnostic dimensional approaches in advancing our understanding of the biological underpinnings of mental illness.

2.2.5 Towards a systematic and developmentally-informed understanding of the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan

Whilst several previous reviews have examined the correlates of transdiagnostic dimensional phenotypes, most have not followed a systematic approach (Conway et al., 2019b; Kotov et al., 2017, 2021; Latzman & DeYoung, 2020; Perkins et al., 2020; Waszczuk et al., 2020). Furthermore, those which focused specifically on genetic or neuroimaging research examined only a select number of studies (Latzman & DeYoung, 2020; Perkins et al., 2020; Waszczuk et al., 2020). Research investigating the biological correlates of transdiagnostic dimensions is rapidly developing and it is therefore important to *systematically* and comprehensively review the current evidence-base. A single review has systematically explored risk and protective factors (including biological factors) associated with transdiagnostic dimensions; however, the included studies were restricted to a narrow age range (i.e., 10-24 years old; Lynch et al., 2021). Whilst this is an important first step, research has long demonstrated age- and developmentally-specific differences in the expression of mental illness that are driven by normative and non-normative changes in genetic, neurobiological, and environmental factors (Wilson & Olino, 2021). Research across the lifespan is therefore critical to accurately characterizing the structure and underlying biology of psychopathology (Lahey et al., 2017a).

2.2.6 The current study

Chapter 2 aims to extend previous research by systematically evaluating evidence from studies investigating the biological correlates (i.e., genomic, brain structural, and brain functional) of latent transdiagnostic dimensions of psychopathology in the general population and across the lifespan. The review covers a wide range of biological correlates at various levels of specificity (i.e., associations with general and specific/lower-order transdiagnostic dimensions). Synthesizing this research will provide a comprehensive understanding of the current evidence-base and identify promising and understudied directions for future research aiming to advance the field.

2.3 Methods

2.3.1 Study protocol

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix E, Table S1). The study protocol was published prospectively (Hoy et al., 2022) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021262717). Deviations from the protocol are outlined in Appendix E.1.

2.3.2 Search strategy

A comprehensive search strategy was employed across Embase, MEDLINE, and PsycINFO (Appendix E, Table S2). An initial search was run in July 2021 and re-run in March 2023. The search strategy captured three broad domains, including: latent variable models of psychopathology, genetics, and neuroimaging. Specifically, the overall strategy functioned as follows: (latent variable model terms AND psychopathology terms) AND (molecular genetic OR genomic terms) OR (brain structural OR brain functional neuroimaging terms). Reference lists of included articles were manually searched for additional citations.

2.3.3 Study eligibility

Eligibility criteria were developed using the Population Exposure Comparator Outcome (PECOS) framework. No criteria were imposed for the comparator component because research investigating dimensional models of psychopathology does not require the use of control groups (Lynch et al., 2021). The following inclusion and exclusion criteria were applied:

2.3.4 Inclusion criteria

Population

1. Only studies investigating general population samples were eligible for inclusion.
2. Studies investigating any age group were eligible.
3. Only studies investigating human participants were eligible.

Exposure(s)

1. Studies using any latent variable modeling technique (e.g., factor analysis, principal component analysis, structural equation modeling) to investigate symptom- or disorder-level latent transdiagnostic dimensions as the exposure were eligible for inclusion.
    a. Studies investigating any latent transdiagnostic dimension(s) of psychopathology (e.g., general psychopathology, externalizing, internalizing, thought disorder) were eligible.
    b. Studies investigating any latent structural model(s) of psychopathology (e.g., bifactor models, hierarchical models, correlated factor models) were eligible.
2. Studies using any technique to investigate molecular genetic or genomic variables as the exposure (with the exception of candidate gene studies) were eligible for inclusion.
3. Studies using any neuroimaging technique to investigate any brain structural or brain functional variable as the exposure were eligible for inclusion.
4. Both whole-brain and region of interest neuroimaging studies were eligible.

Outcome(s)

1. For studies that treat psychiatric phenotypes (i.e., symptom- or disorder-level latent transdiagnostic dimensions) as the exposure, the outcome measure must include at least one biological variable (i.e., molecular genetic, genomic, brain structural, and/or brain functional).

2. For studies that treat biological variables as the exposure, at least one symptom- or disorder-level latent transdiagnostic dimension (e.g., general psychopathology, externalizing, internalizing) must be measured as the outcome.
3. Only studies reporting empirical data were included.

Study characteristics

1. Only peer-reviewed studies were included.
2. Both cross-sectional and longitudinal studies were eligible. For longitudinal studies, all timepoints were considered.
3. Studies including any sample size were eligible.
4. Studies written in any language were eligible.

2.3.5 Exclusion criteria

Population

1. With the exception of severe psychopathology (e.g., schizophrenia, autism), studies in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or maltreatment) were not eligible for inclusion.
2. Studies of non-human animals were excluded.

Exposure(s)/Outcome(s)

1. Studies investigating individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories were excluded.
2. Studies in which psychopathology was not measured using latent variable techniques (e.g., total scores on transdiagnostic instruments) were excluded.

3. Studies that included biometric genetic measures (e.g., twin, family, and adoption studies) were excluded.
4. Candidate gene studies were excluded.
5. Neurophysiological studies (e.g., studies using electroencephalography to measure neural activity) were excluded.
6. Neuroscientific studies using techniques other than neuroimaging (e.g., post-mortem studies) were excluded.

Study characteristics

1. Grey literature and conference abstracts were excluded.
2. Publications that did not report original empirical findings (e.g., reviews, opinion pieces, letters, books, or book chapters) were excluded.

2.3.6 Selection procedure

Two reviewers (i.e., NH and SL) were involved in screening and study selection procedures. Following de-duplication, reviewer one (NH) screened all titles and abstracts to identify eligible studies. Reviewer two (SL) independently screened a random selection of 25% of the titles and abstracts to ensure accuracy of study selection. Following title and abstract screening, the full-texts of all included articles were screened by both reviewers to further assess study eligibility. Cohen's kappa was calculated to measure inter-rater agreement (for title and abstract screening and full-text screening) between the two reviewers, with a high level of agreement defined as a Cohen's kappa of .80 or above (McHugh, 2012). Disagreements were resolved through consultation among the two reviewers. Where disagreements could not be resolved, a third member of the research team (i.e., LM, SR, or MW) was consulted to reach consensus.

2.3.7 Data extraction

All citations were imported to Covidence (Veritas Health Innovation, 2023) for title, abstract and full-text screening. Study data were extracted by NH using a data extraction spreadsheet developed by the research team.

2.3.8 Data synthesis and quality assessment

The results of all included genomic and neuroscientific (i.e., brain structural, brain functional) studies are reported separately. Given that sufficient data were not available for meta-analyses, a narrative synthesis of the results from included studies was conducted. Following data extraction, the quality of each included study was assessed independently by NH using checklists from the Joanna Briggs Institute (Moola et al., 2020). Cross-sectional studies were evaluated using the Checklist for Analytical Cross-Sectional Studies and longitudinal studies were evaluated using the Checklist for Cohort Studies (Moola et al., 2020).

2.4 Results

2.4.1 Study selection

The search strategy returned 7,010 studies (after de-duplication) across the three databases. Of these, 173 remained eligible for inclusion following title and abstract screening. After full-text screening and manual search of citations, 46 studies were selected for inclusion in the review. Cohen's kappa showed a moderate level of agreement for title and abstract screening (k = 0.56) and for full-text screening (k = 0.48). The PRISMA flow chart is provided in the supplementary material (Appendix E, Figure S1). Quality assessments for each of the included studies are presented in Appendix E (Table S3).

2.4.2 Characteristics of included studies

A broad overview of study characteristics is presented in Table 2.1. Briefly, the review included 18 genomic studies, 14 structural neuroimaging studies, 11 functional neuroimaging studies, one study that included both structural and functional neuroimaging measures, and two studies that included both genomic and brain structural measures. There were 16 unique datasets used across the included studies, most commonly from the ABCD Study (n = 13) and the PNC (n = 9; Appendix E, Table S4). The majority of included studies investigated samples of youth (i.e., childhood to young adulthood). In the genomics literature, 13 out of the 18 studies included participants aged 7-22 years old. One study examined latent trajectories of externalizing between the ages of 18 to 32 and the remaining studies included wide age ranges, from adulthood to older adulthood (ages 18-64, 25-75) or midlife to older adulthood (ages 37-73, 40-69, 51-83). In the structural neuroimaging literature, 10 of the 14 studies examined participants aged 6-23 years old. Of the remaining studies, one examined latent disinhibition in the UK Biobank (ages 40-69) and three examined participants from the Dunedin Study (age 45). The 11 included functional neuroimaging studies examined samples ranging from childhood to young adulthood (ages 9-23) and almost half used participants from the ABCD Study (n = 5). Not a single included study across any domain (i.e., genomic, neuroimaging) focused specifically on older adults. In terms of study design, 32 of the included studies were cross-sectional and 14 were longitudinal. The following section synthesizes evidence for relationships between transdiagnostic dimensions and biological variables that were investigated across two or more of the included studies, as well as any notable trends that emerged. Key findings from the genomics and structural neuroimaging literature are presented in Table 2.2 and Table 2.3, respectively. For detailed summaries of all included studies (including effect sizes, where available) see Appendix E (Tables S5-S7).

Table 2.1

Overview of studies selected for inclusion in the systematic review

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
1. Genomic studies							
Allegrini et al. (2020)	TEDS	7 (T1) 9 (T2) 12 (T3) 16 (T4)	L	N = 7,026	PCA	General psychopathology	General PGS (derived from PGSs for ASD, MDD, BIP, SCZ, ADHD, OCD, AN, PTSD)
Avinun et al. (2020)	DNS	18-22	CS	N = 522	Bi-factor model	General psychopathology, internalizing, externalizing, thought disorder	PGSs for vitamin D serum levels
Birkell et al. (2020)	CATSS	9-12	CS	N = 13,457	(1) Bi-factor model	(1) General psychopathology	PGSs for ADHD

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
					(2) Bi-factor model	(2) General psychopathology	
Chen et al. (2022)	CATSS	9-12 (T1) 15 (T2)	L	N = 3,907	(1) Bi-factor (S-1) model (2) Bi-factor (S-1) model	(1) General psychopathology (T1) (2) General psychopathology, emotional symptoms (i.e., internalizing) (T2)	PGSs for SCZ, BIP, MDD, neuroticism, ANX, PTSD, eating disorder, ASD, ADHD, ADHD symptoms, education, intelligence
Cuevas et al. (2021)	MIDUS Biomarker Project	25-75	CS	N = 1,146	Two-factor model	Anxiety/negative affect (i.e., anxious-misery)	PGSs for ANX, MDD, and neuroticism

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Gard et al. (2021)	HRS	51-83	CS	N = 3,001	One-factor model	General psychopathology	General PGSs, internalizing-PGSs, externalizing-PGSs, as well as PGSs for MDD, ANX, ADHD, alcohol dependence, antisocial behavior, cannabis, neuroticism, and height
Grotzinger et al. (2019)	UK Biobank	40-69	CS	N = 332,050	Bi-factor model	General psychopathology	General PGSs and PGSs for SCZ, BIP, MDD, ANX, PTSD
Jermy et al. (2022)	UK Biobank	37-73	CS	N = 119,692	Higher-order model	Internalizing	PGSs for MDD and height

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Jones (2018)	ALSPAC	16	CS	N = 2,863	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology, psychotic experiences (i.e., thought disorder) (2) Psychotic experiences (i.e., thought disorder)	PGSs for SCZ, MDD, BIP, and neuroticism
Lahey et al. (2022)	ABCD	9-10 (T1) 10-11 (T2)	L	N = 4,342	Bi-factor model	General psychopathology, internalizing	PGSs for ADHD
Li et al. (2019)	Add Health	18-26 (T1) 24-32 (T2)	L	N = 7,674	LCG model	Normal (consistently low), high decreasing (initially high then decreasing), moderate (consistently	PGSs for ADHD

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
						moderate), and low increasing (initially low then increasing) levels of externalizing over time.	
Mollon et al. (2021)	PNC	8-22	CS	N = 4,662	(1) Bi-factor model (2) Higher-order model	General psychopathology, anxious-misery, fear, externalizing, psychosis (i.e., thought disorder)	SNP-heritability; genetic correlations; and gene by age interactions
Neumann et al. (2016)	Generation R	6-8	L*	N = 2,115	Bi-factor model	General psychopathology, internalizing, externalizing	SNP-heritability

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Musci et al. (2016)	Community sample	11 (T1) 17 (T2)	L*	N = 488	LTSO model	Latent trait measure of internalizing	PGSs for MDD
Pat et al. (2022)	ABCD	9-10	CS	N = 4,814	(1) Higher-order model (2) Correlated-factors model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatic, detachment	PGSs for MDD, ADHD, ANX, BIP, SCZ, and ASD
Quattrone et al. (2021)	EU-GEI (population-based control group)	18-64	CS	N = 1,497	Bi-factor model	General psychotic symptoms (i.e., thought disorder)	PGSs for SCZ

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Riglin et al. (2020)	ALSPAC	7 (T1) 13 (T2)	L	N = 5,518	Bi-factor model	General psychopathology, emotional (i.e., internalizing), behavioral (i.e., externalizing), neurodevelopmental	PGSs for SCZ, ADHD, ASD, MDD
Waszczuk et al. (2022)	ABCD	9-10	CS	N = 4,717	(1) One-factor model (2) Five-factor model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatoform, detachment	PGSs for adventurousness, disinhibition, number of sexual partners, risk tolerance, drinks per week (1), drinks per week (2), ever smoked regularly, depression, neuroticism, PTSD,

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							insomnia, BIP, SCZ, ADHD, ASD, knee pain, chronic multisite pain, chronic back pain, educational attainment, intelligence, Alzheimer's disease, BMI
2. Structural Neuroimaging Studies							
Cardenas-Iniguez et al. (2021)	ABCD	9-10	CS	N = 8,588	Bi-factor model	General psychopathology, internalizing	FA and MD
Caspi et al. (2020)	Dunedin	45	L*	N = 875	(1) Bi-factor model	(1) General psychopathology (2) Internalizing,	Brain age derived from multiple structural measures (i.e., cortical

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
					(2) Correlated-factor model	externalizing, thought disorder	thickness, cortical surface area, subcortical volume)
Durham et al (2021)	ABCD	9-10	CS	N = 9,607	Bi-factor model	General psychopathology, internalizing	GMV
Kaczkurkin et al. (2019)	PNC	8-21	CS	N = 1,394	Bi-factor model	General psychopathology, anxious-misery, psychosis (i.e., thought disorder), behavioral (i.e., externalizing), and fear	CT and GMV

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Mewton et al. (2022)	ABCD	9-10	CS	N = 10,868	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	CT, SA, and cortical and subcortical GMV
Moberget et al. (2019)	PNC	8-23	CS	N = 1,401	PCA	General psychopathology	CT, cerebellar GMV, subcortical GMV
Neumann et al. (2020)	Generation R	6-10	L*	N = 3,030	Bi-factor model (with correlated specific factors orthogonal to the general factor)	General psychopathology, internalizing, externalizing	FA, MD, AD, RD; ROI-based analyses of FA in the left pons, two regions in the right pons, the left and right lemniscus, and the medial peduncle (i.e., attempted replication of Romer et al., 2018)

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Parkes et al. (2021)	PNC	8-22	CS	N = 1,271	Bi-factor model	General psychopathology, anxious-misery, fear, externalizing, psychosis-positive, psychosis-negative	GMV measured as raw cortical volume and as deviations from normative cortical volume
Romer et al. (2018)	DNS	18-22	CS	MRI analysis: N = 1,200 DTI analysis: N = 951	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	GMV and FA
Romer et al. (2019)	Dunedin	45	L*	N = 875	Bi-factor model	General psychopathology	GMV and FA

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Romer et al. (2021)	Dunedin	45	L*	N = 875	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	CT, SA, GMV
Romer et al. (2023)	ABCD	9-10 (T1) 10-11 (T2) 11-12 (T3)	L	N = 9,220	(1) Higher-order model (2) Bi-factor model	(1-2) General psychopathology, internalizing, externalizing, neurodevelopmental, somatic, and detachment	CT, SA, and cortical and subcortical GMV
Snyder et al. (2017)	Community sample	6-10	L*	N = 254	(1) Bi-factor model	(1) General psychopathology, internalizing,	GMV

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
					(2) Correlated-factor model	externalizing (2) Internalizing, externalizing	
van Rooij et al. (2021)	UK Biobank	40-69	CS	N = 15,258	PCA	Behavioral disinhibition	Independent components of GMV characterized by high loadings in the temporal/parietal and frontal cortices (component 1), occipital and frontal cortices (component 2), temporal cortex and subcortical regions (component 3), and the temporal cortex (component 4).

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
3. Functional neuroimaging studies							
Cui et al. (2022)	PNC	8-23	CS	N = 790	(1) Correlated-factor model (2) Bi-factor model	(1) Fear, anxious-misery, externalizing, psychosis (2) General psychopathology, fear, anxious-misery, externalizing, psychosis (i.e., thought disorder)	Functional network topography
Elliot et al. (2018)	DNS	18-22	CS	N = 605	Bi-factor	General psychopathology	Connectome-wide intrinsic functional connectivity
Hong et al. (2023)	ABCD	9-10	CS	N = 6,905	One-factor model	General psychopathology	Within- and between-network connectivity

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							(AUD, CON, CPN, DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and 'unassigned' network)
Kaczkurkin et al. (2018)	PNC	11-23	CS	N = 833	Bi-factor model	General psychopathology, anxious-misery, fear, behavioral (i.e., externalizing), psychosis (i.e., thought disorder)	Regional cerebral blood flow and seed-based functional connectivity of the dorsal anterior cingulate

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Karcher et al. (2021)	ABCD	9-10	CS	Discovery: N = 3,790 Replication: N = 3,791	Nested hierarchical linear models derived from EFA (using oblique rotation): (1) One-factor model (2) Two-factor model (3) Three-factor model (4) Four-factor model (5) Five-factor model	(1) General psychopathology (2) internalizing and externalizing (3) internalizing, externalizing, neurodevelopmental (4) internalizing, externalizing, neurodevelopmental. somatoform (5) internalizing, externalizing, neurodevelopmental, somatoform, detachment	Within- and between-network connectivity (AUD, CON, CPN, DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and an 'unassigned' network)

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Kim-Spoon et al. (2021)	Community sample	13-14 (T1) 14-15 (T2) 15-16 (T3) 16-17 (T4)	L	N = 167	LCSM	Substance use	ROI-based analysis of task-based (i.e., economic lottery choice task) neural activation in the insula cortex
Lees et al. (2021)	ABCD	9-10	CS	N = 9,074	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	Within- and between-network functional connectivity (CON, CPN, DMN, DAN, FPN, RST, SAL, VAN, AUD, SMH, SMM, VIS); connectivity between these networks and several subcortical ROIs (i.e., the cerebellum, thalamus, caudate,

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							putamen, pallidum, hippocampus, amygdala, nucleus accumbens, ventral diencephalon) Task-based (i.e., emotional n-back task) activation across large-scale functional networks
Shanmugan et al. (2016)	PNC	8-22	CS	N = 1,129	Bi-factor model	General psychopathology, anxious-misery, fear, behavioral (i.e., externalizing), psychosis (i.e., thought disorder)	Task-based (i.e., fractal n-back task) neural activation across large-scale functional networks

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
Sripada et al. (2021)	ABCD	9-10	CS	N = 6,593	Bi-factor	General psychopathology	Within- and between-network functional connectivity (DMN, VIS, FPN, SAL, VAN, DAN, CPN, RST, AUD, CON, SMM, SMH, the cerebellum, a subcortical network, and an 'unassigned' network)
Xia et al. (2018)	PNC	8-22	CS	Discovery: N = 663 Replication: N = 336	sCCA	Mood (i.e., anxious-misery), psychosis (i.e., thought disorder), fear, externalizing	Whole-brain resting state functional connectivity
Zhang et al. (2022)	UK Biobank	40-69	CS	N = 6,389	CCA	General psychopathology	Amplitude and connectivity strength in

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							the DMN, SAL, and CEN
3. Structural and functional neuroimaging studies							
Modabbernia et al. (2022)	ABCD	9-10	CS	MRI analysis: N=8,114 DTI analysis: N=7,171 fMRI analysis: N=5,484	(1) ICA (2) EFA (3) ICA (4) EFA	(1) Negative affect (i.e., internalizing), opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental) (2) Internalizing, externalizing, neurodevelopmental (3) Negative affect (i.e., internalizing),	CT, SA, GMV, FA, MD, RD, AD, within- and between-network functional connectivity

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
						opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental), somatic (4) Internalizing, externalizing, neurodevelopmental, somatic, detachment	
4. Genomic and structural neuroimaging studies							
Alnaes et al. (2018)	PNC	8-22	CS	Genomic analysis: N = 2,946 DTI analysis: N = 748	ICA	General psychopathology	SNP-heritability; multimodal DTI measures of white matter microstructural and

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							connectivity features (i.e., fractional anisotropy, the principal DTI eigen value, radial diffusivity, mean diffusivity, mode of anisotropy, dominant fiber population, secondary fiber population, and connectivity density) decomposed into independent components (using ICA)
Fernandez-Cabello et al. (2022)	ABCD	9-10	CS	N=7,124	CCA	Internalizing and externalizing	General PGSs (derived from PGSs for AN,

Authors	Sample	Age	Design	Analytic sample size	Model(s)	Transdiagnostic dimensions	Biological variable(s)
							ADHD, ASD, BIP, MDD, OCD, SCZ, and Tourette syndrome) and PGSs for ADHD, ASD, BIP, MDD, OCD, SCZ, educational attainment; Several brain structural measures (i.e., CT, SA, WMV, FA and several measures of diffusivity)

Note. ABCD, Adolescent Brain and Cognitive Development Study; AD, axial diffusivity; Add Health, National Longitudinal Study of Adolescent to Adult Health; ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; AN, anorexia nervosa; ANX, anxiety; ASD, autism spectrum disorder; AUD, auditory network; BIP, bipolar disorder; CATSS, Child and Adolescent Twin Study in Sweden; CS, cross-sectional; CT, cortical thickness; CON, cingulo-opercular network; CPN, cingulo-parietal network**;** CCA, canonical correlation analysis; CEN, central executive network; DAN, dorsal attention network; DMN, default mode network; DNS, Duke Neurogenetics Study; DTI, diffusion tensor imaging; EFA, exploratory factor analysis; EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; FA, fractional anisotropy; FPN, frontoparietal network; fMRI, functional magnetic resonance imaging; GMV, gray matter volume; HRS, Health and Retirement Study; ICA, independent component analysis; L, longitudinal; LCSM, latent change score model; LGC, latent growth curve model; LTSO, latent state-trait-occasion model; MD, mean diffusivity; MDD, major depressive disorder; MIDUS, Midlife in the United States Study; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PCA, principal component analysis; PGS, polygenic scores; PNC, Philadelphia Neurodevelopmental Cohort; PTSD, posttraumatic stress disorder; RD, radial diffusivity; ROI, region of interest; RST, retrosplenial-temporal network; SA, surface area; SAL, salience network; sCCA, sparse canonical correlation analysis; SCZ, schizophrenia; SMH, sensorimotor-hand network; SMM, sensorimotor-mouth network; SNP, single nucleotide polymorphism; T1-4, Time 1–4; TEDS, Twins Early Development Study; VAN, ventral attention network; VIS, visual network; WMV, white matter volume. This table provides a broad overview of studies included in the review. Dimensions that were measured within a given latent variable model but not considered transdiagnostic are not reported (for full description of structural models, see Appendix E, Tables 5-7).

2.4.3 Genomic studies

2.4.3.1 Associations with polygenic scores

2.4.3.1.1 General polygenic scores

General psychopathology. A polygenic p-factor (i.e., defined as the first principal component extracted from PGSs for a range of psychiatric disorders) was positively associated with general psychopathology across childhood and early adolescence (ages 7-16; Allegrini et al., 2020) and in two studies spanning midlife to older adulthood (ages 40-83; Gard et al., 2021; Grotzinger et al., 2019).

2.4.3.1.2 ADHD-PGSs

General psychopathology. ADHD-PGSs were associated with greater general psychopathology across six studies, spanning childhood to adolescence (ages 7-16; Brikell et al., 2020; Chen et al., 2022; Lahey et al., 2022; Pat et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021) but showed no association with general psychopathology in one study of midlife and older adult participants (ages 51-83; Gard et al., 2021).

Internalizing. The internalizing dimension was negatively associated with ADHD-PGSs in children (age seven; Riglin et al., 2020) and showed mixed results in preadolescents and adolescents. ADHD-PGSs were negatively associated with internalizing in two studies of preadolescents (ages 9-10) from the ABCD study (at baseline but not at first follow-up) after controlling for general (Lahey et al., 2022; Waszczuk et al., 2021) and specific dimensions (Lahey et al., 2022). However, another study of ABCD participants found no evidence of association with ADHD-PGSs when controlling for other PGSs (Pat et al., 2022). Two studies found no association between internalizing and disorder-level ADHD-PGSs in adolescents (ages 13, 15; Chen et al., 2022; Riglin et al., 2020) but a significant negative association was observed between internalizing and symptom-level ADHD-PGSs at age 15 (Chen et al., 2022).

Externalizing. ADHD-PGSs showed no association with externalizing in bivariate analyses of preadolescents (ages 9-10; Waszczuk et al., 2021); however, there was evidence of a positive association in analyses of the same sample when controlling for general and lower-order transdiagnostic dimensions, as well as multiple PGSs (Pat et al., 2022). ADHD-PGSs were also associated with 'high decreasing' and 'moderate' (but not low increasing) trajectories of externalizing between the ages of 18 and 32 based on longitudinal analyses using latent growth curve models (Li, 2019).

Neurodevelopmental. The neurodevelopmental dimension was not associated with ADHD-PGSs in childhood (age seven; Riglin et al., 2020) but was positively associated with ADHD-PGSs in two studies of preadolescents (ages 9-10; Pat et al., 2022; Waszczuk et al., 2021) from the ABCD study and in one study of adolescents (age 13; Riglin et al., 2020).

2.4.3.1.3 Depression-PGSs

General psychopathology. Two studies found a positive association between depression-PGSs and general psychopathology at baseline in the ABCD cohort (using one-factor and higher-order models; Pat et al., 2022; Waszczuk et al., 2021). Another study found no association in a different sample of preadolescents (ages 9-12) when general psychopathology was modeled using a bi-factor approach (Chen et al., 2022). Depression-PGSs were also not associated with general psychopathology in childhood (age 7; Riglin et al., 2020) or across three studies of adolescents (ages 13-16; Chen et al., 2022; Jones et al., 2018; Riglin et al., 2020). However, they were positively associated with general psychopathology across two studies in midlife and older adulthood (Gard et al., 2021; Grotzinger et al., 2019).

Internalizing. Depression-PGSs showed no association with internalizing in childhood (age 7), when modeled using a bi-factor approach and simultaneously regressing multiple PGSs (Riglin et al., 2020). Depression-PGSs were not associated with internalizing in bivariate analyses of the ABCD cohort (after controlling for general psychopathology; Waszczuk et al., 2021) but were positively associated in analyses controlling for general and lower-order transdiagnostic dimensions, as well as other PGSs (Pat et al., 2022). In a multivariate analysis of adolescents (age 13), internalizing was positively associated with depression-PGSs but showed no association with five other polygenic exposures (Riglin et al., 2020). However, another study of adolescents at age 15 (controlling for general and specific transdiagnostic dimensions and other PGSS) found no evidence of association (Chen et al., 2022). Depression-PGSs also showed a positive association with a measure of internalizing extracted from longitudinal assessment data across ages 11 to 17 (Musci et al., 2016). Depression-PGSs were not associated with a latent 'anxiety/negative affect' factor in a cross-sectional study of participants aged 25 to 75 (Cuevas et al., 2021) but were associated with a transdiagnostic measure of depressive and anxious symptoms in midlife to older adult participants from the UK Biobank (Jermy et al., 2022).

Neurodevelopmental. Depression-PGSs were not associated with the neurodevelopmental dimension in one study of the ABCD cohort (i.e., bivariate analyses controlling for general psychopathology; Waszczuk et al., 2021) but were positively associated in another (i.e., multivariate analyses controlling for general and lower-order transdiagnostic dimensions as well as other PGSs; (Pat et al., 2022). One additional study found no evidence of an association between depression-PGSs and a neurodevelopmental dimension in childhood or adolescence (using a bi-factor model and controlling for other PGSs; Riglin et al., 2020).

Externalizing, somatic, and detachment. In bivariate analyses (controlling for general psychopathology), there was no evidence of an association between depression-PGSs and externalizing, somatic, or detachment dimensions in preadolescents from the ABCD study (Waszczuk et al., 2021). However, in multivariate analyses of the same sample, controlling for general and lower-order transdiagnostic dimensions, as well as other PGSs, all three dimensions were positively associated with PGSs for depression (Pat et al., 2022).

2.4.3.1.4 Schizophrenia-PGSs

General psychopathology. Schizophrenia-PGSs were associated with greater general psychopathology in childhood (age 7; Pat et al., 2022) but showed no association across three studies of preadolescents (ages 9-12; Chen et al., 2022; Pat et al., 2022; Waszczuk et al., 2021). Results were mixed for adolescents, with schizophrenia-PGSs associated with greater general psychopathology in two studies (ages 13-16; Jones et al., 2018; Riglin et al., 2020) and showing no association in another (age 15; Chen et al., 2022). General psychopathology was also positively associated with PGSs for schizophrenia in one study of midlife and older adults (ages 40-69; Grotzinger et al., 2019).

Internalizing. Schizophrenia-PGSs were positively associated with internalizing in children (Riglin et al., 2020) but showed no association across three studies spanning preadolescence (Waszczuk et al., 2021) and adolescence (Chen et al., 2022; Riglin et al., 2020).

Thought disorder. PGSs for schizophrenia were positively associated with a positive psychosis dimension (when derived from a correlated-factors model but not a bi-factor model) and with a negative psychosis dimension (when derived from both a bi-factor and correlated-factors model) in adolescents (age 16; Jones et al., 2018). In addition, schizophrenia-PGSs were positively associated with positive, negative, and general psychotic dimensions in participants aged 18 to 64 (Quattrone et al., 2021).

Neurodevelopmental. There was no evidence of an association with schizophrenia-PGSs and a neurodevelopmental dimension across two studies, spanning childhood and adolescence (ages 7-13; Riglin et al., 2020; Waszczuk et al., 2021).

2.4.3.1.5 Autism-PGSs

General psychopathology. One study found a positive association between general psychopathology and autism-PGSs based on bivariate analyses in preadolescents from the ABCD study (Waszczuk et al., 2021). However, three other studies found no evidence of an association across childhood and adolescence (ages 7-15), including in ABCD participants, when simultaneously controlling for other PGSs and/or specific/lower-order transdiagnostic dimensions (Chen et al., 2022; Pat et al., 2022; Riglin et al., 2020).

Internalizing. Autism-PGSs were not associated with internalizing across three studies, spanning childhood and adolescence (ages 7-15; Chen et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021).

Neurodevelopmental. Autism-PGSs were not associated with the neurodevelopmental dimension in childhood or adolescence (ages 7, 13; Riglin et al., 2020) or in preadolescents from the ABCD study (after controlling for general psychopathology; Waszczuk et al., 2021).

2.4.3.1.6 Bipolar-PGSs

General psychopathology. Bipolar-PGSs were not associated with general psychopathology across four studies spanning preadolescence and adolescence (ages 9-15; Chen et al., 2022; Jones et al., 2018; Pat et al., 2022; Waszczuk et al., 2021) but were positively associated in one study of midlife and older adulthood (40-69; Grotzinger et al., 2019).

Internalizing. Bipolar-PGSs were not associated internalizing across two studies, in preadolescents (ages 9-10) and adolescents (age 15; Chen et al., 2022; Waszczuk et al., 2021).

Other specific/lower-order transdiagnostic dimensions. Bipolar-PGSs were also not associated with any transdiagnostic dimension investigated in a single study (i.e., externalizing, psychosis positive, psychosis negative, neurodevelopmental, somatic, and detachment), spanning preadolescence and adolescence (ages 9-10 and 16; Jones et al., 2018; Waszczuk et al., 2021).

2.4.3.1.7 Neuroticism-PGSs

General psychopathology. Neuroticism-PGSs were positively associated with general psychopathology in bivariate analyses of preadolescents from the ABCD study (Waszczuk et al., 2021) but showed no association in another preadolescent sample that controlled for specific transdiagnostic dimensions and multiple PGSs (Chen et al., 2022). Neuroticism-PGSs were also positively associated with general psychopathology across two adolescent samples (ages 15-16; Chen et al., 2022; Jones et al., 2018) and in a single study of midlife to older adult participants (ages 51-83; Gard et al., 2021).

Internalizing. Neuroticism-PGSs were not associated with internalizing (after controlling for general psychopathology) in preadolescents (ages 9-10; Waszczuk et al., 2021) but were positively associated in adolescents (age 15) when controlling for other PGSs and latent factors (Chen et al., 2022). In addition, neuroticism-PGSs were positively associated with a ‘anxiety/negative affect factor’ in a cross-sectional study of participants aged 25 to 75 years old (Cuevas et al., 2021).

2.4.3.1.8 PTSD-PGSs

General psychopathology. PGSs for PTSD were positively associated with general psychopathology in one study of ABCD participants (i.e., bivariate analyses controlling for general psychopathology; Waszczuk et al., 2021) but not in another longitudinal study of preadolescents (ages 9 and 12) and adolescents (age 15) (controlling for general and specific factors, as well as other PGSs; Chen et al., 2022). General psychopathology was positively associated with PGSs for PTSD in one study of midlife and older adults (ages 51-83; Gard et al., 2021).

Internalizing. PTSD-PGSs were not associated with internalizing in preadolescents (after controlling for general psychopathology; Waszczuk et al., 2021) or in a sample of adolescents (age 15; Chen et al., 2022).

2.4.3.1.9 Anxiety-PGSs

General psychopathology. Anxiety-PGSs showed no association with general psychopathology across two studies spanning childhood and adolescence (ages 9-15; Chen et al., 2022; Pat et al., 2022) but were positively associated in two studies of midlife and older adult participants (ages 40-83; Gard et al., 2021; Grotzinger et al., 2019).

Internalizing. PGSs for anxiety were not associated with internalizing at age 15 (Chen et al., 2022) or with an ‘anxiety/negative affect’ factor in a cross-sectional study of participants aged 25 to 75 (Cuevas et al., 2021).

2.4.3.2 SNP-heritability

General psychopathology. Significant SNP-heritability was observed for general psychopathology in children (ages 6-8) from the Generation R cohort (Neumann et al., 2016). In youths from the PNC (ages 8-22), two studies found significant SNP-heritability associated with general psychopathology (Alnæs et al., 2018; Mollon et al., 2021); however, this association did not survive false discovery rate (FDR) correction in one study (Mollon et al., 2021).

Table 2.2

Associations between transdiagnostic dimensions and polygenic scores investigated in two or more studies

Authors	Age	Modeling approach	G-PGS	ADHD				SCZ					DEP				NEUR		ASD				BIP	ANX	PTSD	INTEL		EDU	
			GP	GP	INT	EXT	ND	GP	INT	EXT	TD	ND	GP	INT	EXT	ND	GP	INT	GP	INT	EXT	ND	GP	GP	GP	GP	INT	GP	INT
Allegrini et al. (2020)	7	Principal component analysis																											
	9																												
	12																												
	16																												
Riglin et al. (2020)[1,2,3]	7	Bi-factor																											
	13																												

Waszczuk et al. (2022)[1]	9-10	One-factor, Five-factor
Pat et al. (2022)[3]	9-10	Higher-order
Lahey et al. (2022)[1,2]	9-10	Bi-factor
	10-11	
Chen et al. (2022)[1,2,3]	9-12	Bi-factor (S-1)
	15	
Birkell et al. (2020)[1,2]	9-12	Bi-factor
Jones (2018)[1,2]	16	Bi-factor
Musci et al. (2016)	11-17	LTSO
Li et al. (2019)	18-32	Latent growth curve

Quattrone et al. (2021)	18-64	Bi-factor
Cuevas et al. (2021)[3]	25-75	One-factor
Jermy et al. (2022)	37-73	Higher-order
Grotzinger et al. (2019)	40-69	Bi-factor
Gard et al. (2021)	51-83	One-factor

Note. ADHD, attention-deficit/hyperactivity disorder; ANX, anxiety; ASD, autism spectrum disorder; BIP, bipolar; DEP, depression; EDU, education; EXT, externalizing; GP, general psychopathology; G-PGS, general polygenic score; INT, internalizing; INTEL, intelligence; LTSO, latent trait-state-occasion model; ND, neurodevelopmental; NEUR, neuroticism; PTSD, posttraumatic stress disorder; SCZ, schizophrenia; TD, thought disorder. This table details evidence of associations between polygenic scores and general and specific/lower-order transdiagnostic dimensions investigated in two or more included studies. Significant positive associations are highlighted in green, significant negative associations in blue, and non-significant associations in grey. Blank cells indicate that no association was tested. Cuevas et al. (2021) examined a latent anxiety/negative affect dimension (i.e., the anxious-misery subdimension of internalizing).

[1]Study controlled for general psychopathology.

[2]Study controlled for other specific/lower-order dimensions.

[3]Study controlled for other PGSs.

2.4.4 Structural neuroimaging studies

2.4.4.1 Associations with gray matter structure

2.4.4.1.1 Cortical thickness

General psychopathology. Two studies found no evidence of an association between global cortical thickness and general psychopathology, either at baseline or across the first three waves of data collection, in preadolescents from ABCD study (ages 9-12; Mewton et al., 2022; Romer et al., 2023). In the PNC (ages 8-22), reduced cortical thickness was associated with greater general psychopathology in a single structural network (out of 18 brain-wide structural covariance networks) comprising the precuneus and temporoparietal junction; however, this association did not survive sensitivity analyses (i.e., controlling for maternal education and excluding participants on psychotropic medication; Kaczkurkin et al., 2019). Another study of the PNC found no evidence of an association with global cortical thickness, whilst follow-up univariate analyses (not controlling for global thickness) found that general psychopathology was negatively associated with cortical thickness specifically within the cuneus, fusiform, postcentral, precentral, precuneus, superior parietal, and transverse temporal regions (Moberget et al., 2019). In contrast to research in youths, global cortical thickness was significantly negatively associated with general psychopathology in midlife participants (age 45) from the Dunedin study (Romer et al., 2023).

Internalizing. Internalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD cohort at baseline (Mewton et al., 2022; Modabbernia et al., 2022; Romer et al., 2023) or longitudinally across the first two follow-ups (Romer et al., 2023). However, lower global cortical thickness at baseline did predict steeper reductions in internalizing across the first three waves of the ABCD study (Romer et al., 2023). Follow-up analyses revealed that this association was driven by cortical thickness within 16 (of 68) parcellated brain regions (corrected for global cortical thickness). In the PNC (ages 8-21), anxious-misery showed no association with cortical thickness across 18 brain-wide structural networks in youths (ages 8-21; Kaczkurkin et al., 2019). In addition, the fear dimension was negatively associated with cortical thickness in 13 structural networks; however, these associations were no longer significant when controlling for global cortical thickness (Kaczkurkin et al., 2019). In contrast, internalizing was significantly negatively associated with global cortical thickness at midlife (age 45; Romer et al., 2021).

Externalizing. Externalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD study at baseline (Mewton et al., 2022; Modabbernia et al., 2022; Romer et al., 2023) or longitudinally across the first three waves of data collection (Romer et al., 2023), nor with any structural covariance network (across 18 brain-wide networks) in participants aged 8 to 22 from the PNC (Kaczkurkin et al., 2019). Global cortical thickness was, however, negatively associated with externalizing at midlife (age 45) in participants from the Dunedin Study (Romer et al., 2021).

Thought disorder. Global cortical thickness was not associated with the thought disorder dimension in preadolescents (using baseline data from the ABCD study; Mewton et al., 2022). Similarly, a psychosis dimension showed no association with global cortical thickness (Moberget et al., 2019) or with regional cortical thickness across 18 brain-wide structural covariance networks (Kaczkurkin et al., 2019) in two studies of youths (ages 8-23) from the PNC. However, global cortical thickness was negatively associated with thought disorder in midlife participants from the Dunedin study (Romer et al., 2021).

Neurodevelopmental. The neurodevelopmental dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Modabbernia et al., 2022; Romer et al., 2023) or across the first two follow-ups (Romer et al., 2023).

Detachment. The detachment dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Modabbernia et al., 2022; Romer et al., 2023) and across the first two follow-ups (Romer et al., 2023).

Somatic. The somatic dimension showed no association with global cortical thickness at baseline (or across the first two follow-ups) in ABCD participants, when derived from a higher-order model (Romer et al., 2023) and a correlated-factors model (Modabbernia et al., 2022) but was *positively* associated when derived from independent component analysis (ICA; Modabbernia et al., 2022).

2.4.4.1.2 Surface area

General psychopathology. Higher general psychopathology predicted lower global surface area (SA) at baseline in preadolescents from the ABCD study (ages 9-10; Mewton et al., 2022). Likewise, lower global SA predicted greater levels of general psychopathology at baseline and across the first two follow-up waves of the ABCD study (ages 9-12; Romer et al., 2023). In contrast, global SA was not associated with general psychopathology at midlife (age 45; Romer et al., 2021).

Internalizing. Internalizing predicted lower global SA at baseline in preadolescents from the ABCD cohort, when derived from higher-order and correlated-factor models (Mewton et al., 2022; Modabbernia et al., 2022) but not when derived from ICA (Modabbernia et al., 2022). In addition, when global SA was included as a predictor (in another study of ABCD participants), there was no evidence of an association with internalizing at baseline or across the first two follow-ups (ages 9-12; Romer et al., 2023). There was also no evidence of an association between global SA and internalizing at midlife (age 45; Romer et al., 2021).

Externalizing. Global SA was negatively associated with externalizing in three studies of preadolescents from the ABCD cohort (Mewton et al., 2022; Modabbernia et al., 2022; Romer et al., 2023) and in midlife participants from the Dunedin study (Romer et al., 2021).

Thought disorder. The thought disorder dimension was negatively associated with global SA in one study of preadolescents (ages 9-10; Mewton et al., 2022) but showed no association in midlife (age 45; Romer et al., 2021).

Neurodevelopmental. The neurodevelopmental dimension was negatively associated with global SA in ABCD participants when derived from a higher-order model (across the first three waves of data collection; Romer et al., 2023) and a correlated-factors model (at baseline; Modabbernia et al., 2022) but showed no association when derived from ICA (at baseline; Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global SA in two studies of preadolescents from the ABCD cohort, at baseline (Modabbernia et al., 2022) and across the first three waves of data collection (Romer et al., 2023).

Somatic. The somatic dimension was not associated with global SA in two studies of ABCD participants, at baseline (Modabbernia et al., 2022; Romer et al., 2023) or across the first three follow-up waves (Romer et al., 2023).

2.4.4.1.3 Gray matter volume

General psychopathology. In preadolescents from the ABCD cohort, general psychopathology predicted lower global GMV at baseline (ages 9-10; Mewton et al., 2022) and lower baseline global GMV predicted greater levels (but not the trajectories) of general psychopathology across the first three waves of data collection (ages 9-12; Romer et al., 2023). In youths from the PNC (ages 8-22), general psychopathology was associated with lower global GMV in one study (Kaczkurkin et al., 2019) and with greater negative deviations from normative cortical volume (but not raw global cortical volume) in another (Parkes et al., 2021). Exploratory whole-brain analyses found that general psychopathology was associated with widespread regionally-specific reductions in GMV across six studies spanning childhood to early adulthood (ages 6-23; Durham et al., 2021; Kaczkurkin et al., 2019; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023; Snyder et al., 2017).

In contrast, whole-brain analyses in young adults from the DNS (ages 18-22) found that greater general psychopathology was associated with lower GMV in the bilateral lingual gyrus and right intracalcarine regions (of the visual cortex), as well as the left posterior cerebellum, after controlling for total GMV (Romer et al., 2018). Whole-brain analyses (not controlling for global GMV) in midlife participants (age 45) also found that general psychopathology was negatively associated with GMV in relatively few regions (Romer et al., 2021). Of note, an ROI-based study of participants at midlife (age 45) replicated the negative association between general psychopathology and GMV in the visual cortex but not in the cerebellum (Romer et al., 2018; Romer et al., 2019). Similarly, general psychopathology was negatively associated with cerebellar GMV in ROI-based analyses of youths from the PNC (ages 8-22; Moberget et al., 2019) but failed to replicate in participants at midlife (age 45; Romer et al., 2019).

Internalizing. Internalizing showed few (predominately positive) significant regional associations with GMV in exploratory whole-brain analyses of children (age 6-10; Snyder et al., 2017). Internalizing predicted lower global GMV at baseline in ABCD participants (ages 9-10), when derived from a higher-order model (Mewton et al., 2022) but not when derived from ICA or a correlated-factors model (Modabbernia et al., 2022). In whole-brain analyses of ABCD participants (at baseline), internalizing was associated with widespread reductions in GMV when derived from a higher-order model (none of which remained significant after controlling for global GMV; Mewton et al., 2022) and was not associated with any region when derived from a bi-factor model (Durham et al., 2021). In addition, global cortical and subcortical volume did not predict internalizing (higher-order model) at baseline or across the first two follow-ups (ages 9-12) in a subsequent study of ABCD participants (Romer et al., 2023). In the PNC (ages 8-22), lower global cortical volume (i.e., raw volume and deviations from normative cortical volume) did not predict the anxious-misery dimension and whole-brain analyses revealed relatively few (predominately positive) associations with regional GMV (Parkes et al., 2021). In contrast, the anxious-misery dimension predicted increased global GMV and was positively associated with GMV in 17 (out of 18) brain-wide structural networks (none of which remained significant after controlling for global GMV) in another study of the same sample (Kaczkurkin et al., 2019). Also in the PNC, lower global cortical volume and greater negative deviations from normative cortical volume predicted higher scores on the fear dimension (Parkes et al., 2021). Follow-up whole-brain analyses (not controlling for global GMV) also found that the fear dimension was associated with lower GMV in relatively few regions. Similarly, the fear dimension (when included as a predictor) was negatively associated with GMV in only eight out of 18 brain-wide structural covariance networks (none of which remained significant after controlling for global GMV) in the PNC (Kaczkurkin et al., 2019). In midlife (age 45), whole-brain analyses (not controlling for global GMV) revealed associations between internalizing and only four anatomical regions (all of which were shared across other transdiagnostic dimensions; Romer et al., 2021).

Externalizing. Externalizing showed relatively few regional associations with GMV based on whole-brain analyses of a childhood community sample (ages 6-10; Snyder et al., 2017). When derived from a higher-order model, externalizing predicted lower global GMV at baseline in ABCD participants (ages 9-10; Mewton et al., 2022) and lower global GMV predicted greater externalizing at baseline and across the first two follow-ups (ages 9-12; Romer et al., 2023). However, there was no evidence of association with global GMV when externalizing was derived from ICA or a correlated-factors model in baseline ABCD data (Modabbernia et al., 2022). In addition, whole-brain analyses of ABCD participants (at baseline) found that externalizing predicted widespread regional reductions in GMV; however, no associations remained significant after controlling for global GMV (Mewton et al., 2022). In the PNC (ages 8-22), global cortical volume (i.e., raw cortical volume and deviations from normative cortical volume) did not predict externalizing (Parkes et al., 2021). Follow-up whole-brain analyses found negative associations between externalizing and GMV in relatively few regions. Similarly, another study of the PNC found that externalizing predicted lower cortical volume in only two (i.e., superior parietal and fusiform cortices) of 18 brain-wide structural networks and these associations did not survive sensitivity analyses (controlling for maternal education and psychotropic medication use; Kaczkurkin et al., 2019). Lastly, whole-brain analyses of midlife participants (age 45) also found relatively few associations between externalizing and regional GMV (Romer et al., 2021).

Thought disorder. The thought disorder dimension was negatively associated with global cortical volume in preadolescents from the ABCD study (ages 9-10; Mewton et al., 2022). Follow-up analyses revealed widespread reductions in regional GMV, none of which remained significant after controlling for global GMV. In the PNC (ages 8-22), lower global cortical volume (i.e., lower raw volume and greater negative deviations from normative cortical volume) predicted greater scores on a psychosis-positive (but not psychosis-negative) dimension (Parkes et al., 2021). Follow-up whole-brain analyses revealed few associations between psychosis-positive or psychosis-negative dimensions. Also in the PNC, a general psychosis dimension did not predict GMV in any of 18 brain-wide structural networks. Similarly, whole-brain analyses of participants at midlife (age 45) found few associations between thought disorder and regional GMV (Romer et al., 2021).

Neurodevelopmental. When derived from a higher-order model, the neurodevelopmental dimension predicted lower global GMV at baseline in ABCD participants (ages 9-10; Mewton et al., 2022) and lower global cortical and subcortical GMV predicted higher scores on the neurodevelopmental dimension at baseline and across the first two follow-ups (ages 9-12; Romer et al., 2023). However, there was no evidence of association with global GMV when the neurodevelopmental dimension was derived from ICA or a correlated-factors model using baseline ABCD data (Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global cortical and subcortical volume across the first three waves of the ABCD study when derived from a higher-order model (Romer et al., 2023) but showed no association at baseline when derived from a correlated-factor model or ICA (Modabbernia et al., 2022).

Somatic. Two studies found no association between the somatic dimension and global GMV in ABCD participants at baseline (Modabbernia et al., 2022; Romer et al., 2023), or across the first two follow-up waves (Romer et al., 2023).

2.4.4.2 Associations with white matter microstructure

General psychopathology. Lower global fractional anisotropy (FA) (i.e., average fractional anisotropy across 12 white matter tracts) was associated with higher general psychopathology in children (ages 6-10) from the Generation R cohort (Neumann et al., 2016). In ABCD participants (ages 9-10), there were no significant associations between general psychopathology and FA in any of 17 bilateral white matter (WM) tracts following FDR correction (Cardenas-Iniguez et al., 2022). In contrast, exploratory whole-brain analyses in young adults from the DNS (ages 18-22) found that general psychopathology predicted lower FA specifically within the bilateral pons, when controlling for global FA (Romer et al., 2018). Follow-up ROI analyses (of white matter tracts within the pons and cerebellum) found that greater general psychopathology predicted lower FA in the right and left lemniscus, as well as the left superior peduncle (again controlling for whole-brain FA). The association between general psychopathology and lower FA in the pons (but not the cerebellum) when controlling for global FA, was subsequently replicated in participants at midlife (age 45; Romer et al., 2019). Analyses using an alternative model (not controlling for global FA) found that general psychopathology predicted lower FA in the medial peduncle of the cerebellum (Neumann et al., 2020). Lastly, general psychopathology showed no evidence of association with global medial diffusivity in children (ages 6-10; Neumann et al., 2020) or with any of 17 bilateral WM tracts in preadolescents (ages 9-10; Cardenas-Iniguez et al., 2022).

Internalizing. Global FA was not associated with internalizing in children (ages 6-10) from the Generation R cohort (Neumann et al., 2020). In ABCD participants (ages 9-10), internalizing was negatively associated with global FA when derived from a correlated-factor model but not from ICA (Modabbernia et al., 2022) and showed no association with any of 17 WM tracts when measured using a bi-factor model (Cardenas-Iniguez et al., 2022). ROI-based analyses in young adults (ages 18-22) found that internalizing was associated with lower pons FA (Romer et al., 2018). Internalizing showed no association with mean diffusivity (across three studies; Cardenas-Iniguez et al., 2022; Modabbernia et al., 2022; Neumann et al., 2020), or axial and radial diffusivity (across two studies; Modabbernia et al., 2022; Neumann et al., 2020), spanning childhood (ages 6-10) and preadolescence (ages 9-10).

Externalizing. Externalizing was positively associated with global FA in one study of children (ages 6-10; Neumann et al., 2020). In preadolescents (ages 9-10), global FA was not associated with two measures of externalizing, derived from a correlated-factor model and ICA (Modabbernia et al., 2022). ROI-based analyses in young adults (ages 18-22) found no association between externalizing and pons FA (Romer et al., 2018). Externalizing (bi-factor model) was negatively associated with global radial diffusivity in children (ages 6-10; Neumann et al., 2020) but showed no association in preadolescents from the ABCD study when derived from a correlated-factor model and ICA (ages 9-10; Modabbernia et al., 2022). There was no evidence of association between externalizing and mean or axial diffusivity across two studies of children (ages 6-10) and preadolescents (ages 9-10; Modabbernia et al., 2022; Neumann et al., 2020).

Table 2.3

Associations between transdiagnostic dimensions and global or whole-brain regional measures of brain structure investigated in two or more studies

Authors	Age	Structural model(s)	Neuroimaging: exposure/ outcome	GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
				Cortical thickness								
Mewton et al. (2022)	9-10	H-O	Outcome	x	x	x	x					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)	9-10 (T1) 10-11 (T2) 11-12 (T3)	H-O; B-F	Exposure									
Kaczkurkin et al. (2019)	8-21	B-F	Outcome	-	x	-						
Moberget et al. (2019)	8-23	PCA; ICA	Exposure	-		-						
Romer et al. (2021)	45	B-F; CF	Outcome	--	--	--						
				Surface area								
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1) 10-11 (T2) 11-12 (T3)	H-O; B-F	Exposure	--								

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Romer et al. (2021)	45	B-F; CF	Outcome	x	x		x					

Gray matter volume

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Snyder et al. (2017)	6-10	B-F; C-F	Outcome	--	+	-						
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Durnham et al. (2021)[1]	9-10	B-F	Outcome	--	x							
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1) 10-11 (T2) 11-12 (T3)	H-O; B-F	Exposure	--								
Parkes et al. (2021)	8-22	B-F	Exposure	--		-	-				+	-
Kaczkurkin et al. (2019)[1]	8-22	B-F	Outcome	--		-	x				++	
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								
Romer et al. (2021)[1]	45	B-F; CF	Outcome	-	-	-	-					

Fractional anisotropy

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)[1]	6-10	B-F	Exposure	-	x	+						
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x	X						
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								

Mean diffusivity

GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x	x						
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									

Radial diffusivity

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									

Axial diffusivity

				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									

Note. A-M, anxious-misery; B-F, bi-factor model; CF, correlated-factors model; DET, detachment; EFA, exploratory factor analysis; EXT, externalizing; GP, general psychopathology; H-O, higher-order model; ICA, independent component analysis; INT, internalizing; ND, neurodevelopmental; PCA, principal component analysis; SOM, somatic; T1-2, time 1-2; TD, thought disorder. This table provides a broad overview of evidence of relationships between transdiagnostic dimensions and global/whole-brain measures of brain structure investigated in two or more studies. Colored cells indicate whether associations with global brain structure were positive, negative, or non-significant (green, blue, and grey squares, respectively). For whole-brain analyses of regional associations, significant positive effects are indicated by a plus sign (+), negative effects by a minus sign (-), and non-significant associations are marked with an 'x'. One sign indicates few regional associations and two signs (i.e., ++/--) indicates that associations were widespread. Blank cells indicate that no association was tested. Relationships between transdiagnostic dimensions and brain structure were counted as having been examined in more than one study regardless of differences in modeling approaches, measurement of brain structure (e.g., global/whole-brain measures), or the direction of association investigated (e.g., neuroimaging variables treated as the exposure or outcome) across studies. In addition, some studies included analyses across multiple latent variable approaches and significant associations indicated here may refer only to one approach or more.

[1]Study controlled for global effects (e.g., total GMV, total FA).

2.4.5 Functional neuroimaging studies

2.4.5.1 Functional connectivity

General psychopathology. Four studies investigated the relationship between general psychopathology and functional connectivity in preadolescents (ages 9-10) from the ABCD cohort (at baseline; Hong et al., 2023; Karcher et al., 2021; Lees et al., 2021; Sripada et al., 2021). General psychopathology was measured using higher-order (Lees et al., 2021), bi-factor (Sripada et al., 2021), and one-factor models (Hong et al., 2023; Karcher et al., 2021). Greater general psychopathology was associated with lower functional connectivity within the default mode network (DMN) across three studies (Hong et al., 2023; Karcher et al., 2021; Sripada et al., 2021) and showed no association in one study (using a higher-order model; Lees et al., 2021). General psychopathology was also associated with lower functional connectivity within the dorsal attention network (DAN) across three studies (Hong et al., 2023; Lees et al., 2021; Sripada et al., 2021) but showed no association in one (using a one-factor model; Karcher et al., 2021). General psychopathology was associated with higher functional connectivity within the visual network (VIS; Hong et al., 2023) in one study (one-factor model), with lower functional connectivity in another (bi-factor model; Sripada et al., 2021) and showed no association in the remaining two studies (Karcher et al., 2021; Lees et al., 2021). No association was found for functional connectivity within the cingulo-opercular (CON), cingulo-parietal (CPN), salience (SAL), ventral attention (VAN), auditory (AUD), and somatomotor hand (SMH) networks across all four studies (Hong et al., 2023; Karcher et al., 2021; Lees et al., 2021; Sripada et al., 2021). There was also no evidence of association between general psychopathology and within-network connectivity in an ‘unassigned’ network across three studies (Hong et al., 2023; Karcher et al., 2021; Sripada et al., 2021), or with within-network connectivity in the cerebellum across two studies (Lees et al., 2021; Sripada et al., 2021).

Two studies of ABCD participants found that general psychopathology was associated with higher connectivity between the DMN and DAN (Hong et al., 2023; Lees et al., 2021) and between the VAN and frontoparietal (FPN) networks (Lees et al., 2021; Sripada et al., 2021). One study found that general psychopathology significantly increased the proportion of variance explained in functional network connectivity between the DMN and VAN (relative to a baseline model with only covariates); however, this was not replicated in a hold-out sample of ABCD participants (Karcher et al., 2021). An additional study found that general psychopathology was associated with lower connectivity between the DMN and VAN networks (Sripada et al., 2021). Several other associations with between-network connectivity were identified in only a single study and showed no association in the remaining studies (Appendix E, Table S6). Lastly, in young adults from the DNS (ages 18-22), connectome-wide analyses found that general psychopathology was associated with functional connectivity in four regions located within the visual network, including the left lingual gyrus, right middle occipital gyrus, and two parcels within the left middle occipital gyrus (Elliott et al., 2018). Follow-up analyses revealed that general psychopathology was associated with higher connectivity between the visual association cortex and DMN and between the visual association cortex and FPN. In contrast, general psychopathology was associated with lower connectivity between the visual association cortex and somatomotor network.

Specific/lower-order transdiagnostic dimensions. Four studies investigated the relationship between specific/lower-order transdiagnostic dimensions and within- and between-network functional connectivity. However, no significant associations were reported across more than one study aside from a single finding. Specifically, the neurodevelopmental dimension was associated with lower connectivity within the DMN in the ABCD cohort (ages 9-10; Karcher et al., 2021) and participants from the PNC (ages 8-22; Modabbernia et al., 2022).

2.4.6 Other analyses

There were several relationships between transdiagnostic dimensions and biological variables that were only investigated in a single study and are not reported here (Appendix E, Tables S5-7). There were three functional neuroimaging studies that examined different brain regions and experimental tasks (i.e., n-back, emotional n-back, and an economic choice lottery task; Kim-Spoon et al., 2021; Lees et al., 2021; Shanmugan et al., 2016). Other studies included analyses of regional cerebral blood flow (Kaczkurkin et al., 2018), PGSs and brain structure (Fernandez-Cabello et al., 2022), multimodal DTI measures (Alnæs et al., 2018), and brain age derived from multiple structural neuroimaging measures (Caspi et al., 2020). Finally, one study examined the relationship between brain structure and a latent measure of behavioral disinhibition (van Rooij et al., 2021).

2.5 Discussion

This systematic review aimed to synthesize evidence from research investigating the biological correlates of latent transdiagnostic dimensions of psychopathology in the general population, across the lifespan. The following section summarizes key findings by broad biological domain (i.e., genomic, neuroimaging) and phenotype (i.e., general psychopathology and specific/lower-order transdiagnostic dimensions). Implications for research investigating associations across the lifespan, as well as potential developmental and age-specific associations emerging from the included studies, are discussed. Interpretations of general psychopathology in the context of genomic and neurobiological evidence are discussed. Methodological issues are highlighted, including those which point to the need for caution in interpretation and those which may explain some of the heterogeneity in results observed across included studies. Finally, directions for future research are provided and limitations of the current review are addressed.

2.5.1 Genomic research studies

General psychopathology. General psychopathology was non-specifically associated with genetic risk for a wide range of psychiatric disorders and maladaptive traits in the general population. Several disorder- and trait-specific PGSs were significantly positively associated with general psychopathology across multiple studies (i.e., ADHD, neuroticism, depression, schizophrenia, anxiety, and PTSD). Additional studies examined associations between general psychopathology and general PGSs that reflect genetic risk for multiple psychiatric disorders (i.e., 'polygenic p-factors'). These genomic p-factors emerged across different samples (TEDS, UK Biobank, HRS) and developmental periods (childhood to adolescence and midlife to older adulthood) and were consistently found to predict phenotypic measures of general psychopathology (Allegrini et al., 2020; Gard et al., 2021; Grotzinger et al., 2019). The results of included studies align with twin and molecular genetic research demonstrating evidence of widespread pleiotropy and shared genetic associations across psychiatric disorders (Martin et al., 2018; Waszczuk et al., 2020; Wray et al., 2014). They also provide compelling evidence that estimates of general psychopathology reflect an underlying genetic liability towards diverse manifestations of mental illness, supporting the biological validity of general psychiatric phenotypes.

Specific/lower-order transdiagnostic dimensions. Specific/lower-order transdiagnostic dimensions were also significantly associated with a wide range of PGSs in the general population. However, positive associations among these dimensions showed a greater level of specificity than those found for general psychopathology. That is, associations were predominately found for PGSs that capture genetic risk for disorders and traits which form part of their constituent dimensions. For example, internalizing was mostly positively associated with PGSs that reflect risk for internalizing-related disorders and traits, such as depression (Jermy et al., 2022; Musci et al., 2016; Pat et al., 2022; Riglin et al., 2020) and neuroticism (Chen et al., 2022; Cuevas et al., 2021). Conversely, externalizing was mostly associated with externalizing-related PGSs (e.g., ADHD, disinhibition, number of sexual partners, adventurousness; Li, 2019; Pat et al., 2022; Waszczuk et al., 2021). These findings are consistent with hierarchical dimensional models of psychopathology, which predict that genetic variants associated with specific symptoms/syndromes (e.g., depression) captured by a given dimension (e.g., internalizing) will be more strongly associated with that dimension than with others (e.g., externalizing; Waszczuk et al., 2020). However, this was not entirely consistent across exposure-outcome pairings (e.g., anxiety-PGSs were not associated with internalizing-related phenotypes across multiple studies) and further research is needed to confirm this pattern of association (Chen et al., 2022; Cuevas et al., 2021).

The included studies also found evidence of shared and unique genetic associations across specific/lower-order dimensions. For instance, PGSs that were significantly associated with a given specific/lower-order dimension were consistently also associated with general psychopathology across studies, indicating shared genetic influences. There was *some* evidence of shared genetic associations across specific/lower-order dimensions (e.g., depression-PGSs were positively associated with internalizing, externalizing and neurodevelopmental dimensions; Pat et al., 2022) but these were only found *within* individual studies. In addition, dimension-specific associations were reported *within* several individual studies (Chen et al., 2022; Lahey et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021) but there was limited evidence of unique and replicable associations between specific/lower-order dimensions and PGSs found *across* studies. Notable exceptions to this include consistent negative associations between internalizing and ADHD-PGSs (Chen et al., 2022; Lahey et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021) and positive associations between internalizing and PGSs for intelligence and educational attainment in early development Chen et al., 2022; Waszczuk et al., 2021). Several quantitative genetic studies have demonstrated evidence of unique genetic influences on transdiagnostic dimensions (Lahey et al., 2011; Waldman et al., 2016), subdimensions (Kendler et al., 2003; Waszczuk et al., 2014), and measures of specific psychiatric symptoms or syndromes (Kendler et al., 2013). Research using genomic structural equation modeling has also found evidence of genetic variants that are uniquely associated with transdiagnostic dimensions when defined by genetic correlations rather than symptom- or disorder-level correlations (Grotzinger et al., 2022). The relative lack of dimension-specific associations found across studies included in the review may thus reflect certain methodological limitations rather than an absence of unique genetic associations across different levels of the structural hierarchy.

For instance, case-control genome-wide association studies (GWASs) based on categorically defined psychiatric phenotypes likely capture genetic variants that are highly pleiotropic. It is possible that PGSs constructed from these studies capture non-specific variance in psychopathology and therefore lack the specificity needed to identify dimension-specific associations (Waszczuk et al., 2021). Future GWASs investigating phenotypes at different levels of the structural hierarchy (e.g., internalizing, externalizing) may yield more precise PGSs that are better able to capture unique associations (Waszczuk et al., 2023). Some heterogeneity in the results may also be explained by different approaches to the construction of PGSs themselves (Appendix E, Table S5). PGSs for the same phenotype can be constructed using the summary statistics from different GWASs, which may identify different genetic variants associated with the target phenotype. Discovery GWASs can also differ substantially in sample size (across GWASs of the same phenotype and across GWASs of different phenotypes), with lower sample sizes limiting power to detect effects of different genetic variants and lowering the accuracy of a given PGS (Andlauer & Nöthen, 2020). Researchers may also adopt different p-value thresholds in deciding which genetic variants were significantly associated with a given phenotype in discovery GWASs (Andlauer & Nöthen, 2020). These and other factors impact the composition of PGSs and may explain why some significant associations failed to replicate across studies.

2.5.2 Neuroimaging research studies

2.5.2.1 Gray matter structure

General psychopathology. General psychopathology was predominately associated with broad, non-specific reductions in gray matter structure across the included studies. For instance, the included studies found evidence that general psychopathology was significantly negatively associated with global measures of CT (Romer et al., 2021), SA (Mewton et al., 2022; Romer et al., 2023), and GMV (Kaczkurkin et al., 2019; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). Whole-brain analyses also tended to reveal evidence of widespread regional associations across each of these metrics (Durham et al., 2021; Mewton et al., 2022; Romer et al., 2021; Romer et al., 2023; Snyder et al., 2017). Importantly, regional associations tended to be largely or entirely non-significant after controlling for global effects, further suggesting that reductions in gray matter structure are widely distributed (Durham et al., 2021; Kaczkurkin et al., 2019; Mewton et al., 2022; Romer et al., 2023).

These results provide compelling evidence that shared neurobiological vulnerabilities underpin diverse manifestations of psychopathology in the general population. In line with this, alterations in gray matter structure have been independently linked to various psychiatric disorders and cross-disorder research demonstrates that these associations are largely shared across diagnostic categories (Goodkind et al., 2015; Opel et al., 2020). The predominant pattern of global/widespread associations also aligns with theoretical predictions that the biological correlates of higher-order dimensions will show broad, non-specific associations with different biological mechanisms and processes (Zald & Lahey, 2017). However, evidence of global alteration does not necessarily imply that all brain regions are equally affected. Meta-analytic research indicates that brain-wide patterns of covariance in gray matter structural networks that are altered across different disorders show non-random organization and may be driven by reductions within specific large-scale networks, including prefrontal and temporal regions (Hettwer et al., 2022). Consistent with these findings, two ROI-based analyses found that general psychopathology was associated with lower GMV in prefrontal and temporal regions (Parkes et al., 2021; Snyder et al., 2017) and functional imaging research pointed to a central role of disrupted connectivity in the DMN (which comprises both the prefrontal cortex and medial temporal lobe).

Specific/lower-order transdiagnostic dimensions. Specific/lower-order dimensions were similarly associated with broad, non-specific reductions in gray matter structure across various metrics. This included negative global and regional associations with CT (Romer et al., 2021), SA (Mewton et al., 2022; Modabbernia et al., 2022; Romer et al., 2021; Romer et al., 2023), and GMV (Kaczkurkin et al., 2019; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). However, some studies reported fewer regionally-specific associations with specific/lower-order dimensions compared to general psychopathology (Kaczkurkin et al., 2019; Parkes et al., 2021; Snyder et al., 2017). Moreover, regional associations with a given specific/lower-order dimension tended to overlap with those found for general psychopathology and/or other specific/lower-order dimensions. There was evidence of dimension-specific associations *within* several studies, specifically between: fear and CT (Kaczkurkin et al., 2019); internalizing and CT (Romer et al., 2023); externalizing and SA (Romer et al., 2021); internalizing and GMV (Snyder et al., 2017); and anxious-misery and GMV (Kaczkurkin et al., 2019; Parkes et al., 2021). However, only one of these associations (i.e., anxious-misery and *greater* GMV) was reported across more than a single study and both studies were conducted in participants from the PNC (Kaczkurkin et al., 2019; Parkes et al., 2021).

It is difficult to draw conclusions regarding the lack of dimension-specific associations found across studies given limited research and substantial methodological differences (e.g., sample size, latent variable models, measurement of brain structure). More consistent evidence may emerge from studies attempting to directly replicate existing research. Alternatively, the lack of dimension-specific associations may indicate that brain structural alterations are shared across higher-order dimensions (e.g., general psychopathology, internalizing, externalizing), whilst other factors (e.g., environmental) contribute more to differential symptom expression. However, though more specific than general psychopathology, many of the specific/lower-order dimensions included in these studies capture a broad range of psychiatric symptoms. Unique biological correlates may be more likely to emerge at lower levels of the structural hierarchy. For example, the relationship between internalizing and GMV showed mixed results across studies, including non-significant (Durham et al., 2021; Romer et al., 2023), negative (Mewton et al., 2022), and positive associations (Snyder et al., 2017). However, two studies examined the internalizing subdimensions of anxious-misery and fear in the PNC and both found that fear was negatively associated with GMV whilst anxious-misery was positively associated with GMV (Kaczkurkin et al., 2019; Parkes et al., 2021). These divergent associations among lower-order subdimensions may explain the inconsistencies between studies investigating internalizing more broadly (i.e., contrasting patterns of association between lower-order subdimensions may effectively cancel each other out); however, this interpretation should be considered cautiously given that it is based on only two studies of the same sample.

2.5.2.2 White matter microstructure

General psychopathology. Few studies investigated the relationship between white matter microstructure and transdiagnostic dimensions. Studies of children and preadolescents (ages 6-10) found that general psychopathology was negatively associated with global FA (Neumann et al., 2020) and showed no evidence of regionally-specific associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). In contrast, research in young adults (18-22) found that general psychopathology was associated with reduced FA specifically within the bilateral pons, after controlling for global effects (Romer et al., 2018). This association was subsequently replicated in a sample of participants at midlife (age 45; Romer et al., 2019) but not in childhood (ages 6-10; Neumann et al., 2020). These findings *may* indicate that regionally-specific associations with FA emerge later in development, perhaps due to neurodegeneration of certain white matter pathways as a consequence of prolonged exposure to psychopathology. However, further research is needed to replicate these findings before meaningful conclusions can be drawn.

Specific/lower-order transdiagnostic dimensions. Associations with specific/lower-order transdiagnostic dimensions were more mixed. Internalizing was negatively associated with global but not regional FA in a single study (Neumann et al., 2020). However, other analyses found no evidence of global (Modabbernia et al., 2022) or regional associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). Conversely, externalizing was positively associated with global and regional FA in a single study (Neumann et al., 2020) but showed no association with either global (Modabbernia et al., 2022) or regional FA in others (Cardenas-Iniguez et al., 2022). Regional associations were not statistically significant for both phenotypes in the one study that controlled for global effects (Neumann et al., 2020), which may indicate a distributed effect. The positive association observed between externalizing and FA is intriguing, particularly as externalizing and related disorders have previously been linked to greater levels of FA (Cardenas et al., 2013; Teeuw et al., 2022). However, as above, further research is needed to replicate this finding.

2.5.2.3 Functional connectivity

General psychopathology. General psychopathology was associated with widespread alterations in connectivity within and between several large-scale networks across the included studies. However, the findings discussed below (i.e., those reported across multiple studies) were all from cross-sectional studies of ABCD participants and thus, the extent to which they generalize to different samples and developmental periods is unclear. In terms of within-network connectivity, the strongest evidence was found for *lower* connectivity within the DMN and DAN (Hong et al., 2023; Karcher et al., 2021; Sripada et al., 2021). The DMN represents a network of brain regions that exhibit correlated patterns of activity during rest (i.e., when an individual is not engaged in a particular task or otherwise exposed to some external stimulus; Raichle, 2015). This network is responsible for various cognitive functions related to internal mental activity (e.g., spontaneous thought) and self-referential mental processes (e.g., self-monitoring, introspection; Andrews-Hanna, 2012). In contrast, the DAN is involved with various attentional processes and is primarily characterized by its association with top-down control in task-based fMRI studies (Corbetta & Shulman, 2002; Fox et al., 2005). Findings from the included studies may thus indicate that general psychopathology is broadly associated with alterations in functional networks dedicated to both internally- and externally-focused cognitive processes. Importantly, impaired cognitive function (e.g., attentional control) and dysregulated thought are core features of many psychiatric disorders. Interestingly, the DMN neurotypically exhibits 'anti-correlations' (i.e., opposing patterns of activity between networks) with other control networks, including the DAN (Fox et al., 2005). Reduced negative correlations between the two networks indicate further disruption to the balance of networks supporting internally- and externally-focused cognition and have also been implicated in several disorders (Hu et al., 2017; Owens et al., 2020; Patriat et al., 2016; Posner et al., 2016). In line with this, two included studies found that general psychopathology was associated with *greater* connectivity between the DMN and DAN (Hong et al., 2023; Lees et al., 2021).

Reduced negative correlations between these networks may serve as a transdiagnostic feature of broad mental illness; however, additional research is needed to replicate these findings (particularly across other samples and age groups).

2.5.3 Biological associations with transdiagnostic dimensions across the lifespan

As noted, the majority of included studies were restricted to cross-sectional analyses of youth (i.e., childhood to young adulthood). This focus on younger samples and the relative lack of longitudinal analyses makes it difficult to draw conclusions about developmental associations. However, some findings *may* reflect age-specific differences and warrant further investigation in future research.

2.5.3.1 Genomic research studies

Longitudinal genomic studies were conducted only in childhood and adolescent samples (ages 7-16; Allegrini et al., 2020; Chen et al., 2022; Lahey et al., 2022; Riglin et al., 2020). There was evidence of age-specific differences in genetic associations with different transdiagnostic dimensions *within* most of these studies (Chen et al., 2022; Lahey et al., 2022; Riglin et al., 2020). Two of these studies revealed PGSs that became significantly associated with a given phenotype in a genetically coherent manner in later developmental periods (Chen et al., 2022; Riglin et al., 2020). For example, depression-PGSs were not associated with internalizing in childhood but were positively associated in adolescence (Riglin et al., 2020). These findings align with epidemiological research demonstrating increases in the prevalence of internalizing-related disorders between childhood and adolescence, which suggest a developmental role in the activation of genetic influences on internalizing during puberty (Moffitt et al., 2007). Of note, PGSs were primarily constructed using summary statistics from GWASs of adult samples, which may capture genetic risk that emerges in later developmental periods, potentially explaining why positive associations only emerged in later developmental periods across these studies (Allegrini et al., 2022). Future research should examine these associations using PGSs from GWASs of similar age groups and explicitly test whether PGSs show greater genetic coherence with specific/lower-order dimensions in later development.

Some results *across* studies also point to potential developmental associations. For example, general psychopathology showed some evidence of developmental stability in its association with general PGSs (i.e., polygenic p-factors; Allegrini et al., 2020; Gard et al., 2021; Grotzinger et al., 2019) and neuroticism-PGSs (Chen et al., 2022; Gard et al., 2021; Jones et al., 2018; Waszczuk et al., 2021). Both of these PGSs were consistently positively associated with general psychopathology across different development periods, including midlife to older adulthood. In contrast, ADHD-PGSs may show developmental differences in association with general psychopathology. ADHD-PGSs were positively associated with general psychopathology across six studies (spanning childhood to adolescence; Brikell et al., 2020; Chen et al., 2022; Lahey et al., 2022; Pat et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021) but showed no association in a sample of midlife to older adult participants (Gard et al., 2021). Meta-analytic evidence indicates that ADHD declines significantly in adulthood (Farone et al., 2006) and age-specific differences in the prevalence of ADHD have been observed between younger elderly adults and older elderly adults (Michielsen et al., 2012). Therefore, this lack of association may indicate age-specific declines in the contribution of genetic risk for ADHD to the general expression of psychopathology in later life. However, the lack of association between ADHD-PGSs and general psychopathology in older adults was only found in a single study. It should also be noted that the ADHD-PGSs for this study were constructed using summary statistics from a GWAS that predominately used childhood samples (Demontis et al., 2019) and thus, these PGSs may simply show less association in older samples.

2.5.3.2 Structural neuroimaging studies

Only one study examined the relationship between brain structure and transdiagnostic dimensions longitudinally (Romer et al., 2023), finding that lower global CT in preadolescence was uniquely associated with steeper reductions in (but not the mean levels of) internalizing across time (ages 9-12). Across studies, general psychopathology was consistently negatively associated with cortical SA but not CT (Mewton et al., 2022; Romer et al., 2023) in ABCD participants (ages 9-12). However, the inverse was found in a single study of participants at midlife from the Dunedin cohort (age 45), such that general psychopathology was negatively associated with CT but not SA (Romer et al., 2021). This pattern of association was largely consistent with that found for specific/lower-order dimensions (Mewton et al., 2022; Modabbernia et al., 2022; Romer et al., 2023).

These two metrics (CT, SA) are genetically distinct components of GMV, which follow different developmental trajectories and undergo significant structural changes throughout childhood and early adulthood. CT tends to peak in childhood before decreasing linearly throughout childhood and adolescence, whilst surface area reaches its peak in preadolescence, plateaus, and then decreases subtly across adolescence and early adulthood (Tamnes et al., 2017; Wierenga et al., 2014). In contrast, midlife represents a period of relative stability in terms of cortical structure, where neurodegenerative and ageing processes become the predominate drivers of change (Oschwald et al., 2019; Peters, 2006). The negative association between SA and general psychopathology in preadolescence may therefore reflect disruptions to normative neurodevelopmental processes (which may precede or follow from the onset of psychopathology). Conversely, the negative association between CT and general psychopathology may reflect accelerated ageing or neurodegenerative processes that follow from prolonged exposure to mental illness. This is supported by another included study, which found that general psychopathology was associated with advanced brain age (calculated from various indices of brain structure) at age 45 (Caspi et al., 2020). Further research is needed to replicate this association at midlife and longitudinal research should specifically examine whether the relationship between brain structure (i.e., SA and CT) and general psychopathology changes across development.

2.5.4 Interpretations of general psychopathology in the context of genomic and neurobiological research

The interpretation of general psychopathology is the subject of ongoing debate in the literature. Prominent substantive interpretations suggest that general psychopathology reflects trait negative emotionality (e.g., neuroticism), impaired emotion regulation, cognitive deficits, and/or disordered thought processes (Caspi & Moffitt, 2018; Smith et al., 2020). Each of these constructs can be broadly captured under the domains of impaired emotional functioning (e.g., negative emotionality, impaired regulation of emotion) and impaired cognitive functioning (e.g., cognitive deficits, disordered thought processes), which aligns with a more parsimonious and all-encompassing interpretation offered for general psychopathology i.e., that it reflects general *impairment* (Smith et al., 2020). In line with this interpretation, it is proposed here that a vast array of genetic variants act pleiotropically to predispose individuals to general impairments in the structural and functional neural mechanisms supporting cognitive and emotional functioning, which in turn contribute to the expression of general psychopathology. Individual differences in the type (e.g., specific SNPs) and number of contributing genetic variants (as well as in environmental factors) allow for variation in the nature and severity of alterations to brain structure and function, which may account for the observed variations in levels of general psychopathology between individuals.

Several findings from the included studies support the interpretation that general psychopathology reflects impairment in cognitive and emotional functioning. For example, general psychopathology was consistently inversely associated with PGSs for educational attainment and intelligence (Chen et al., 2022; Waszczuk et al., 2021). In terms of trait- and disorder-specific associations, the strongest evidence was found for neuroticism- and ADHD-PGSs. PGSs for neuroticism capture genetic risk for trait negative emotionality and were consistently positively associated with general psychopathology across four studies (Chen et al., 2022; Gard et al., 2021; Jones et al., 2018; Waszczuk et al., 2021). ADHD-PGSs were positively associated with general psychopathology across six of the included studies (Brikell et al., 2020; Chen et al., 2022; Lahey et al., 2022; Pat et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021). ADHD is characterized by marked deficits in cognitive (e.g., attentional control, working memory, response-inhibition) and emotional functioning (e.g., emotion regulation, emotion recognition, negative emotionality). In general population samples, ADHD-PGSs have been found to be associated with impaired cognitive function (independently of their association with ADHD symptoms; Martin et al., 2015; Stergiakouli et al., 2016) and trait negative emotionality (Du Rietz et al., 2018). It is possible that ADHD-GWASs capture the pleiotropic effects of genetic variants associated with broader domains of cognitive and emotional impairment, in addition to more specific variance at the level of lower-order dimensions (e.g., externalizing, neurodevelopmental) or specific disorders (e.g., ADHD-specific variance).

These and other genetic variants associated with the expression of mental illness may exert their influence indirectly via their impact on early brain development and subsequent impact on cognitive and emotional functioning. It is well-established that cognitive and emotional processes emerge from complex and coordinated interactions among large-scale structural and functional brain networks, which are themselves under genetic influence (Elliott et al., 2019b; Guimarães et al., 2022; Rasch et al., 2010). It is also important to note that while cognitive and emotional functioning are separable domains, they are deeply interconnected and supported by shared structural and functional neural correlates (Okon-Singer et al., 2015; Pessoa, 2008).

Indeed, many aspects of impaired emotional functioning (e.g., excessive rumination, maladaptive information processing/recall, poor emotional regulation) are connected to important facets of cognitive function (e.g., attentional control, response inhibition).

Interestingly, associations between greater cognitive function and brain structure (i.e., CT and SA) essentially reflect the inverse of associations found between greater general psychopathology and brain structure in the included studies. For example, greater cognitive function is associated with larger SA but not CT in preadolescents and with greater CT in midlife (Schnack et al., 2015). Genetic influences on cognitive function (e.g., PGSs for educational attainment) have likewise been found to be positively associated with global brain volume in population-based samples (Elliott et al., 2019a) and specifically with global volume and SA but not CT in young adults (Mitchell et al., 2020). Similarly, trait negative emotionality has been linked to smaller global brain volume and widespread reductions in white matter microstructure (Bjørnebekk et al., 2013) and GWASs have demonstrated negative genetic correlations between neuroticism and global SA (Grasby et al., 2020). Finally, functional brain networks that were consistently associated with general psychopathology in the included studies (e.g., the DMN and DAN) are also linked to cognitive and emotional functioning. For example, anti-correlations between the DMN and DAN have consistently been linked to cognitive performance (Hampson et al., 2010; Owens et al., 2020; Wang et al., 2019), which aligns with evidence that general psychopathology is associated with greater connectivity between these two networks. High negative emotionality has likewise been linked to alterations in whole-brain functional connectivity (Servaas et al., 2015) and specifically to lower connectivity within the DMN (Li et al., 2022) and DAN (Simon et al., 2020), which is further consistent with associations found for general psychopathology in the included studies.

2.5.5 Methodological considerations

2.5.5.1 Modeling approaches

The findings of this review must be interpreted in light of considerable heterogeneity in methodological approaches taken across studies. Most importantly, included studies varied substantially in terms of observable indicators of psychopathology (e.g., assessment scales) and in the statistical models used to extract transdiagnostic dimensions from those indicators. As noted in **Chater 1**, commonly used factor analytic models (e.g., bi-factor and higher-order models) differ substantially in the ways that they model relationships between latent dimensions and observed indicators of psychopathology. Although each model is closely related, the interpretation of general and specific/lower-order dimensions and the nature of their associations with external (e.g., biological) variables differs depending on which statistical approach is adopted. Indeed, there were several examples across the included studies in which different modeling approaches produced divergent patterns of association between transdiagnostic dimensions and biological variables. For example, ADHD-PGSs were positively associated with both externalizing and neurodevelopmental dimensions across multiple studies. However, ADHD-PGSs were only positively associated with externalizing when using a higher-order model (Pat et al., 2022) or when modeling externalizing in isolation within a LGC model (Li, 2019) and there was no evidence of association when using a bi-factor model (Riglin et al., 2020) or otherwise controlling for the effects of general psychopathology (Waszczuk et al., 2021). In contrast, ADHD-PGSs were consistently positively associated with the neurodevelopmental dimension across multiple structural models, including the bi-factor model (Pat et al., 2022; Riglin et al., 2020; Waszczuk et al., 2021). Of note, one study found that the positive association between ADHD-PGSs and the neurodevelopmental dimension was the only significant association to emerge across 22 different PGSs after controlling for general psychopathology (Waszczuk et al., 2021). Consideration of these different modeling approaches suggests that ADHD-PGSs may be more strongly associated with the neurodevelopmental dimension than externalizing. This is also supported by quantitative genetic research, which similarly found that ADHD was significantly correlated with the neurodevelopmental dimension (and no others) after controlling for general psychopathology and that this association was largely driven by genetic effects (Du Rietz et al., 2021).

2.5.5.2 Genomic methods

Effect sizes were small across the included genomic studies (i.e., > 0.15; Appendix E, Table S5), which is common in research investigating associations between PGSs and psychiatric phenotypes (Bogdan et al., 2018; Choi et al., 2020). Studies also varied considerably in sample size (i.e., from N = 488 to N = 332,050 participants) and in the size of discovery GWAS used to construct PGSs, both of which impact the ability to detect significant associations (Bogdan et al., 2018). Indeed, both PTSD- and MDD-PGSs showed significant associations with general psychopathology in preadolescents when constructed from well-powered GWASs and no association when constructed from GWASs with considerably smaller sample sizes. Greater consistency in the associations observed across studies will likely emerge from the use of larger sample sizes and PGSs constructed from more powered GWASs.

In the genomics literature, associations with a given PGS were also found to vary between studies that did and did not control for the effects of other PGSs. For example, ADHD-PGSs were negatively associated with internalizing in two studies of ABCD participants that controlled for general and specific/lower-order dimensions but not other PGSs (Lahey et al., 2022; Waszczuk et al., 2021). However, another study of the same sample found no evidence of association when controlling for other PGSs (Pat et al., 2022). In addition, some PGSs were not associated with a given dimension when examined in isolation but showed significant positive associations when controlling for other PGSs. The clearest example of this was found for the relationship between depression-PGSs and internalizing, externalizing, somatic and detachment dimensions in ABCD participants (Pat et al., 2022; Waszczuk et al., 2021). These results highlight the importance of carefully considering the inclusion of other PGSs (even if not directly important to a given analysis) when examining polygenetic associations with transdiagnostic dimensions. Not controlling for other PGSs can introduce confounding effects associated with genetic influences not accounted for in the analysis, which may explain differences in the results observed across studies. However, SNPs can also overlap substantially between different PGSs, meaning that the inclusion of multiple PGSs in a single model can introduce multicollinearity among predictors (Choi et al., 2020). Multicollinearity among predictors can produce unstable coefficient estimates, difficulties interpreting the individual contributions of a given predictor, and may also result in different observations regarding the significance and magnitude of associations (Vatcheva & Lee, 2016).

2.5.5.3 Neuroimaging methods

In the neuroimaging literature, controlling for global effects (e.g., total GMV) substantially impacted findings. As mentioned, regionally-specific associations between transdiagnostic dimensions and numerous measures of brain structure (including both gray matter structure and white matter microstructure) tended to be largely or entirely non-significant after controlling for global effects. This coupled with consistent evidence that transdiagnostic dimensions are associated with global measures of brain structure suggests that the neural architecture underlying broad expressions of psychopathology is widely distributed throughout the brain. This has important implications for research investigating the neurobiological underpinnings of psychopathology, which has historically focused on identifying neurobiological associations within relatively discrete brain regions. Controlling for global effects (e.g., total GMV, average CT) is important because it helps isolate regionally-specific associations that are independent of overall brain size or global morphological variation. Indeed, regional associations with general and specific/lower-order dimensions that consistently survive controlling for global effects (e.g., lower pontine FA, cerebellar GMV) may serve as particularly important biological markers. However, there is still value in examining regional associations without controlling for global effects. In these analyses, associations reflect specific rather than relative differences, which may be informative when global measures are themselves meaningfully related to psychopathology.

Another important consideration is the directionality of associations between biology and psychopathology. Measures of brain structure and function are often investigated for their potential as predictive markers of psychopathology; however, research indicates that psychopathology can also precede neurobiological abnormalities (Blok et al., 2023). Disentangling the temporal ordering of associations between biology and psychopathology is therefore critical to accurately modeling the structure and biological underpinnings of mental illness and to developing effective predictive models. Few of the included studies examined longitudinal associations between brain structure or function and transdiagnostic dimensions. One study found that baseline measures of brain structure (i.e., SA and GMV) in the ABCD cohort predicted general and specific/lower-order dimensions across the first three waves of data collection (Romer et al., 2023). Conversely, another found that general psychopathology (derived from psychiatric assessment data across the lifespan) was associated with more advanced brain age at midlife (age 45; Caspi et al., 2020). These findings likely indicate bi-directional effects between brain structure and psychopathology; however, further longitudinal research is needed to better characterize these relationships.

2.5.6 Directions for future research

The review identified several directions for future research. Firstly, future research should directly investigate whether different biological correlates emerge for a given transdiagnostic dimension depending on the latent variable approach used in the analysis. Studies attempting to identify dimension-specific associations should control for the effects of other transdiagnostic dimensions (including general and specific/lower-order phenotypes) where possible. In terms of biological approaches, studies aiming to identify associations between transdiagnostic dimensions and PGSs may benefit from simultaneously modeling multiple PGSs where possible (ensuring that correlations among PGSs are appropriately controlled for). Future research may also benefit from GWASs that specifically target transdiagnostic phenotypes (e.g., internalizing, externalizing) rather than disorder-specific phenotypes. Likewise, studies aiming to identify robust regional associations between transdiagnostic dimensions and brain structure should control for global effects. Neuroimaging studies should also explore the contribution of specific brain regions (e.g., frontal and temporal regions) or networks (e.g., the DMN and DAN) to observed global associations. The review also identified several understudied transdiagnostic dimensions (e.g., thought disorder, somatic, detachment dimensions) and biological measures (e.g., task-based neural activation, white matter microstructure) that may yield further insights into the biological correlates of transdiagnostic dimensions of psychopathology. Finally, research across different age groups and developmental periods is needed to inform our understanding of relationships between biological factors and transdiagnostic dimensions across the lifespan. In particular, there is a clear need for research investigating the biological correlates of transdiagnostic dimensional phenotypes specifically in older adults.

2.5.7 Limitations of the review

There are several limitations to the review that are important to discuss. Firstly, there were notable methodological differences between the included studies (e.g., latent variable models, size of discovery and test samples, PGS construction and other measurement of biological variables, covariates included in analyses), which likely accounts for much of the heterogeneity observed in the results. Secondly, several associations were investigated in only one or few studies, preventing the ability to draw meaningful conclusions for these exposure/outcome relationships. Thirdly, only studies of general population samples were eligible for inclusion. Whilst this increases the generalizability of results, it is possible that biological variables will show different patterns of association at greater levels of symptom severity (e.g., in clinical samples). Fourth, although the review was intended to synthesize evidence from research investigating the biological correlates of transdiagnostic dimensions *across the lifespan*, the vast majority of included studies (particularly within the neuroimaging literature) were limited to samples of youth and young adults. Therefore, it was not possible to draw strong conclusions about age- and developmentally-specific biological associations across different transdiagnostic dimensions. Fifth, several factors relating to sample characteristics may influence the generalizability of findings from the review. For instance, a substantial number of the included studies were conducted using ABCD data and findings may not replicate across different samples of the same age group. More broadly, the majority of reviewed studies are based on Western samples, further adding to the issue of generalizability. This was particularly problematic in the genomics literature, where analyses were often explicitly restricted to samples of European ancestry. This is due to the fact that PGSs are primarily constructed from GWASs of European samples and tend to perform poorly when applied to samples of other ancestries (Martin et al., 2019), suggesting that polygenetic associations with general and specific/lower-order dimensions may not replicate across different racial and ethnic groups. Sixth, the review only included studies examining relatively broad dimensions and subdimensions. The inclusion of studies investigating specific individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories was beyond the scope of the current study; however, there will likely be important biological associations at these lower-levels of the structural hierarchy. Finally, the findings of this review are presented via narrative synthesis rather than meta-analysis. This was due to vast methodological differences across studies and the limited number of associations between a given symptom dimension and biological variable that were examined across multiple studies.

2.5.8 Conclusions

To our knowledge, this is the first systematic review to synthesize evidence from studies investigating the latent structure and underlying biology of psychopathology in the general population and to characterize these relationships across the lifespan. The findings of this review suggest that general psychopathology reflects broad genetic and neurobiological vulnerabilities that are shared across different manifestations of mental illness. The review found limited evidence of biological correlates that are uniquely associated with specific/lower-order transdiagnostic dimensions (e.g., internalizing, externalizing); however, this is likely due to substantial methodological differences and limitations between the existing studies. Several factors must be carefully considered when interpreting the results of studies investigating biological associations with general and specific/lower-order transdiagnostic dimensions. This includes use of different latent variable models (e.g., bi-factor v. higher-order models), as well as the inclusion of biological controls (e.g., different PGSs, global measures of brain structure) and phenotypic covariates (e.g., controlling for general and specific/lower-order dimensions) in analyses. Several promising avenues for future research and important gaps in the current evidence base were identified. Most notably, there is a need for more research across different age groups and developmental periods, particularly older adulthood, in order to develop a more comprehensive understanding of the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan.

Chapter 3

Investigating the hierarchical structure and age-invariance of psychopathology and cognitive dysfunction in 112,712 older adults from the UK Biobank

Preface

Chapter 2 provided a comprehensive and systematic review of studies investigating the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan. This review identified a critical gap in the current evidence-base: not a single study has examined the genetic or neural correlates of transdiagnostic dimensions specifically in older adulthood. This gap extends beyond biological research, with few studies investigating the latent structure and hierarchical organization of psychopathology in older adult populations more generally (Kotov et al., 2017; Lahey et al., 2017a). Our understanding of the latent structure and biological correlates of psychopathology across the lifespan is therefore limited, with current knowledge skewed heavily towards early developmental periods. The predominant focus on early development is no doubt driven by the fact that most forms of psychopathology emerge during this period, coinciding with critical neurodevelopmental processes, driving heightened vulnerability to adverse mental health outcomes, and consequently positioning youth as a key target in prevention research. However, investigating the latent structure and biological correlates of psychopathology in older adulthood is equally important for several reasons: 1) psychopathology remains prevalent in later life but exhibits distinct symptom presentations and associative patterns that may alter its latent structure (Jeste et al., 2005; Lutz et al., 2018); 2) psychopathology is linked to a range of adverse outcomes that are uniquely relevant to older adults (e.g., physical health conditions, cognitive decline, and dementia; Lou et al., 2019; Hudon et al., 2020; Richmond-Rakerd et al., 2022); and 3) there are age-specific genetic and neurobiological processes in older adulthood (e.g., altered gene expression, neurodegeneration; Sibille, 2013) that are likely associated with psychopathology in ways that are distinct from those in early development. More broadly, investigating the latent structure and biological correlates of psychopathology in older adulthood is critical to forming a comprehensive model of mental illness across the lifespan and to understanding how its underlying biology persists or transforms across different age groups and developmental periods.

Chapter 3 represents a critical first step towards addressing this gap, by comprehensively examining the latent hierarchical structure of psychopathology in a large general population sample of older adults from the UK Biobank (N = 112,712; aged 55-78 years old). This study aligns with the key recommendations from the literature regarding approaches to modeling the latent structure of psychopathology detailed in **Chapter 1**, including: 1) symptom-level analysis in the general population; 2) rigorous comparison of multiple competing models of psychopathology; 3) assessment of model-based reliability estimates; and 4) thorough evaluation of model parameters and interpretability. Another novel feature of this study is the examination of whether a dimension capturing cognitive dysfunction can be incorporated into the latent hierarchical structure of psychopathology in later life. Some studies have examined the inclusion of cognitive phenotypes within hierarchical dimensional models in younger age groups and across broad age ranges (Eadeh et al., 2021; Forbes et al., 2024b; Ringwald, 2024; Rotstein et al., 2023); however, this approach may hold particular utility in older adult research given the prominence of cognitive impairment in this population. Finally, this study additionally examines whether the hierarchical structure of psychopathology remains invariant across age groups throughout later life. These secondary analyses provide novel insight into the stability of hierarchical dimensional models in older adulthood and the extent to which age differences in the expression of mental illness and cognitive dysfunction reflect structural versus mean-level variation in general and specific/lower-order dimensions, contributing to ongoing efforts to characterize mental and cognitive health in aging populations.

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Supplementary materials for **Chapter 3** are available in Appendix F.

[6] This manuscript has been submitted for publication and is currently under review with the *Journal of Psychopathology and Clinical Science*.

3.1 Abstract

Aims To examine the hierarchical dimensional structure of psychopathology in older adulthood. **Methods** Confirmatory factor analysis (CFA) was used to examine the latent structure of psychopathology in participants aged 55-78 years old from the UK Biobank (N = 112,712; 44.6% male; M = 65.05 years). Four commonly studied CFA models were examined, including: one-factor, correlated-factors, bi-factor, and higher-order models. The best-fitting model was selected based on traditional model-fit indices, model-based reliability estimates, and evaluation of model parameters. After determining the best-fitting model, multigroup CFA was used to examine measurement invariance across four age groups (i.e., 55-59, 60-64, 65-69, and 70-78 years old). **Results** The higher-order model was selected as the best-fitting CFA model, including a higher-order dimension of general psychopathology and four lower-order dimensions of internalizing, addictions and substance use, thought disorder, and cognitive dysfunction. This model demonstrated acceptable fit to the data (CFI = 0.936; TLI = 0.933; RMSEA = 0.042) and superior reliability of the lower-order factors (H = 0.850-0.974) compared to specific factors of the bi-factor model (H = 0.676-0.924). This model also demonstrated configural, lower-order metric/scalar, and higher-order metric/scalar invariance across age groups (change in CFI values ≤ 0.002). **Conclusions** The structure of psychopathology can be organized hierarchically in older adulthood and is age-invariant throughout later life. Results additionally support the inclusion of a cognitive dysfunction dimension within hierarchical dimensional models of psychopathology in older adulthood. These findings have important implications for our understanding of the latent structure of psychopathology across the lifespan and the utility of hierarchical dimensional models in characterizing mental and cognitive health in ageing populations.

3.2 Introduction

The number of older adults is predicted to reach 1.4 billion by 2030, representing one in six people globally (World Health Organization, 2023). This demographic shift creates an urgent need to better understand the factors which impact healthy ageing in later life. Approximately 14% of older adults currently experience at least one psychiatric disorder, accounting for 10.6% of the total disability-adjusted life years in this population (World Health Organization, 2023). In addition, a range of psychiatric conditions are known to be associated with impairments in various domains of cognitive functioning across the lifespan and specifically in older adulthood (Abramovitch et al., 2021; East-Richard et al., 2020). Novel approaches are needed to improve our understanding of the complex interaction between psychopathology and cognition in later life and guide the development of more effective diagnostic approaches and treatment strategies. As outlined in **Chapter 1**, hierarchical dimensional models provide a valuable framework for investigating the structure of psychopathology and may thus offer important insights into the nature and organization of mental illness in older adults. Moreover, the established relationship between mental illness and cognition suggests the possibility that dimensions capturing cognitive dysfunction can be meaningfully incorporated into the hierarchical structure of psychopathology. Incorporating cognitive dysfunction into this hierarchical framework in later life may facilitate efforts to better characterize the relationship between mental illness and cognition in ageing populations.

3.2.1 Hierarchical dimensional models of psychopathology in older adulthood

The prevalence of most common psychiatric disorders is lower in older adults compared to younger age groups (Gum et al., 2009; Streiner et al., 2006) and continues to decrease with increasing age (Reynolds et al., 2015). Studies also report differences in symptom presentation across a range of disorders in older adulthood, partly driven by the onset of various age-related conditions (e.g., cognitive decline, physical health issues) that interact with mental illness (Jeste et al., 2005; Lutz et al., 2018). These and other age-specific factors may impact the structure of psychopathology in later life and therefore, it is important to examine the extent to which hierarchical models identified in younger samples also emerge in older adults. Numerous studies have identified latent dimensions of internalizing in older adults (Buchan et al., 2014; Eaton et al., 2011; Sunderland et al., 2013) and one study found that a model including externalizing and subdimensions of internalizing (i.e., fear and distress) was invariant across seven age groups, ranging from early adulthood (i.e., 18-24 years old) to older adulthood (i.e., 75+ years old; Hoertel et al., 2015). These studies indicate that the latent structure of psychopathology in older adulthood is ostensibly similar to that reported in younger samples; however, no studies have examined the *hierarchical* structure of psychopathology specifically in aging populations. Moreover, it remains unclear whether other transdiagnostic dimensions commonly reported in younger age groups (e.g., thought disorder) are also present in older adulthood and whether dimensions that may be uniquely important to this population (e.g., cognitive dysfunction) can be incorporated into hierarchical dimensional models in later life.

3.2.2 Incorporating cognitive phenotypes into hierarchical dimensional models of psychopathology

Research demonstrates that dysfunction across various domains of cognition is associated with a range of psychiatric disorders (Forbes et al., 2024a). Whilst studies have historically aimed to identify disorder-specific associations with general and/or specific deficits in cognitive functioning, meta-analytic evidence indicates that impairment across various cognitive domains is better understood as a transdiagnostic feature of mental illness (Abramovitch et al., 2021; East-Richard et al., 2020). In addition, although cognition has traditionally been treated as a distinct construct, more recent research has begun to investigate whether cognitive dysfunction can be incorporated into the structure of psychopathology (Eadeh et al., 2021;

Forbes et al., 2024b; Ringwald, 2024; Rotstein et al., 2023). There is evidence of shared biological mechanisms underlying the expression of psychopathology and cognition (Lee et al., 2021; McTeague et al., 2017), supporting the possibility that transdiagnostic dimensional models including both psychiatric and cognitive dimensions will provide a valid and informative framework for capturing the covariance between these constructs. If cognition can be incorporated into hierarchical models of psychopathology, this would provide a novel approach for investigating common and dissociable mechanisms that underly mental illness and cognitive function and may facilitate the development of more effective diagnostic approaches and intervention strategies.

Studies investigating whether cognitive phenotypes can be incorporated into dimensional models of psychopathology have so far produced inconsistent results. Two studies concluded that a cognitive dimension (defined by performance-based measures of cognitive function) was independent of the structure of psychopathology in youth (Eadeh et al., 2021; Rotstein et al., 2023) and one study concluded that a cognitive dimension (defined by performance-based and self-report measures) was independent of a broader model including multiple common factors (i.e., a 'Big Everything' model including common factors of psychopathology, personality, personality pathology, and cognition) in university students (Littlefield et al., 2021). Two of these studies were limited in their coverage of psychopathology (e.g., they did not include indicators of psychotic disorders), the size and representativeness of their samples (e.g., samples enriched for ADHD, at-risk university students), and in the number of structural models that were evaluated (Eadeh et al., 2021; Littlefield et al., 2021). The third study concluded that a psychopathology-only model provided better fit to the data compared to models including psychiatric and cognitive dimensions in a representative sample of adolescents, based on minor differences in global fit statistics (Rotstein et al., 2023). However, comparisons were based on non-nested models with different sets of observed indicators (i.e., models with and without cognitive indicators), which are not comparable on the basis of these fit statistics. All three models including transdiagnostic psychiatric and cognitive indicators (i.e., a one-factor model and correlated- and higher-order models that included a distinct cognitive dimension) demonstrated excellent model-fit, with the one-factor model providing the best fit overall. Finally, two data-driven exploratory studies found that cognitive indicators loaded onto broader constructs that included additional psychiatric indicators (Forbes et al., 2024b; Ringwald, 2024). Ringwald and colleagues (2024) used exploratory meta-analytic factor analysis (including case-control data and neurocognitive test data derived from three meta-analyses in participants of various age groups) and found that cognitive indicators and psychotic disorders loaded onto a separate dimension (alongside internalizing and externalizing). Forbes and colleagues (2024) used hierarchical principal component analysis/hierarchical clustering and found that self-reported cognitive and neurodevelopmental symptoms loaded onto a shared dimension that also separated into two distinct lower-order dimensions (i.e., neurodevelopmental, cognitive difficulties) in a representative sample of participants aged 16 to 91 years old.

These inconsistencies highlight the need for further research investigating the incorporation of cognitive phenotypes in hierarchical dimensional models of psychopathology. Studies focused specifically on older adults are currently lacking but may provide unique insights due to the greater prevalence of cognitive impairment in later life and established interactions between psychopathology and cognition in this population (Jeste et al., 2005; Lutz et al., 2018). Importantly, the nature and meaning of a cognitive dimension may differ in this population due to the inclusion of indicators reflecting normative cognitive ageing and neurocognitive conditions compared to neurodevelopmental indicators of cognition in younger samples. In addition, given that cognitive function and psychopathology decline progressively in older adulthood, there may also be important age-specific differences in the structure or latent means of transdiagnostic dimensions of psychopathology and cognitive dysfunction in later life.

3.2.3 The current study

Chapter 3 aims to examine the symptom-level hierarchical structure of psychopathology in a large general population sample of older adults from the UK Biobank (Bycroft et al., 2018). A secondary aim was to explore whether a cognitive dysfunction dimension could be incorporated into this structure. Finally, additional analyses aimed to determine whether this hierarchical dimensional structure is invariant across age groups throughout older adulthood and whether there were age-specific differences in the latent means of transdiagnostic dimensions of psychopathology and cognitive dysfunction in this population. Given the exploratory nature of this study, no hypotheses were specified a priori.

3.3 Methods

3.3.1 Participants and study design

Data were drawn from the UK Biobank, a population-based study of 502,536 participants recruited from the United Kingdom between 2006 and 2010 (Bycroft et al., 2018). Follow-up assessments of cognitive function were completed online by a subsample of participants (n = 110,995 to 209,817) between 2014 and 2015 and symptom-level assessments of mental health were completed online by a subsample (n = 157,366) of participants between 2016 and 2017. Online follow-up data was selected due to its more comprehensive and detailed measurement of psychopathology, as well as the larger sample sizes available for assessments of cognitive function, compared to baseline data collection. The UK Biobank sample and study procedures are described in detail elsewhere (Bycroft et al., 2018; Davis et al., 2020; Sudlow et al., 2015). Participants were included in the current study if they were aged 55 years or older at the time they completed the cognitive assessments (N = 112,712; male = 44.6%; mean age = 65.05 years old; Caucasian ethnicity = 92.0%). No exclusions were imposed based on the presence of major or mild cognitive impairment or severe psychopathology (e.g., schizophrenia). Detailed characteristics of the analytic sample are provided in Table 3.1. Details regarding data access approvals, ethical approvals, participant consent, and data availability are provided in the supplementary material (Appendix J).

3.3.2 Indicators of psychopathology

Indicators of psychopathology were drawn from the UK Biobank Mental Health Questionnaire (MHQ) completed between 2016 and 2017. The current study used 39 symptom-level self-report indicators of depression, mania, anxiety, addictions, alcohol use, cannabis use, unusual or psychotic experiences, post-traumatic stress, and suicidality/self-harm (Category IDs: 138-146; https://tinyurl.com/muzmcays). Detailed information regarding all psychiatric indicators included in the current study, as well as any data cleaning and transformations performed on these variables, are provided in Appendix F (Table S1).

3.3.3 Indicators of cognitive function

Indicators of cognitive function were drawn from various online follow-up assessments completed between 2014 and 2015 (Category IDs: 118, 120-122; https://tinyurl.com/ep6ffsmb). These tests collectively capture a range of different cognitive domains, including: processing speed and visual attention (Trail Making Task A); executive function (Trail Making Task B); verbal and numerical reasoning and problem-solving skills (Fluid Intelligence Test); numerical working memory and short-term memory (Numeric Memory Test); processing speed, attention, and visuospatial working memory (Symbol Digit Substitution Test). Further details regarding the procedures for each cognitive test, the specific outcome variables used, as well as any data cleaning and transformations that were performed, are provided in the supplementary material (Appendix F.1, Table S1). Raw cognitive test scores were used to preserve the full range of individual differences in cognitive performance; however, sensitivity analyses adjusting for age and education were also conducted.

3.3.4 Demographic covariates

Covariates included in this study were age at baseline and estimated years of education. Baseline age was defined as the age at which participants completed the online cognitive assessments. Years of education was derived from self-reported educational attainment (Field ID: 6138), which was converted into a continuous variable based on the International Standard Classification of Education (ISCED) framework. This approach is consistent with prior research using the UK Biobank data (Wang et al., 2024; Xie et al., 2023; Zhao et al., 2024). Additional details are provided in Appendix F (Table S2).

3.3.5 Analytic plan

Analyses were not pre-registered; however, all analytic code has been made publicly available through Open Science Framework (OSF; https://osf.io/hdxqp/files/osfstorage) and is provided in the supplementary material (Appendix I).

3.3.5.1 Model estimation and selection

Dimensional models of psychopathology were examined using confirmatory factor analysis (CFA). All models were estimated using weighted least-squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). All indicators of psychopathology were categorical (i.e., binary and ordinal) and all indicators of cognitive function were continuous. Four commonly studied confirmatory factor models were examined: a one-factor model, a correlated-factors model, a bi-factor model, and a higher-order factor model (Appendix F, Figures S1-S2). Assignment of indicators to specific/lower-order factors was based on prior research examining the latent structure of psychopathology (Kotov et al., 2017, 2020, 2021; Krueger et al., 2021; Watson et al., 2022) and cognition (Deary, 2001; Spearman, 1904). For all models estimated in the full sample, the first factor loading was fixed to 1 for model identification. Further details regarding model-specification for dimensional models estimated in the full sample are provided in the supplementary material (Appendix F.2). In accordance with the recommendations outlined in **Chapter 1** (Figure 1.3), the best-fitting model was selected via assessment of absolute and incremental model-fit (e.g., CFI, TLI, and RMSEA values), alternative model-based estimates of reliability (see Appendix F.3 for details) and evaluation of model parameters (e.g., the significance, direction, and magnitude of standardized factor loadings).

3.3.5.2 Sensitivity analyses

A series of sensitivity analyses were conducted to evaluate the influence of method variance and demographic covariates on the latent structure of the best-fitting model and the strength of associations between lower-order factors and the general factor prior to measurement invariance testing. First, the best-fitting model was re-estimated with the addition of two method factors (i.e., cognitive methods, psychopathology methods) to account for differences in the timing of assessment (i.e., cognitive assessments conducted between 2014-2015 v. psychopathology assessments conducted between 2016-2017) and measurement approaches (i.e., continuous performance-based measures of cognitive performance v. categorical self-report indicators of psychopathology; Appendix F, Figure S3). Second, the best-fitting model was re-estimated whilst controlling for age and years of education to account for the use of raw cognitive test scores that are known to be sensitive to these demographic covariates (Piccininni et al., 2023). Due to missing data on years of education (n = 1003), the sample size for these analyses was reduced to N = 111,709. For the final sensitivity analysis, the best-fitting model was re-estimated whilst controlling for both method variance (i.e., including the two method factors described above) and demographic covariates (i.e., age and education) simultaneously.

Further details regarding the methodology of these sensitivity analyses are provided in the supplementary material (Appendix F.4).

3.3.5.3 Multigroup measurement invariance

After determining the optimal CFA model in the full sample, multigroup CFA was conducted across four age bands (i.e., ages 55-59; 60-64; 65-69; 70-78) to examine measurement invariance. The final age band (70–78 years) was widened to account for the smaller number of participants in the 70–74 and 75–78 age ranges, ensuring more balanced sample sizes across groups. Measurement invariance was conducted in a step-wise fashion, beginning with configural invariance, lower-order metric/scalar invariance, and higher-order metric/scalar invariance. Note that for models including binary indicators and WLSMV estimation, a metric invariance model is not identifiable and it is recommended to test for metric and scalar invariance in a single step (Muthén & Muthén, 2018). In the context of higher-order models, it is also necessary to examine metric/scalar invariance of the first- and second-order factors separately in two steps (Chen et al., 2005; Rudnev et al., 2018). Model-specifications for each of the three invariance tests are detailed in the supplementary material (Appendix F.5). All models were estimated using the WLSMV estimator and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). Chi-square testing was not used to assess invariance, as it is overly sensitive to large sample sizes (Cheung & Rensvold, 2002; Meade et al., 2008). Instead, invariance was assessed by examining changes in CFI values between models. Two recommended cut-off values were used, including a change in CFI values of ≤ 0.01 (Cheung & Rensvold, 2002) and the more conservative threshold of ≤ 0.002 (Meade et al., 2008).

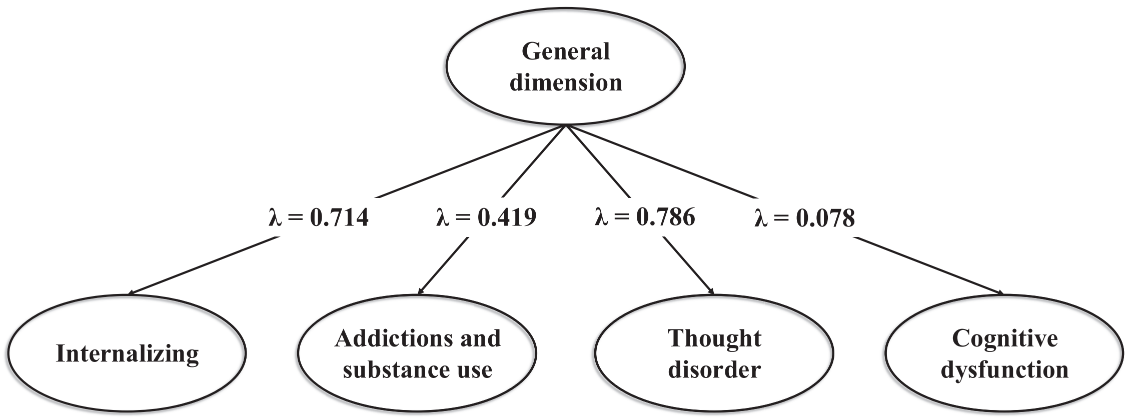
3.4 Results

3.4.1 Dimensional models of psychopathology estimated in the full sample

Model-fit indices and model-based estimates of reliability for dimensional models estimated in the full sample are detailed in Table 3.2. The significance, direction, magnitude, and standard errors of the standardized factor loadings for each model are presented in Table 3.3. The higher-order model (Figure 1.3) was selected as the best-fitting model based on the criteria outlined in **Chapter 1** (i.e., traditional model-fit indices, model-based reliability estimates, and interpretability of model parameters). Briefly, the higher-order model demonstrated acceptable fit to the data based on indices of absolute and incremental model-fit (CFI = 0.936; TLI = 0.933; RMSEA = 0.042) and the lower-order factors demonstrated superior reliability and replicability (H = 0.841 to 0.974) compared to the specific factors of the bi-factor model (H = 0.676 to 0.924). Standardized factor loadings for all observed indicators from the higher-order model were also significant, positive in direction and substantial in magnitude (i.e., $\lambda > 0.3$) across all latent factors. Model-selection considerations are detailed extensively in the supplementary material (Appendix F.6). For the higher order model, the thought disorder factor demonstrated the strongest loading on the general factor ($\lambda = 0.786$), followed by internalizing ($\lambda = 0.714$), addictions and substance use ($\lambda = 0.419$), and cognitive dysfunction ($\lambda = 0.078$). Sensitivity analyses revealed that the loadings of cognitive dysfunction on the general factor were substantially increased in models that controlled for method factors, demographic covariates, and both method factors and demographic covariates (described below and detailed in Appendix F.4).

Figure 3.1

Simplified path diagram of the best-fitting measurement model estimated in the full sample of older adults from the UK Biobank



Note. This figure depicts the best-fitting model identified through confirmatory factor analyses comparing one-factor, correlated-factors, higher-order, and bi-factor models. The higher-order model was selected as the best-fitting model based on traditional indices of absolute and incremental model-fit, alternative model-based estimates of reliability, and evaluation of model parameters. Latent factors are represented as ellipses, including a general higher-order factor defined by the shared variance of four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction). Standardized factor loadings of the lower-order dimensions on the general higher-order factor are shown. Observed indicators that defined the lower-order dimensions are omitted. The higher-order model was estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017).

3.4.2 Sensitivity Analyses

Detailed descriptions of the results of sensitivity analyses are provided in the supplementary material (Appendix F.4). The model including method factors to account for differences in the measurement of psychopathology and cognition demonstrated acceptable fit to the data (CFI = 0.942; TLI = 0.938; RMSEA = 0.040). The loading of cognitive dysfunction on the general factor increased substantially relative to our model without method factors (i.e., from $\lambda = 0.078$ to $\lambda = 0.138$); however, there was also a notable decrease in the loadings of addictions and substance use on the general factor (i.e., from $\lambda = 0.419$ to $\lambda = 0.067$). The model including demographic covariates (i.e., age, education) also demonstrated acceptable fit to the data (CFI = 0.934; TLI = 0.931; RMSEA = 0.041). The cognitive dysfunction dimension again demonstrated substantially stronger loadings on the general factor compared to our model without covariates (i.e., $\lambda = 0.135$ compared to $\lambda = 0.078$) and there was little change in the magnitude of factor loadings for the other lower-order dimensions. Finally, the model including both method factors and covariates demonstrated acceptable fit to the data (CFI = 0.938; TLI = 0.934; TLI = 0.040), with stronger loadings of cognitive dysfunction on the higher-order general dimension ($\lambda = 0.184$) that were comparable and slightly higher than the loadings of the addictions and substance use dimension ($\lambda = 0.154$).

Table 3.1

Participant characteristics for the full sample and the four age-stratified subsamples

		Full sample (N = 112,712)		55-59 years (n = 20,594)		60-64 years (n = 29,963)		65-69 years (n = 36,816)		70-78 years (n = 25,331)	
Age		**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
		65.05	5.19	57.47	1.19	62.08	1.41	66.92	1.34	72.02	1.74
Sex (male)		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
		50,256	44.6	7976	38.7	12,616	42.1	16,811	45.7	12,853	50.7
Ethnicity											
Caucasian		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	British	103,658	92.0	18,451	89.6	27,345	91.2	34,252	93.0	23,610	93.2
	Irish	2552	2.3	535	2.6	767	2.6	741	2.0	509	2.0
	White	84	0.1	12	0.1	25	0.1	32	0.1	15	0.1
	Other White background	3702	3.3	800	3.9	1033	3.4	1098	3.0	771	0.3
Asian or Asian British		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Indian	493	0.4	119	0.6	159	0.5	129	0.4	86	0.3
	Chinese	205	0.2	61	0.3	77	0.3	49	0.1	18	0.1
	Pakistani	82	0.1	29	0.1	30	0.1	11	0.03	12	0.05
	Bangladeshi	8	0.007	3	0.01	3	0.01	1	0.003	1	0.004
	Other Asian background	163	0.1	41	0.2	41	0.1	47	0.1	34	0.1

		Full sample (N = 112,712)		55-59 years (n = 20,594)		60-64 years (n = 29,963)		65-69 years (n = 36,816)		70-78 years (n = 25,331)	
Black or Black British		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Caribbean	280	0.2	121	0.6	76	0.3	48	0.1	35	0.1
	African	192	0.2	74	0.4	57	0.2	41	0.1	20	0.1
	Other Black background	9	0.007	1	0.005	4	0.01	3	0.008	1	0.004
Mixed		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	White and Asian	148	0.1	46	0.2	15	0.1	40	0.1	26	0.1
	White and Black Caribbean	59	0.1	32	0.2	10	0.03	11	0.03	6	0.02
	White and Black African	46	0.04	20	0.1	15	0.1	5	0.01	6	0.02
	Mixed	4	0.003	-	-	2	0.007	1	0.003	1	0.004
	Other mixed background	133	0.1	46	0.2	34	0.1	37	0.1	16	0.1
Non-specified		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Other ethnicity	505	0.4	139	0.7	170	0.6	135	0.4	61	0.2
	Do not know	30	0.03	4	0.02	7	0.02	15	0.04	4	0.02
	Prefer not to answer	318	0.3	50	0.2	72	0.2	106	0.3	90	0.4

	Full sample (N = 112,712)		55-59 years (n = 20,594)		60-64 years (n = 29,963)		65-69 years (n = 36,816)		70-78 years (n = 25,331)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Missing	49	0.04	9	0.04	17	0.1	14	0.03	9	0.04

Note. This table outlines the participant characteristics for the full sample and the four age-stratified subsamples of older adults aged 50-59, 60-64, 65-69 and 70-78 years old that were included in the current study. Baseline age was determined as the age at which participants completed the online cognitive assessments.

Table 3.2

Model-fit statistics and model-based reliability estimates for dimensional models of psychopathology estimated in the full sample

	Traditional model-fit statistics			
Dimensional models	**CFI**		**TLI**	**RMSEA**
One-factor model	0.836		0.828	0.067
Higher-order model[1]	**0.936**		**0.933**	**0.042**
Bi-factor model	**0.962**		**0.958**	**0.033**
	Model-based estimates of reliability			
Bi-factor model	**ECV**	**PUC**	**OmegaH/Hs**	**H**
General psychopathology	**0.539**	**0.682**	**0.811**	**0.975**
Internalizing	0.066		0.004	0.676
Addictions and substance use	0.213		**0.792**	**0.924**
Thought disorder	0.099		0.649	**0.834**
Cognitive dysfunction	0.083		**0.759**	**0.841**
Higher-order model	**ECV**	**PUC**	**OmegaH**	**H**
General psychopathology	-	-	-	-
Internalizing	-	-	-	**0.974**
Addictions and substance use	-	-	-	**0.944**
Thought disorder	-	-	-	**0.850**
Cognitive dysfunction	-	-	-	**0.841**

Note. CFI, Comparative Fit Index; ECV, Explained Common Variance; H, H coefficient; OmegaH, Omega Hierarchical; PUC, Percentage of Uncontaminated Correlations; RMSEA, Root Mean Square Error of Approximation; TLI, Tucker-Lewis Index. This table presents model-fit indices and model-based estimates of reliability for dimensional models estimated in the full sample (N = 112,712). Bold text denotes values that meet recommended thresholds for each index, whether by exceeding or falling below the specified cutoffs (see

Appendix F.3). All models were constructed using confirmatory factor analysis and estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017).

[1] Model fit statistics for the correlated-factors model are not presented because they are equivalent to those of the higher-order model.

Table 3.3

Standardized factor loadings and standard errors of the four confirmatory factor analysis models estimated in the full sample of older adults from the UK Biobank

	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
Observed indicators of psychopathology and cognition	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Internalizing										
Indicators of depression										
Recent feelings of depression	**0.826**	0.004	**0.378**	0.008	**0.873**	0.001	**0.873**	0.001	**0.871**	0.001
Recent lack of interest/pleasure in doing things	**0.788**	0.004	**0.428**	0.008	**0.850**	0.002	**0.850**	0.002	**0.848**	0.002
Recent changes in speed/amount of moving or speaking	**0.689**	0.005	0.184	0.008	**0.696**	0.004	**0.696**	0.004	**0.692**	0.004
Recent feelings of inadequacy	**0.780**	0.003	0.177	0.008	**0.787**	0.002	**0.787**	0.002	**0.785**	0.002
Recent tiredness or low energy	**0.659**	0.004	**0.337**	0.007	**0.685**	0.002	**0.685**	0.002	**0.680**	0.002

Observed indicators of psychopathology and cognition	**Bi-factor model (general factor)**		**Bi-factor model (specific factors)**		**Higher-order model**		**Correlated-factors model**		**One-factor model**	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Recent poor appetite or overeating	**0.644**	0.004	0.249	0.007	**0.660**	0.003	**0.660**	0.003	**0.656**	0.003
Recent trouble concentrating	**0.724**	0.003	0.240	0.007	**0.739**	0.003	**0.740**	0.003	**0.736**	0.003
Recent trouble falling/staying asleep or sleeping too much	**0.579**	0.003	0.255	0.006	**0.593**	0.003	**0.593**	0.003	**0.588**	0.003
Indicators of anxiety										
Recent feelings of nervousness or anxiety	**0.870**	0.001	0.006	0.008	**0.864**	0.001	**0.864**	0.001	**0.861**	0.001
Ever worried more than most would in similar situation	**0.654**	0.003	-0.057	0.007	**0.642**	0.003	**0.642**	0.003	**0.638**	0.003
Recent ease of annoyance or irritability	**0.730**	0.002	0.110	0.007	**0.728**	0.002	**0.728**	0.002	**0.725**	0.002
Recent feelings of foreboding	**0.812**	0.002	-0.020	0.008	**0.803**	0.002	**0.803**	0.002	**0.800**	0.002
Recent inability to stop or control worrying	**0.941**	0.001	-0.036	0.009	**0.936**	0.001	**0.936**	0.001	**0.935**	0.001

Observed indicators of psychopathology and cognition	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	SE	λ	SE	λ	SE	λ	SE	λ	SE
Recent restlessness	**0.740**	0.003	0.064	0.008	**0.736**	0.003	**0.736**	0.003	**0.732**	0.003
Recent trouble relaxing	**0.845**	0.002	0.070	0.008	**0.841**	0.001	**0.841**	0.001	**0.838**	0.001
Recent worrying too much about different things	**0.910**	0.001	-0.025	0.009	**0.905**	0.001	**0.905**	0.001	**0.903**	0.001
Indicators of suicidality/self-harm										
Recent thoughts of suicide or self-harm	**0.757**	0.005	0.204	0.009	**0.767**	0.004	**0.767**	0.004	**0.764**	0.004
Self-harmed in past year	**0.549**	0.019	0.028	0.018	**0.543**	0.019	**0.542**	0.019	**0.540**	0.019
Indicators of post-traumatic stress										
Repeated disturbing thoughts of past stressful experience	**0.648**	0.005	-0.536	0.006	**0.692**	0.002	**0.692**	0.002	**0.687**	0.002

Observed indicators of psychopathology and cognition	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Felt very upset when reminded of past stressful experience	**0.657**	0.006	-0.607	0.006	**0.693**	0.002	**0.693**	0.002	**0.688**	0.002
Avoided activities/situations because of past stressful experience	**0.609**	0.005	-0.444	0.006	**0.621**	0.003	**0.621**	0.003	**0.616**	0.003
Addictions and substance use										
Indicators of alcohol use										
Frequency of inability to cease drinking	0.261	0.007	**0.821**	0.004	**0.859**	0.004	**0.858**	0.004	**0.448**	0.006
Frequency of failure to fulfil normal expectations due to drinking	0.266	0.008	**0.764**	0.005	**0.816**	0.006	**0.815**	0.006	**0.428**	0.007
Frequency of guilt/remorse after drinking	0.259	0.006	**0.792**	0.004	**0.835**	0.004	**0.835**	0.004	**0.409**	0.005

Observed indicators of psychopathology and cognition	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Frequency of needing a morning drink after heavy drinking session	**0.323**	0.020	**0.678**	0.014	**0.784**	0.018	**0.779**	0.018	**0.464**	0.019
Frequency of memory loss due to drinking	0.186	0.007	**0.801**	0.004	**0.780**	0.005	**0.780**	0.005	**0.358**	0.006
Been injured or injured someone else through drinking	0.189	0.008	**0.546**	0.008	**0.586**	0.009	**0.585**	0.009	0.259	0.008
Known person ever concerned about/recommend a reduction in drinking	0.178	0.006	**0.714**	0.005	**0.697**	0.006	**0.697**	0.006	0.285	0.006
Indicators of addiction										
Ever addicted to a behavior or miscellaneous	0.298	0.012	0.296	0.014	**0.547**	0.016	**0.551**	0.016	**0.319**	0.011
Ever addicted to alcohol	**0.322**	0.009	**0.695**	0.007	**0.813**	0.008	**0.809**	0.008	**0.433**	0.008
Ever addicted to illicit or recreational drugs	0.266	0.020	**0.780**	0.017	**0.816**	0.021	**0.819**	0.021	**0.369**	0.020

Observed indicators of psychopathology and cognition	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	SE	λ	SE	λ	SE	λ	SE	λ	SE
Ever addicted to prescription or over-the-counter medication	**0.362**	0.013	0.282	0.016	**0.602**	0.018	**0.594**	0.017	**0.381**	0.012
Indicators of cannabis use										
Frequency of taking cannabis	0.092	0.005	**0.393**	0.006	**0.373**	0.006	**0.388**	0.006	0.127	0.005
Thought disorder										
Indicators of psychosis										
Ever believed an un-real conspiracy against self	**0.397**	0.014	**0.655**	0.015	**0.713**	0.017	**0.712**	0.017	**0.433**	0.013
Ever believed in un-real communications or signs	0.263	0.015	**0.783**	0.014	**0.579**	0.017	**0.578**	0.017	**0.327**	0.014
Ever heard an un-real voice	**0.315**	0.010	**0.765**	0.011	**0.611**	0.012	**0.611**	0.012	**0.358**	0.010
Ever seen an un-real vision	0.264	0.008	**0.670**	0.011	**0.505**	0.010	**0.504**	0.010	0.296	0.008

Observed indicators of psychopathology and cognition	**Bi-factor model (general factor)**		**Bi-factor model (specific factors)**		**Higher-order model**		**Correlated-factors model**		**One-factor model**	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Indicators of Mania										
Ever had a prolonged period of mania/excitability	**0.387**	0.007	**0.515**	0.012	**0.657**	0.009	**0.657**	0.009	**0.402**	0.007
Ever had a period of extreme irritability	**0.502**	0.004	0.288	0.009	**0.841**	0.008	**0.842**	0.008	**0.498**	0.004
Cognitive dysfunction										
Indicators of cognitive function										
Fluid Intelligence	0.053	0.004	**0.505**	0.003	**0.512**	0.003	**0.519**	0.003	0.059	0.004
Symbol Digit Substitution	0.043	0.004	**0.646**	0.003	**0.648**	0.003	**0.647**	0.003	0.053	0.004
Numeric Memory	0.044	0.004	**0.369**	0.004	**0.375**	0.004	**0.380**	0.004	0.049	0.004
Trail Making Task A	0.026	0.005	**0.682**	0.003	**0.675**	0.003	**0.672**	0.003	0.038	0.004
Trail Making Task B	0.056	0.005	**0.873**	0.002	**0.874**	0.002	**0.868**	0.002	0.067	0.004

Observed indicators of psychopathology and cognition	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	SE	λ	SE	λ	SE	λ	SE	λ	SE
Loadings of lower-order factors on the general factor										
Internalizing	-	-	-	-	**0.714**	0.008	-	-	-	-
Addictions and substance use	-	-	-	-	**0.419**	0.007	-	-	-	-
Thought disorder	-	-	-	-	**0.786**	0.011	-	-	-	-
Cognitive dysfunction	-	-	-	-	0.078	0.006	-	-	-	-

Note. This table presents the standardized factor loadings and standard errors for the four dimensional models estimated in the full sample of participants from the UK Biobank (N = 112,712). All models were constructed using confirmatory factor analysis (CFA) and estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). Standardized factor loadings that are positive in direction and substantial in magnitude (i.e., > 0.3) are highlighted in bold. Table S1 (Appendix F) provides the data-field codes for each observed indicator, the exact wording used in assessing each psychiatric symptom, as well as details regarding any transformations that were performed on psychiatric or cognitive indicators prior to their inclusion in CFA models.

3.4.3 Multigroup measurement invariance testing

Given the improved loadings of cognitive dysfunction on the general factor in sensitivity analyses, measurement invariance was first tested using the model including both method factors and covariates. These models retained years of education as a covariate but excluded age, given that the aim was to test whether the factor structure varies across age groups. The configural invariance model failed to converge due to model complexity and consequently, method factors were dropped and the final model used for invariance testing included only years of education as a covariate. Preliminary model testing revealed that for participants aged 70-78 years old, an indicator capturing alcohol use (i.e., needing a morning drink after heavy drinking session) had zero cells in the bivariate correlation tables with two indicators of thought disorder (i.e., believed un-real conspiracy against self and believed un-real communications or signs) and one indicator of internalizing (i.e., self-harmed past year). This internalizing indicator (i.e., self-harmed past year) also had zero cells in the bivariate correlation table with two other indicators of alcohol use (i.e., inability to cease drinking and failure to fulfil normal expectations due to drinking). Therefore, these two indicators were dropped from the model prior to measurement invariance testing.

Model-fit indices for each of the three invariance models are presented in Table 3.4. The configural invariance model demonstrated acceptable model-fit (CFI = 0.934; RMSEA =0.044), indicating that the overall factor structure was comparable across age groups (i.e., the same indicators loaded on the same factors in all four age groups). The first-order metric/scalar invariance model also showed acceptable model-fit (CFI = 0.939; RMSEA = 0.040) and a slight increase in the CFI value compared to the configural invariance model, indicating lower-order metric/scalar invariance (Cheung & Rensvold, 2002; Meade et al., 2008). The second-order metric/scalar invariance model also showed acceptable model-fit (CFI = 0.940; RMSEA =0.040) and again showed a slight increase in the CFI value relative to the first-order invariance model, indicating higher-order metric/scalar invariance (Cheung & Rensvold, 2002; Meade et al., 2008).

Given that first- and second-order scalar invariance was established across age groups, differences in the latent means of lower- and higher-order factors were also examined (Table 3.4). Differences in lower-order latent means across age groups were examined using the lower-order metric/scalar invariance model (in which lower-order means are allowed to vary) and differences in latent means for the general factor were examined using the higher-order metric/scalar invariance model (in which higher-order means are allowed to vary). Standardized latent means for the lower-order factors were examined across age groups with the latent means for each lower-order factor fixed to 0 in the reference group (i.e., participants aged 55-59 years old). The latent means for internalizing, externalizing, and thought disorder were significantly lower in all age groups compared to the 55-59 year old age group (SEs ranged from 0.035 to 0.081; all p-values < 0.01). In contrast, the latent means for cognitive dysfunction were significantly higher across all age groups compared to the 55-59 year old age group (SEs range from 0.036 to 0.042; all p-values < 0.001). Finally, standardized latent means for the general factor were examined across groups after fixing the general factor to 0 for the 55-59 year old age group. The latent means for the general factor were significantly lower across all age groups compared to the 55-59 year old age group (SEs ranged from 0.051 to 0.055; all p-values < 0.001).

Table 3.4

Results for measurement invariance testing and differences in latent means for lower- and higher-order dimensions

	Chi-square (df)	CFI	RMSEA
Configural invariance model	184278.567 (3416)	**0.934**	**0.044**
First-order metric/scalar invariance model	169279.125 (3717)	**0.939**	**0.040**
Second-order metric/scalar invariance model	167725.390 (3723)	**0.940**	**0.040**

Latent mean differences across age groups

Age groups	Latent factors	Standardized estimates	Standard errors	p-values
60-64 years old (n = 29,980)				
	Internalizing	**-0.272**	**0.039**	**p < 0.001**
	Addictions and substance use	**-0.230**	**0.078**	**P = 0.003**
	Thought disorder	**-0.995**	**0.061**	**p < 0.001**
	Cognitive dysfunction	**4.546**	**0.042**	**p < 0.001**
	General	**-0.366**	**0.053**	**p < 0.001**
65-69 years old (n = 36,816)				
	Internalizing	**-0.535**	**0.036**	**p < 0.001**
	Addictions and substance use	**-0.438**	**0.075**	**p < 0.001**
	Thought disorder	**-1.333**	**0.058**	**p < 0.001**
	Cognitive dysfunction	**4.079**	**0.036**	**p < 0.001**
	General	**-0.753**	**0.051**	**p < 0.001**

Latent mean differences across age groups				
Age groups	**Latent factors**	**Standardized estimates**	**Standard errors**	**p-values**
70-78 years old (n = 25,331)				
	Internalizing	**-0.641**	**0.038**	**p < 0.001**
	Addictions and substance use	**-0.769**	**0.081**	**p < 0.001**
	Thought disorder	**-1.369**	**0.061**	**p < 0.001**
	Cognitive dysfunction	**4.433**	**0.036**	**p < 0.001**
	General	**-0.903**	**0.055**	**p < 0.001**

Note. CFI, Confirmatory Fit Index; RMSEA, Root Mean Square Error of Approximation; df, degrees of freedom. Participants were stratified by age into four categories, including: 55-59 years old (n = 20,594), 60-64 years old (n = 29,980), 65-69 years old (n = 36,816), and 70-78 years old (n = 25,331). All models were constructed using confirmatory factor analysis and estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). All models controlled for years of education. Change in CFI values between models were within recommended thresholds (i.e., ≤ 0.01 and ≤ 0.002; Cheung & Rensvold, 2002; Meade et al., 2008), indicating invariance. To examine differences in latent means, the means for the lower- and higher-order factors were fixed to 0 in the reference group (i.e., those aged 55-59 years old). All mean difference tests were statistically significant.

3.5 Discussion

This study examined the latent hierarchical structure of psychopathology in a large general population sample of older adults. There was evidence to support a hierarchical dimensional model of psychopathology in older adulthood, consistent with research in younger age groups, as outlined in **Chapter 1** (Kotov et al., 2017, 2021). Specifically, the best-fitting model was a higher-order model comprising four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, and cognitive dysfunction) and a general higher-order dimension defined by their shared variance. Four other novel results emerged from these analyses, including: 1) that a dimension capturing cognitive dysfunction can be incorporated into the hierarchical structure of psychopathology in older adults, albeit with caution; 2) that a dimension capturing psychotic-like symptoms (i.e., thought disorder) can be incorporated into this hierarchical structure in older adults; 3) that this structure is invariant across four age groups in later life, spanning 55 to 78 years old; and 4) that there are significant age-specific differences in the latent means of higher- and lower-order dimensions of psychopathology and cognitive dysfunction throughout older adulthood.

3.5.1 Cognitive dysfunction can be incorporated into hierarchical dimensional models of psychopathology in older adulthood

One significant finding from this study is that a dimension capturing cognitive dysfunction can be incorporated into the higher-order structure of psychopathology in older adulthood, although its loading was notably lower than that of the psychopathology dimensions (as discussed below). This finding aligns with three previous studies examining the incorporation of cognitive dimensions within hierarchical dimensional models of psychopathology (Forbes et al., 2024b; Ringwald, 2024; Rotstein et al., 2023). The current study is most similar to that of Rotstein and colleagues (2023), who examined multiple CFA models including psychiatric and cognitive phenotypes in adolescents. They found that a one-factor model demonstrated the best overall fit to the data (CFI = 0.989; TLI = 0.988; RMSEA = 0.040) compared to other models including separable cognitive dimensions (i.e., correlated-factors and higher-order models). However, the higher-order model in their study also demonstrated excellent model fit (CFI = 0.988; TLI = 0.987; RMSEA = 0.042) and indicators of cognition showed substantially stronger loadings on the lower-order cognitive dimension (i.e., λ ranged from 0.80 to 0.859) compared to their loadings on the general dimension of the one-factor model (i.e., λ ranged from -0.226 to -0.241). This suggests that cognition may be better modeled as a correlated but separable lower-order dimension as in the current study, rather than being absorbed into a unidimensional latent construct alongside psychiatric indicators.

Two other studies found that cognitive indicators loaded onto broader constructs capturing additional psychiatric indicators (i.e., a psychosis/cognitive dimension and a neurodevelopmental/cognitive dimension; Forbes et al., 2024b; Ringwald, 2024). Both of these studies adopted data-driven exploratory approaches to modeling the structure of psychopathology. Forbes and colleagues (2024) found that a neurodevelopmental and cognitive difficulties dimension formed two distinct lower-order constructs including a separate dimension capturing self-report indicators of cognitive function that is ostensibly consistent with the distinct cognitive dysfunction dimension identified in the current study. In contrast, Ringwald and colleagues (2024) did not find evidence to support a distinct cognitive dimension. Of note, this study included data from case-control studies, which differs from the unselected sample used in the current study and in prior studies examining the inclusion of cognitive dimensions within hierarchical dimensional models of psychopathology (Eadeh et al., 2021; Forbes et al., 2024b; Rotstein et al., 2023). As noted by the authors, this approach may have led to inflated correlations between psychiatric and cognitive indicators, especially for psychotic disorders in which deficits in cognitive function are particularly prominent (Jonas et al., 2024). Further research is needed to examine where cognitive dysfunction fits within the hierarchical structure of psychopathology, including its placement within higher-order transdiagnostic dimensions and its potential bifurcation into a more distinct dimension at lower levels of the structural hierarchy.

3.5.2 The weak loading of cognitive dysfunction on the general factor

It should be noted that the cognitive dysfunction dimension demonstrated a weak loading on the general factor (i.e., $\lambda = 0.078$), consistent with prior research (Rotstein et al., 2023). This finding may be partly driven by methodological differences between the assessment of cognition and psychopathology. Firstly, indicators of cognitive function were assessed at a different timepoint to the indicators of psychopathology. Studies report a near-linear decline in performance on neurocognitive tests comparable to those included in the current study (e.g., tests of processing speed, executive function, reasoning); however, this decline corresponds to approximately one standard deviation from age 60 to age 80 (Salthouse, 2010). Participants of the UK Biobank are also generally healthier and more socio-demographically advantaged compared to the sampling population (Fry et al., 2017) and have shown relatively low levels of cognitive decline in longitudinal analyses (Cornelis et al., 2019). It is thus unlikely that scores on these cognitive tests would have changed substantially between the time cognition was assessed and the subsequent assessment of psychopathology. However, the method variance associated with differences in timing of assessment may have impacted the strength of the association between cognitive dysfunction and the general factor.

Secondly, the cognitive indicators were measured differently to the psychopathology indicators, using performance-based rather than self-report measures. Previous research examining the inclusion of cognitive dimensions has also relied on performance-based cognitive measures (Eadeh et al., 2021; Ringwald, 2024; Rotstein et al., 2023) and it is certainly an advantage to demonstrate that cognitive test data can be incorporated alongside self-report data in dimensional models of psychopathology (Forbes, 2025; Ringwald, 2024). Indeed, cognitive function is primarily assessed using performance-based measures and this approach mitigates biases that are inherent in self-report (e.g., social desirability, recall bias, lack of insight into one's own cognitive difficulties, interactions between psychopathology and perceived cognitive issues). However, this additional method variance will also have weakened the strength of association between cognitive dysfunction and the general factor in the current study.

It is notable that despite these suboptimal measurement conditions, the model still demonstrated acceptable overall fit and that the cognitive dysfunction dimension showed substantial reliability (i.e., H = 0.841) and a significant (albeit small) association with the general factor. Importantly, sensitivity analyses demonstrated substantial increases in the loading of cognitive dysfunction on the general factor when controlling for method factors (i.e., differences in the timing and measurement of psychopathology and cognition) and when controlling for sociodemographic covariates (i.e., age, education) that are known to influence cognitive performance in older adults (Piccininni et al., 2023). In fact, the cognitive dysfunction dimension demonstrated comparable (and even slightly stronger) loadings compared to the addictions and substance use dimension in this model (Appendix F.5).

3.5.3 Thought disorder can be incorporated into the hierarchical structure of psychopathology in older adults

Thought disorder is one of the most widely studied dimensions included in hierarchical models of psychopathology (Kotov et al., 2020). Thought disorder indicators also tend to demonstrate the strongest loadings on general factors (Caspi et al., 2014; Laceulle et al., 2015; Levin-Aspenson et al., 2021; Martel et al., 2017; Mewton et al., 2022) and are thus considered an important component of the overall hierarchical structure of psychopathology (Caspi & Moffitt, 2018). However, prior work investigating transdiagnostic dimensional models of psychopathology in older adults has focused primarily on the lower-order dimensions of internalizing and externalizing (Buchan et al., 2014; Eaton et al., 2011; Hoertel et al., 2015; Sunderland et al., 2013) and their subdimensions (e.g., fear and distress, disinhibited-externalizing and substance use; Hoertel et al., 2015). This is the first study to demonstrate that a thought disorder dimension can also be modeled in older adulthood. Consistent with prior research, the thought disorder dimension from our best-fitting model demonstrated the strongest loading on the general factor. Interestingly, however, internalizing showed the strongest loading in supplementary models that controlled for method variance. Finally, the inclusion of a thought disorder dimension was a strength to the current study given that psychotic symptoms/disorders are strongly associated with cognitive function (Jonas et al., 2024) and that this dimension has not been included in some prior studies of younger samples that examined structural models including psychiatric and cognitive dimensions (Eadeh et al., 2021).

3.5.4 Age-invariance of the hierarchical dimensional structure of psychopathology in older adulthood and age-specific differences in latent means

Another important finding of this study is that the higher-order structure of psychopathology was invariant across four age groups throughout older adulthood, from 55 to 78 years old. These findings extend previous research indicating that a model including distress, fear, and externalizing was invariant from early adulthood to older adulthood (including from ages 55-64, 65-75 and 75 years and older; Hoertel et al., 2015). Establishing invariance is critical to demonstrating whether the structural relationships between latent constructs are not influenced by certain biases in measurement (e.g., age-specific biases) and to allowing for meaningful comparisons of latent constructs to be made across groups (Putnick & Bornstein, 2016).

Importantly, whilst the structural relationships between psychopathology and cognitive dysfunction remained stable throughout older adulthood, there were also significant age-specific differences in the latent means of each construct. Latent means for the lower-order dimensions of psychopathology and the general factor were significantly lower across all age groups compared to the reference group (i.e., those aged 55-59 years old), consistent with epidemiological research indicating that the prevalence of psychiatric disorders decreases with increasing age in later life (Gum et al., 2009; Reynolds et al., 2015; Streiner et al., 2006). In contrast, latent means for cognitive dysfunction were significantly higher in all age groups compared to the reference group, which is likewise consistent with studies indicating cognitive impairment increases with increasing age in later life (Deary et al., 2009; Murman, 2015). Whilst these findings provide new insights into age-specific differences in transdiagnostic dimensions of psychopathology and cognitive dysfunction in older adults, analyses were cross-sectional. Future research should investigate the *longitudinal* measurement invariance of hierarchical dimensional models in older adults, as well as mean changes in latent factors within individuals, throughout later life.

3.5.5 Strengths, limitations, and directions for future research

There are several other strengths and limitations to the current study that are important to consider in interpreting these results. Research investigating the structure of psychopathology has primarily been conducted in samples ranging from childhood to midlife (Hoy et al., 2023; Kotov et al., 2017). The current study thus provides important insight regarding the extent to which this hierarchical structure holds in later life. Another key strength is that the symptom-level hierarchical structure of psychopathology was examined in large (i.e., N > 112,000) general population sample. Large-scale unselected samples like the UK Biobank are better able to capture the true distribution of psychopathology and cognition, providing more statistical power to accurately estimate the relationships between transdiagnostic dimensions and more generalizable and reliable findings than studies in clinical samples. However, the findings of this study are based only on participants from the United Kingdom that were predominately Caucasian and may not generalize to those from low- and middle-income countries or other racial/ethnic backgrounds. Measurement models also included an extensive set of psychiatric indicators compared to other studies in older adults, which allowed capturing dimensions of psychopathology that are commonly studied in younger samples (e.g., thought disorder). However, it was not possible to capture broad externalizing due to the absence of personality pathology measures in the sample (e.g., antagonism, disinhibition). Future research should thus examine these models using broader measurement of externalizing psychopathology, though this is largely dependent on the availability of datasets in older adulthood that include detailed psychiatric and cognitive phenotyping. Future research may also examine whether hierarchical dimensional models of psychopathology differ in samples of older adults with known deficits in cognitive function (e.g., cases of mild cognitive impairment, dementia) and with clinically significant psychopathology. Finally, it would be useful to examine the biological (e.g., structural neuroimaging, genomic) correlates of these dimensions and to determine whether they demonstrate utility in predicting important age-specific outcomes in older adulthood (e.g., dementia).

3.5.6 Conclusions

This is the first study to examine the hierarchical dimensional structure of psychopathology in older adulthood. In a large general population sample of participants aged 55 years and over, a higher-order model demonstrated the best fit to the data when compared to a range of other commonly studied dimensional models (e.g., one-factor, bi-factor). This study also demonstrates that dimensions capturing cognitive dysfunction and thought disorder can be incorporated into the hierarchical structure of psychopathology in older adulthood (alongside dimensions of internalizing and addictions and substance use). Furthermore, additional analyses demonstrated that this higher-order model is invariant from ages 55 to 78 years old and that there are significant differences in the latent means of transdiagnostic dimensions of psychopathology and cognitive dysfunction across age groups. The findings of this study are consistent with those in younger samples (as outlined in **Chapter 1**), supporting the continuity of hierarchical dimensional models of psychopathology across the lifespan. These findings have important implications for our understanding of the structure of psychopathology across the lifespan, providing evidence that the hierarchical organization of mental illness described in **Chapter 1** extends from early life into older adulthood. They also inform our understanding of the relationship between psychopathology and cognition throughout older adulthood. In particular, these results suggest that hierarchical dimensional models may provide a useful and novel framework for investigating common and dissociable mechanisms (e.g., biological) that underly the expression of mental illness and cognitive functioning in later life and highlight the need for examining potential age-specific differences in the nature of these associations.

Chapter 4

A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood

Preface

The systematic review presented in **Chapter 2** revealed that not a single study has investigated the biological correlates of transdiagnostic dimensions of psychopathology specifically in older adults. **Chapter 3** proceeded to demonstrate that the latent hierarchical structure identified in younger samples also emerges in older adulthood and that this structure is invariant across age groups throughout later life. **Chapter 4** builds upon the findings of preceding chapters in two primary ways. Firstly, it examines the latent hierarchical structure of psychopathology in a different sample of older adults that captures a later stage of life (i.e., 70-90 years old). Consistent with the methodology in **Chapter 3**, this study follows the key recommendations outlined in **Chapter 1** (Figure 1.3) for determining the best-fitting model of psychopathology. These include the use of symptom-level analysis in a general population sample, rigorous comparison of competing models of psychopathology, evaluation of model-based reliability estimates, and careful consideration of model parameters and interpretability. Secondly, this is the first study to investigate the neurobiological correlates of transdiagnostic dimensions of psychopathology in older adulthood.

One of the key findings from **Chapter 2** is that general and specific/lower-order dimensions of psychopathology have consistently demonstrated significant associations with global and regional measures of gray matter structure from childhood to adulthood. This chapter thus examines associations with various global and regional measures of gray matter volume and cortical thickness to determine whether these same associations emerge in later life. **Chapter 2** also identified that studies investigating the relationship between transdiagnostic dimensions and brain structure have primarily been conducted using cross-sectional analyses. **Chapter 4** builds on this observation by including both cross-sectional and longitudinal analyses, assessing the extent to which transdiagnostic dimensions relate to intra-individual changes in brain structure over six years of follow-up in older adulthood. Finally, as outlined in **Chapter 1**, general and specific/lower-order dimensions have also consistently been found to predict a range of adverse outcomes in younger samples. However, the extent to which these phenotypes hold utility in predicting important age-specific outcomes in later life has not been thoroughly investigated. **Chapter 4** addresses this gap by reporting the first analysis to examine whether transdiagnostic dimensions of psychopathology can be used to predict all-cause incident dementia (assessed over 12 years of follow-up) in older adulthood.

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Figure 4.1

Screenshot of "A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood" by Hoy et al. (2023) published in Psychological Medicine

A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood

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Supplementary materials for **Chapter 4** are available in Appendix G.

4.1 Abstract

Aims To examine whether transdiagnostic phenotypes derived from hierarchical dimensional models of psychopathology are associated with brain structure and incident dementia in older adults. **Methods** Data were drawn from a longitudinal study of older adults aged 70-90 years at baseline (N = 1072; 44.8% male). Confirmatory factor models (i.e., one-factor, correlated-factors, higher-order, and bi-factor) were fit to baseline psychiatric symptoms, with model-fit assessed via traditional model-fit indices, model-based reliability estimates, and evaluation of model parameters. Bayesian Plausible Values were generated for each latent factor from the best-fitting model for use in subsequent analyses. Linear mixed models examined intra-individual change in global and regional gray matter volume (GMV) and cortical thickness over six years. Logistic regression examined whether transdiagnostic symptom dimensions predicted all-cause incident dementia over 12 years. **Results** A higher-order model provided the best-fit to the data (BIC = 28691.85; ssaBIC = 28396.47; CFI = 0.926; TLI = 0.92; RMSEA = 0.047), including a general higher-order dimension and three lower-order dimensions of internalizing, disinhibited-externalizing, and substance use. Baseline transdiagnostic symptom dimensions did not predict change over time in total cortical and subcortical GMV or average cortical thickness; regional GMV or cortical thickness in the frontal, parietal, temporal, or occipital lobes; or regional GMV in the hippocampus and cerebellum (all p-values > 0.5). Finally, baseline transdiagnostic symptom dimensions did not predict all-cause incident dementia across follow-ups (all p-values > 0.5). **Conclusions** There was no evidence to support a relationship between transdiagnostic dimensions, gray matter structure, and incident dementia in older adults. Future research should examine these relationships in larger samples and using psychiatric indicators capturing past history of chronic mental illness rather than current symptoms.

4.2 Introduction

As the number and proportion of older adults continues to expand globally (World Health Organization, 2022), it is increasingly important to understand the mechanisms and processes that impact healthy ageing in this population. In particular, novel approaches are urgently needed to identify potential targets for the prevention of neurodegeneration and dementia in later life. Indeed, recent estimates suggest that approximately 152.8 million people will be diagnosed with dementia by the year 2050 (Nichols et al., 2022). An extensive body of research indicates that psychiatric disorders are associated with alterations in brain structure and function across the lifespan, including accelerated brain ageing (Cole et al., 2019; Wrigglesworth et al., 2021). Several psychiatric disorders are also associated with greater likelihood of dementia diagnoses in later life (Richmond-Rakerd et al., 2022) and genomic research indicates shared biological mechanisms between psychiatric and neurodegenerative diseases (including dementia; Wingo et al., 2022). These associations appear to cut across traditional diagnostic categories, with a range of putatively distinct psychiatric disorders being non-specifically associated with both neurodegeneration and dementia risk. This suggests that hierarchical dimensional models of psychopathology (as detailed in **Chapter 1**) may facilitate research aiming to disentangle the relationships between psychopathology, neurodegeneration, and dementia in later life. Importantly, **Chapter 3** demonstrated that the hierarchical dimensional structure of psychopathology identified in younger samples also emerges in older adulthood. The current chapter builds on these findings by investigating whether general and specific/lower-order dimensions of psychopathology can be used to predict alterations in brain structure and all-cause incident dementia in later life.

4.2.1 Hierarchical dimensional models of psychopathology in neuroscientific research

As outlined in **Chapter 1**, the underlying neurobiology of mental illness is closely aligned with the structure of psychopathology identified through phenotypic research. For example, the neural correlates of specific psychiatric disorders are associated with subclinical symptom expression in general population samples, supporting the dimensionality of mental illness (Besteher et al., 2020). Meta-analytic evidence further indicates that abnormalities in both brain structure and function are largely shared across putatively distinct diagnostic categories (Goodkind et al., 2015; McTeague et al., 2017; Sha et al., 2019), consistent with the correlational structure of psychopathology identified through phenotypic research. These findings indicate that the neural architecture underlying mental illness is poorly aligned with the discrete categorical boundaries of traditional classification systems. In contrast, hierarchical models directly estimate the observed dimensionality and correlational structure of psychopathology (e.g., comorbidity). The phenotypes derived from these models show greater validity and reliability than discrete (e.g., categorical) phenotypes, with the resulting increase in power substantially decreasing the need for larger sample sizes (Kotov et al., 2020, 2021; Krueger et al., 2021; Markon et al., 2011; Watson et al., 2022). Another key advantage of hierarchical dimensional models is that they allow researchers to investigate the neurobiological correlates of psychopathology at multiple levels of analysis (i.e., the correlates of general and specific/lower-order symptom dimensions; Latzman & DeYoung, 2020; Zald & Lahey, 2017) and across the full spectrum of mental illness. This facilitates research aiming to disentangle shared from unique associations, which would be otherwise obscured in case-control studies of individual psychiatric disorders. Given these advantages, the use of hierarchical dimensional models may generate new discoveries with respect to the relationship between psychopathology and brain health in older adulthood.

However, the systematic review in **Chapter 2** found that not a single study has investigated associations between brain structure and transdiagnostic symptom dimensions specifically in older adults (Hoy et al., 2023). In younger samples, transdiagnostic symptom dimensions were consistently associated with pervasive alterations in gray matter structure across several studies (Hoy et al., 2023). For example, general and specific/lower-order dimensions (e.g., internalizing, externalizing) were associated with lower global measures of gray matter volume (GMV) and surface area in multiple studies spanning childhood to young adulthood (Kaczkurkin et al., 2018; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). These findings highlight the utility of transdiagnostic dimensional models in psychiatric neuroscience, which has historically aimed to identify disorder-specific correlates within relatively discrete brain regions. Further research is needed to determine whether transdiagnostic phenotypes are also associated with reduced gray matter structure in older adulthood. In particular, establishing that these phenotypes can be used to change in gray matter structure over time in older adults would provide novel targets for interventions focused on age-related neurobiological decline in this population.

4.2.2 Hierarchical dimensional models of psychopathology as a novel framework for investigating the relationship between psychopathology and dementia

An extensive body of evidence indicates that psychiatric illness is associated with cognitive decline and dementia risk in older adulthood. Several systematic reviews and meta-analyses have demonstrated a link between individual psychiatric disorders and dementia risk (Becker et al., 2018; Cai & Huang, 2018; Velosa et al., 2020). A recent population-based study of 1.7 million people also found that those with *any mental disorder* were significantly more likely to develop a dementia diagnosis in older adulthood (Richmond-Rakerd et al., 2022). This research suggests that psychopathology is non-specifically associated with dementia risk; however, no studies have directly examined whether transdiagnostic phenotypes can be used to predict incident dementia in older adults. As previously mentioned, hierarchical dimensional models enable researchers to investigate associations with psychopathology across various levels of specificity. This allows for simultaneously examining whether the association between psychopathology and dementia reflects broad transdiagnostic vulnerability (i.e., general psychopathology) and whether narrower transdiagnostic phenotypes (i.e., specific/lower-order dimensions) confer unique risk. This approach may thus facilitate a more comprehensive understanding of how psychopathology contributes to dementia risk in later life and aid in identifying the most important targets for prevention and intervention efforts.

4.2.3 The current study

Chapter 4 aims to examine the symptom-level hierarchical structure of psychopathology in older adulthood and to determine whether general and specific/lower-order transdiagnostic phenotypes are associated with global and regional measures of gray matter structure. Specifically, this study examines whether transdiagnostic symptom dimensions can be used to predict intra-individual change in gray matter structure over 6 years of follow-up. For the primary analyses, it was hypothesized that higher severity of general and specific/lower-order symptom dimensions at baseline would predict greater decline in total cortical GMV, total subcortical GMV, and average cortical thickness across time. For secondary analyses, it was hypothesized that greater levels of general and/or specific symptom dimensions at baseline would predict greater decline in regional GMV and cortical thickness across time. A secondary aim of **Chapter 4** is to determine whether general and specific/lower-order transdiagnostic dimensions are associated with all-cause incident dementia in later life. For these analyses, it was hypothesized that greater levels of general and/or specific symptom dimensions would predict greater likelihood of a dementia diagnosis at any wave (over 12 years of follow-up). The aims, research questions, and analytic plan were pre-registered on Open Science Framework (OSF; https://rb.gy/1nz92g).

4.3 Methods

4.3.1 Participants and study design

Data were drawn from the Sydney Memory and Ageing Study (MAS; Sachdev et al., 2010), a longitudinal study of community-dwelling older adults in Sydney, Australia. Participants were 1037 older adults aged between 70-90 years old (M = 78.84; SD = 4.82; 44.8% male) at baseline (Table 4.1). Participants were followed across seven waves of data collection, with assessments occurring every two years (alongside brief phone interviews in intervening years). Informants were recruited for the majority of participants (93.9%), provided that they had contact with the participant for at least one hour per week and could answer questions regarding their cognitive ability and daily functioning. Recruitment and study enrollment took place between September 2005 and November 2007. Inclusion criteria were: 1) aged between 70-90 years old; 2) living in the community; 3) able to speak and write in English; and 4) ability to consent. Exclusion criteria were: 1) previous dementia diagnosis or diagnosis of dementia after comprehensive in-study assessment at baseline; 2) psychotic symptoms, schizophrenia diagnoses, or bipolar diagnoses; 3) diagnosis of multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy; 4) medical or psychological conditions that prevent participation; or 5) a Mini-Mental State Examination (Folstein et al., 1975) score of < 24 (adjusted for age, education, and non-English speaking background). The MAS sample and study design are described in detail elsewhere (Sachdev et al., 2010) and further outlined in the supplementary material (Appendix G.1). Details regarding data access approvals, ethical approvals, participant consent, and data availability are provided in the supplementary material (Appendix J).

4.3.2 Indicators of psychopathology

Indicators of psychopathology were derived from multiple self- and informant-report measures administered at baseline. The 15-item Geriatric Depression Scale (GDS) was designed to measure depressive symptoms over the past week in older adults (Yesavage et al., 1982). The Goldberg Anxiety Scale (GAS) is a 9-item measure of anxiety symptoms over the past month (Goldberg et al., 1988). The Kessler 10 (K10) is a 10-item measure of psychological distress over the past 30 days (Kessler, 1994). The Neuropsychiatric Inventory (NPI) assesses a range of psychiatric symptoms in people with dementia (Cummings et al., 1994), administered to informants of non-demented participants at baseline. The current study only included NPI items relating to agitation/aggression, irritability/lability, and disinhibition. Finally, substance use was measured via a combination of self-report items relating to alcohol and nicotine use. Items from these measures were included in subsequent confirmatory factor analysis (CFA) models as indicators of latent internalizing (i.e., GDS, GAS, and K10 items), disinhibited externalizing (i.e., NPI screening items for agitation/aggression, disinhibition, and irritability/lability), and substance use (i.e., alcohol and nicotine use items). Further details of symptom-level indicators included in all CFA models are provided in the supplementary material (Appendix G.2, Table S1).

4.3.3 Structural neuroimaging outcome measures

Details of the neuroimaging protocol are described in detail elsewhere (Sachdev et al., 2010) and outlined in the supplementary material (Appendix G.3). Briefly, all participants were invited to complete brain magnetic resonance imaging (MRI) and consenting participants were further screened for contraindications (i.e., pacemaker, metallic implant or foreign bodies, cochlear implants, ferromagnetic homeostatic clips, claustrophobia). Approximately half of the sample (50.75%) agreed to complete MRI scanning at baseline (n = 544). Following quality control procedures (Jiang et al., 2014) and exclusions due to medical issues that emerged after consenting to MRI scans (e.g., back problems), the final analytic sample size at baseline was n = 532. Follow-up MRI scans were also completed at Wave 2 (n = 417) and Wave 4 (n = 262). Paired samples t-tests and chi-square tests were conducted to examine differences in covariates (i.e., age, sex, education, total GMV, average cortical thickness) between those with complete and incomplete MRI follow-up data (Appendix G, Table S2). Those with complete MRI data were significantly younger at baseline and had larger total GMV at baseline, compared to those with incomplete MRI data. The present study used pre-processed structural neuroimaging data (i.e., cortical and subcortical volume, cortical thickness). Gray matter volume (GMV) and cortical thickness within 68 cortical regions and GMV within 19 subcortical regions (including the brain stem) were used to construct brain structural variables for primary and secondary outcomes. Primary outcomes included global measures of brain structure i.e., total cortical GMV, total subcortical GMV, and average cortical thickness. Secondary outcomes included 10 region of interest (ROI) measures i.e., total GMV and average cortical thickness in the frontal, parietal, temporal, and occipital lobes, as well as total GMV in the bilateral hippocampus and cerebellum. All brain structural variables were winsorized to be within +/- 3 standard deviations (SD) of the mean (M).

4.3.4 All-cause incident dementia outcome

All participants were free of dementia at baseline. Dementia status was determined via consensus diagnosis from a multidisciplinary panel of experts at each wave of data collection, on the basis of available clinical, neuropsychological, laboratory and neuroimaging data. Further details of the diagnostic procedures are described in detail elsewhere (Sachdev et al., 2010) and outlined in the supplementary material (Appendix G.4). For the current study, a single binary variable was used to indicate whether participants were diagnosed with dementia at *any follow-up wave* (across 12 years of follow-up). Participants coded as having dementia at one wave and no dementia at subsequent waves (n = 7) were removed from the analysis.

4.3.5 Model estimation and assessment of model-fit

The latent structure of psychopathology was examined using confirmatory factor analysis (CFA) of symptom-level categorical indicators of mental illness in the full sample at baseline. Four CFA models that are most commonly used to measure the latent structure of psychopathology were fit to the data (i.e., a one-factor model, a correlated-factors model, a bi-factor model, and a higher-order factor model). The use of confirmatory factor analytic models and allocation of indicators to specific/lower-order factors was based on extensive research detailing the latent structure of psychopathology (Caspi et al., 2014; Caspi & Moffitt, 2018; Kotov et al., 2017, 2021; Krueger et al., 2021; Watson et al., 2022). In accordance with the recommendations outlined in **Chapter 1** (Figure 1.3), the best-fitting factor model was selected for inclusion in subsequent analyses based on traditional model-fit indices, model-based estimates of reliability, and evaluation of model parameters (e.g., the significance, direction, and standard errors of the factor loadings). All models were estimated using the weighted least squares mean variance (WLSMV) and robust maximum likelihood (MLR) estimators in Mplus version 8.10 (Muthén & Muthén, 2017). For all models, the first factor loading was freely estimated and the means and variances of the latent factors were fixed to 0 and 1, respectively. Further details regarding model-specification and assessment of model-fit are presented in the supplementary material (Appendices G.5 and G.6). Examples of the Mplus code for each confirmatory factor analysis model are provided on Open Science Framework (https://osf.io/uhds9/) and in the supplementary material (Appendix I).

4.3.6 Bayesian plausible values

Factor scores derived from CFA models provide a single-point estimate of psychopathology for a given symptom dimension. The distributions of these scores are highly skewed when relying on categorical indicators, as in the current study. These scores are also likely to contain substantial random error (i.e., factor indeterminacy; Wu, 2005); however, it was not possible to directly calculate factor determinacy in the current study due to the inclusion of multiple dichotomous indicators (Beauducel & Hilger, 2017; Ferrando & Lorenzo-Seva, 2018; Forbes et al., 2021b). One way to account for these limitations is to use Bayesian plausible values (BPVs), which offer less biased estimations of the population mean and variance of psychopathology by accounting for the uncertainty around factor scores through multiple imputation. BPVs are a *set* of factor scores derived from multiple imputation that provide more reliable estimates and reduced measurement error relative to single-point estimates of factor scores (Muthén & Asparouhov, 2010). Calculating BPVs involves taking multiple random draws (i.e., imputations) from the posterior distribution of factor score estimates, providing a range of plausible values for a given factor score. In the current study, BPVs were generated for each participant and each latent symptom dimension. For each participant, 100 plausible values were estimated for each latent factor (i.e., 100 imputed factor scores from the posterior distribution were estimated for general and specific/lower-order factors) using the MLR-estimated parameters. BPV estimation was conducted in Mplus Version 8.10 (Muthén & Muthén, 2017). The 100 datasets were then analyzed simultaneously in R version 4.3.2 using (generalized) linear regression and (generalized) linear mixed models within a multiple imputation framework (mitml R package; Bates, 2015). An alternative approach would be to estimate associations simultaneously within a structural equation modeling framework; however, this was not feasible in the current study due to model complexity and sample size limitations.

4.3.7 Analytic plan

Primary analyses examined whether baseline general and specific/lower-order symptom dimensions predict intra-individual change in total cortical GMV, total subcortical GMV, and average cortical thickness across follow-up waves. Baseline BPVs for general and specific/lower-order symptom dimensions were entered as predictors in a series of linear mixed models with brain structural measures included as the outcome variable. All linear mixed models examined associations between one set of BPVs (e.g., for general psychopathology) and one brain structural variable (e.g., total GMV). Nesting of longitudinal measurements in participants was handled via the use of random intercepts and wave was represented as a categorical variable. All linear mixed models included sex, age, education, and MRI scanner as covariates. The primary estimate of interest was the wave by dimension interaction (e.g., wave by general psychopathology), which indicates whether there was an association between baseline symptom dimensions and change in brain structural outcomes over time. The following equation provides an example of the linear mixed models used to estimate wave by dimension interactions:

$$\text{Total GMV} = \text{general psychopathology} + \text{wave} + \text{sex} + \text{age} + \text{education} \\ + \text{scanner} + \text{wave*general psychopathology} + (1|\text{ID}).$$

Secondary analyses examined whether baseline general and specific/lower-order symptom dimensions predict intra-individual change in regional measures of GMV and cortical thickness across follow-up waves. Specific outcome measures included: total GMV and average cortical thickness in the frontal, parietal, temporal, and occipital lobes, as well as total GMV in the bilateral hippocampus and cerebellum. These analyses followed the same methodology as for the primary outcomes. All linear mixed models included sex, age, education, MRI scanner, and either total GMV or average cortical thickness, as covariates.

Additional secondary analyses examined whether baseline general and specific/lower-order symptom dimensions predict incident dementia across 12 years of follow-up. Baseline BPVs were entered separately as predictors in a series of logistic regression models, with dementia diagnoses at any follow-up wave included as a binary outcome variable. All analyses were run over 100 imputations and the results were pooled into a final set of estimates within a multiple imputation framework. Missing data was handled via Full Information Maximum Likelihood (FIML) in Mplus version 8.10 (Muthén & Muthén, 2017). Benjamini-Hochberg false discovery rate (FDR) correction was used to correct for multiple testing, with an FDR threshold of 5% ($\alpha = 0.05$; Appendix G.7). Examples of the R code used to conduct these analyses are provided on OSF (https://osf.io/uhds9/) and in the supplementary material (Appendix I). There were two minor deviations from the pre-registered analysis, which are also outlined in the supplementary material (Appendix G.8).

4.3.8 Post-hoc analyses

Most research investigating the neural correlates of transdiagnostic symptom dimensions has been conducted cross-sectionally in samples of youth. To facilitate comparisons with this prior research, post-hoc analyses examined whether general and specific/lower-order dimensions predict baseline measures of gray matter structure in older adulthood. Baseline BPVs for general and specific/lower-order symptom dimensions were entered separately as predictors in a series of linear regression models, with baseline measures of GMV and cortical thickness included as the outcome variables. These analyses examined associations with the same brain structural measures (i.e., global and regional) included in primary and secondary analyses. All analyses included sex, age, education, and MRI scanner as covariates. Analyses of regional brain structure included additional controls for either total GMV or average cortical thickness. All analyses (i.e., primary, secondary, and post-hoc) of regional gray matter structure were also re-run without controlling for total GMV or average cortical thickness in order to examine both absolute and relative effects. A series of unconditional linear mixed models (i.e., without predictors included) were also estimated to examine the trajectories of each brain structural outcome measure over time. Finally, to facilitate comparisons with studies identified in **Chapter 2** and assess the robustness of findings across different modeling approaches, post-hoc analyses were conducted by re-estimating all models (i.e., from primary, secondary, and post-hoc analyses) using BPVs generated from the bi-factor model. For all post-hoc analyses, Benjamini-Hochberg FDR correction was used to correct for multiple comparisons, with an FDR threshold of 5% ($\alpha = 0.05$).

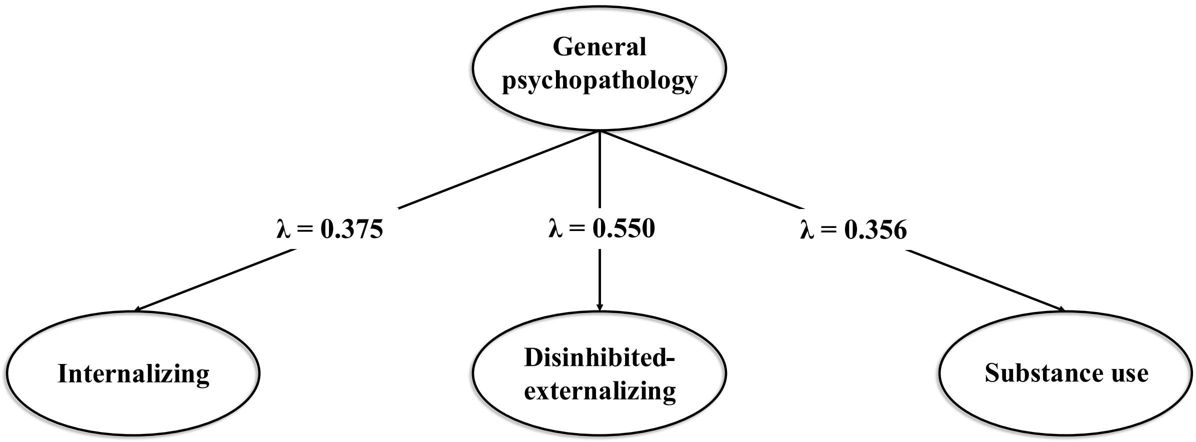
4.4 Results

4.4.1 Structural validity

Model-fit statistics and model-based estimates of reliability for the four CFA models are provided in Table 4.2. Standardized factor loadings and standard errors for all models estimated using MLR are provided in Table 4.3 and standardized factor loadings and standard errors for all models estimated using WLSMV are presented in the supplementary material (Appendix G, Table S3). The best-fitting model based on traditional model-fit statistics (i.e., BIC, ssaBIC, CFI, TLI, and RMSEA values) was the bi-factor model. However, as outlined in **Chapter 1**, bi-factor models tend to provide better fit than competing models when relying solely on traditional fit statistics and there is growing interest in the use of alternative approaches to model selection (Forbes et al., 2021b; Watts et al., 2019). When following the recommended approaches to model-selection outlined in **Chapter 1**, the higher-order model was found to be superior to the bi-factor model. Specifically, the higher-order model (Figure 4.1) was selected for inclusion in subsequent analyses, based on: 1) evaluation of standardized factor loadings (i.e., all significant, positive in direction, and mostly substantial in magnitude); 2) lower standard errors of the factor loadings (i.e., more precise estimates of these parameters); 3) evidence of multidimensionality yet poor reliability of general and specific factors of the bi-factor model based on model-based reliability coefficients (i.e., ECV, PUC, Omega H/HS values); and 4) evidence of greater construct reliability and replicability of specific factors (i.e., greater H coefficient values). Model-selection procedures are detailed extensively in the supplementary material (Appendix G.9). For the higher-order model estimated using MLR, the disinhibited-externalizing factor loaded most strongly on the general factor ($\lambda = 0.550$), followed by internalizing ($\lambda = 0.375$), and substance use ($\lambda = 0.356$). These factor loadings are consistent with those of the higher-order model estimated using WLSMV (disinhibited-externalizing, $\lambda = 0.574$; internalizing, $\lambda = 0.368$; substance use, $\lambda = 0.322$).

Figure 4.2

Simplified path diagram of the best-fitting measurement model estimated in the full sample of older adults from the Sydney Memory and Ageing Study



Note. This figure depicts the best-fitting model identified through confirmatory factor analyses comparing one-factor, correlated-factors, higher-order, and bi-factor models. The higher-order model was selected as the best-fitting model based on traditional indices of absolute and incremental model-fit, alternative model-based estimates of reliability, and evaluation of model parameters. Latent factors are represented as ellipses, including a general higher-order factor defined by the shared variance of three lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use). Standardized factor loadings of the lower-order dimensions on the general higher-order factor are shown. Observed indicators that defined the lower-order dimensions are omitted. All models were estimated using both weighted least squares mean and variance adjustment (WLSMV) and maximum likelihood with robust standard errors (MLR) in Mplus version 8.10 (Muthén & Muthén, 2017). The factor loadings depicted in this figure are from the MLR-estimated model.

Table 4.1

Baseline participant characteristics for the full sample and the MRI subsample

	Full sample (N=1037)		MRI subsample (n=532)[1]	
Categorical covariates	**N**	**%**	**N**	**%**
Sex (male)	465	44.8	242	45.5%
Continuous covariates	**Mean**	**SD**	**Mean**	**SD**
Age (years/continuous)	78.84	4.82	78.41	4.68
Education (years/continuous)	11.60	3.47	11.80	3.60
Total GMV (mm^3)	-	-	552,914.1	52,540.02
Average cortical thickness (mm)	-	-	2.43	0.11
Other characteristics	**N**	**%**	**N**	**%**
Race/ethnicity				
Caucasian	1016	98.4	517	97.2
Asian	10	1.0	9	1.7
Mixed	3	0.3	2	0.4
Other	4	0.4	2	0.4
Dementia Status	**N**	**%**	**N**	**%**
Dementia diagnosis[2]	269	25.9	-	-

Note. This table outlines the baseline characteristics for the full sample of participants from the Sydney Memory and Ageing Study (MAS) and the subsample of participants who completed MRI scanning at baseline.

[1] Follow-up MRI data was collected at Wave 2 (n = 417) and Wave 4 (n = 262).

[2] Dementia diagnosis data indicates the number of participants who received a diagnosis of dementia at *any follow-up wave*. Participants who received a diagnosis at one wave but not at subsequent waves were removed from the analysis (n = 7).

Table 4.2

Model-fit statistics and model-based reliability estimates for all confirmatory factor analysis models estimated in the Sydney Memory and Ageing Study sample

Dimensional models			**Model-fit statistics**				
	LL	**k**	**BIC**	**ssaBIC**	**CFI**	**TLI**	**RMSEA**
One-factor	-14637.38	90	29899.73	29613.88	0.686	0.661	0.097
Correlated-factors	**-14022.93**	**93**	**28691.65**	**28396.27**	**0.926**	**0.92**	**0.047**
Higher-order	**-14023.02**	**93**	**28691.85**	**28396.47**	**0.926**	**0.920**	**0.047**
Bi-factor	**-13846.61**	118	**28642.25**	**28267.32**	**0.950**	**0.941**	**0.040**
	ECV	**PUC**	**OmegaH/Hs**	**H**			
Bifactor model							
General psychopathology	**0.288**	**0.500**	0.295	**0.866**			
Internalizing	0.421	-	0.656	**0.918**			
Disinhibited-externalizing	0.109	-	**0.751**	**0.764**			
Substance use	0.182	-	**0.785**	**0.962**			
Higher-order model							
General psychopathology	-	-	-	-			
Internalizing	-	-	-	**0.949**			
Disinhibited-externalizing	-	-	-	**0.766**			
Substance use	-	-	-	**0.996**			

Note. BIC, Bayesian information criterion; CFI, comparative fit index; ECV, explained common variance; H, H coefficient; k, number of free parameters; LL, loglikelihood; Omega H/HS, omega hierarchical/hierarchical subscale; PUC, percent uncontaminated correlations; RMSEA, root mean square error of approximation; ssaBIC, sample size adjusted BIC; TLI, Tucker-Lewis index. Models were estimated using both weighted least squares mean variance (WLSMV) and maximum likelihood with robust standard errors (MLR) in Mplus version 8.10

(Muthén & Muthén, 2017). Bold text denotes values that were above or below the recommended thresholds for a given index (see Appendix G.9).

Table 4.3

Standardized factor loadings and standard errors of the four confirmatory factor models estimated in the Sydney Memory and Ageing Study

Observed indicators of psychopathology	**Bi-factor model (general factor)**		**Bi-factor model (specific factors)**		**Higher-order model**		**Correlated-factors model**		**One-factor model**	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Internalizing										
Keyed up or on edge	-0.168	0.988	**0.831**	0.185	**0.558**	0.042	**0.558**	0.042	**0.553**	0.031
Worrying a lot	-0.139	0.908	**0.797**	0.179	**0.555**	0.043	**0.555**	0.043	**0.527**	0.034
Irritable	-0.076	0.564	**0.455**	0.096	**0.339**	0.049	**0.339**	0.049	**0.313**	0.043
Difficulty relaxing	-0.055	0.827	**0.702**	0.073	**0.545**	0.045	**0.545**	0.045	**0.478**	0.039
Dropped many activities and interests	**0.374**	0.341	0.284	0.449	**0.448**	0.042	**0.448**	0.041	**0.407**	0.038
Feel that life is empty	**0.664**	0.493	**0.368**	0.846	**0.719**	0.051	**0.719**	0.051	**0.666**	0.045
Often get bored	**0.484**	0.459	**0.326**	0.634	**0.559**	0.049	**0.559**	0.049	**0.464**	0.043
Afraid that something bad is going to happen	**0.305**	0.780	**0.611**	0.402	**0.676**	0.042	**0.676**	0.042	**0.594**	0.037
Feel happy most of the time (reverse coded)	**0.440**	0.608	**0.457**	0.565	**0.639**	0.052	**0.640**	0.052	**0.602**	0.040
Think it is wonderful to be alive now (reverse coded)	**0.513**	0.411	**0.307**	0.639	**0.565**	0.050	**0.565**	0.050	**0.493**	0.043
Feel pretty worthless the way you are now	**0.772**	0.519	**0.399**	0.963	**0.803**	0.041	**0.803**	0.041	**0.759**	0.034
Frequency of feeling tired out for no good reason	**0.501**	0.467	**0.447**	0.570	**0.645**	0.029	**0.645**	0.029	**0.598**	0.023
Frequency of feeling nervous	0.184	0.839	**0.714**	0.223	**0.686**	0.033	**0.686**	0.033	**0.619**	0.026
Frequency of feeling hopeless	**0.595**	0.727	**0.613**	0.710	**0.849**	0.026	**0.849**	0.026	**0.789**	0.022

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Frequency of feeling restless or fidgety	0.111	0.738	**0.567**	0.173	**0.533**	0.045	**0.533**	0.045	**0.476**	0.036
Frequency of feeling depressed	**0.511**	0.740	**0.614**	0.606	**0.800**	0.023	**0.801**	0.023	**0.734**	0.020
Frequency of feeling that everything is an effort	**0.509**	0.475	**0.472**	0.567	**0.667**	0.030	**0.667**	0.030	**0.627**	0.022
Frequency of feeling so sad that nothing could cheer you up	**0.498**	0.756	**0.663**	0.572	**0.833**	0.025	**0.833**	0.025	**0.764**	0.027
Frequency of feeling worthless	**0.674**	0.630	**0.531**	0.799	**0.834**	0.03	**0.934**	0.030	**0.795**	0.023
Disinhibited-externalizing										
Refuses to cooperate or won't let people help/hard to handle	0.112	0.299	**0.704**	0.093	**0.719**	0.089	**0.718**	0.088	0.213	0.076
Acts impulsively without thinking/do or say things not usually done or said in public/embarrasses others	0.212	0.252	**0.769**	0.099	**0.754**	0.092	**0.753**	0.091	0.127	0.103
Irritated and easily disturbed/moods very changeable/abnormally impatient	0.018	0.415	**0.669**	0.116	**0.685**	0.088	**0.683**	0.087	0.188	0.057
Substance use										
Frequency of having a drink containing alcohol	-0.055	0.335	0.265	0.047	0.247	0.034	0.247	0.034	0.102	0.032

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Frequency of six or more standard drinks on one occasion?	-0.054	0.472	**0.424**	0.075	**0.399**	0.047	**0.399**	0.047	0.173	0.040
Frequency of being unable to remember what happened the night before because of drinking?	0.054	0.595	**0.545**	0.157	**0.538**	0.085	**0.537**	0.085	0.213	0.110
Relative, friend, doctor, or other health worker has expressed concerned about drinking or suggested cutting down	0.137	0.877	**0.500**	0.210	**0.511**	0.083	**0.511**	0.083	**0.395**	0.062
Average number of cigarettes per day while smoking	0.191	0.455	**0.895**	0.103	**0.913**	0.009	**0.913**	0.010	**0.826**	0.014
Age when started smoking	0.200	0.560	**0.976**	0.112	**0.998**	0.001	**0.999**	0.001	**0.851**	0.014
Loadings of lower-order factors on the general factor										
Internalizing	-	-	-	-	**0.375**	0.106	-	-	-	-
Disinhibited-externalizing	-	-	-	-	**0.550**	0.235	-	-	-	-
Substance use	-	-	-	-	**0.356**	0.101	-	-	-	-

Note. This table presents the standardized factor loadings and standard errors for the four models of psychopathology estimated in the Sydney Memory and Ageing Study sample. All models were constructed using confirmatory factor analysis (CFA) and estimated using maximum likelihood with robust standard errors (MLR) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). Standardized factor loadings that are positive in direction and substantial in magnitude (i.e., > 0.3) are highlighted in bold. The exact wording used in assessing each psychiatric symptom is provided in the supplementary material (Appendix G, Table S1).

4.4.2 Primary outcomes

Table 4.4 presents the results of analyses examining whether transdiagnostic dimensions of psychopathology at baseline derived from the higher-order factor model predict variations in global measures of brain structure across waves. There was no evidence that general and lower-order dimensions of psychopathology at baseline were associated with change in total cortical GMV, total subcortical GMV, or average cortical thickness across waves in the Sydney MAS sample. Standardized results for analyses of global brain structure are presented in the supplementary material (Appendix G, Table S4).

4.4.3 Secondary outcomes

The results for all secondary outcome measures are presented in the supplementary material (Appendix G, Tables S5-S8). Pooled estimates of the BPVs for general and lower-order dimensions were not associated with change in GMV across time in any cortical or subcortical ROI (Appendix G, Tables S5 and S7). Substance use was associated with increased cortical thickness over time within the parietal lobe at Wave 2 (beta = 0.006; SE = 0.003; $p = 0.049$); however, this association did not survive FDR correction (Appendix G, Table S6). No other symptom dimensions were associated with regional cortical thickness over time. Finally, there was no evidence that general psychopathology ($\beta = 0.04$; SE = 0.07; $p = 0.570$), internalizing ($\beta = 0.02$; SE = 0.05; $p = 0.730$), disinhibited-externalizing ($\beta = 0.08$; SE = 0.06; $p = 0.170$), or substance use ($\beta = -0.09$; SE = 0.06; $p = 0.120$) predicted all-cause incident dementia in the Sydney MAS sample (Appendix G, Table S8).

Table 4.4

Results from analyses examining whether transdiagnostic symptom dimensions derived from the higher-order model predict global measures of gray matter structure at baseline and across follow-up waves

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
General psychopathology												
BL model	-1578	1823.333	-5157.59, 2002.51	0.387	-2196	787.472	-1767.02, 1327.79	0.780	-0.002	0.006	-0.01, 0.01	0.798
LMM												
GP*Wave2	9187	1265.720	-2393.52, 2577.27	0.942	1093	538.220	-948.01, 1166.54	0.839	-0.001	0.004	-9082.25, 0.007	0.850
GP*Wave4	3804	1646.124	-2855.91, 3616.66	0.817	1223	658.623	-1172.12, 1416.72	0.853	-0.003	0.005	-126.51, 0.007	0.606

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
Internalizing												
BL model	**-3319**	**1469.747**	**-6200.30, -438.25**	**0.024**	2278	601.183	-1155.71, 1201.27	0.970	-0.005	0.005	-0.01, 0.004	0.318
LMM												
INT*Wave2	-1721	985.085	-2103.10, 1758.84	0.861	-1696	412.369	-978.03, 638.75	0.681	0.001	0.003	-5333.31, 0.007	0.784
INT*Wave4	1866	1245.753	-576.79, 4308.87	0.134	9701	498.514	-880.33, 1074.35	0.846	-0.002	0.004	-9746.73, 0.005	0.587
Disinhibited-externalizing												

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
BL model	-5992	1378.737	-3305.43, 2107.04	0.664	-1569	604.027	-1343.60, 1029.88	0.795	-0.000	0.005	-0.009, 0.009	0.990
LMM												
DEXT*Wave2	5446	978.383	-1866.16, 1975.08	0.956	1988	415.050	-616.28, 1013.84	0.632	-0.000	0.003	-0.006, 0.006	0.980
DEXT*Wave4	1512	1240.205	-2285.78, 2588.09	0.903	1632	497.070	-813.25, 1139.57	0.743	-0.001	0.004	-0.008, 0.006	0.705
Substance use												
BL model	-1974	1570.047	-5051.80, 1103.81	0.209	-4528	655.149	-1737.33, 831.79	0.490	-0.001	0.005	-0.01, 0.009	0.863

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
LMM												
SUB*Wave2	6314	1057.530	-1441.56, 2704.38	0.550	-9505	434.037	-945.84, 755.74	0.827	-0.004	0.003	-103.33, 0.003	0.287
SUB*Wave4	4447	1264.064	-2922.62, 2033.21	0.725	-5759	526.833	-1033.39, 1032.23	0.999	-0.005	0.004	-130.81, 0.003	0.223

Note. BL, baseline; DEXT, disinhibited-externalizing; GP, general psychopathology; INT, internalizing; LMM, linear mixed models; SUB, substance use. BL Model refers to linear regression models predicting baseline GMV. LMM refers to linear mixed models predicting intra-individual change in GMV across waves. In all models, pooled estimates of multiply imputed general and lower-order factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to False Discovery Rate (FDR) correction, with bold text indicating significant associations. No results were significant after FDR correction.

4.4.4 Post-hoc analyses

Post-hoc analyses revealed no evidence of association between general psychopathology and total cortical GMV, total subcortical GMV, or average cortical thickness at baseline (Table 4.4). Internalizing was negatively associated with total cortical GMV (beta = -3319; SE = 1469.747; p = 0.024) but not total subcortical GMV or average cortical thickness at baseline; however, this significant association did not survive FDR correction. Disinhibited-externalizing and substance use dimensions were also not associated with any global measure of gray matter structure at baseline. When controlling for global effects (i.e., total GMV, average cortical thickness), general psychopathology and lower-order dimensions were not associated with baseline GMV or cortical thickness in any ROI (Appendix G, Table S5-S7). Internalizing was significantly negatively associated with baseline GMV in the bilateral frontal lobe (beta = -1332; SE=585.206; p = 0.023) and bilateral temporal lobe (beta = -8305; SE = 375.023; p = 0.027) when not controlling for total GMV; however, neither association survived FDR correction (Appendix G, Table S5). Disinhibited-externalizing and substance use factors were not associated with baseline GMV or cortical thickness in any ROI when not controlling for global effects (Appendix G, Tables S5-S7). Analyses of unconditional linear mixed-models indicated significant reductions in all brain structural outcome measures across waves, which remained significant after FDR correction (detailed in Appendix G.10). Results from post-hoc analyses using BPVs generated from the bi-factor model were consistent with those found for the higher-order model and are outlined in the supplementary material (Appendix G.11, Tables S8-S12). The results from analyses using BPVs generated for the bi-factor model should be interpreted with caution, given the problems evident in the factor loadings (e.g., the substantial number of factor loadings that were non-significant, negative in direction, and/or small in magnitude; Appendix G.9).

4.5 Discussion

This study examined whether transdiagnostic phenotypes derived from a hierarchical dimensional model of psychopathology are associated with gray matter structure and all-cause incident dementia in older adults. As in **Chapter 3,** and consistent with prior research in younger samples (Kotov et al., 2017; Kotov et al., 2021), confirmatory factor models demonstrated that psychopathology in older adulthood can be organized hierarchically into a set of general and specific/lower-order transdiagnostic symptom dimensions. However, no associations between these dimensions and gray matter structure were significant after FDR correction. Specifically, there was no evidence that baseline estimates of transdiagnostic symptom dimensions predicted intra-individual change in global or regional gray matter structure across time. Post-hoc analyses additionally found no evidence of an association between transdiagnostic symptom dimensions and baseline measures of global and regional gray matter structure. Finally, there was no evidence that transdiagnostic symptom dimensions predicted all-cause incident dementia across 12 years of follow-up.

4.5.1 The neural correlates of transdiagnostic symptom dimensions in older adulthood

The lack of significant associations between transdiagnostic symptom dimensions and gray matter structure in the current study is inconsistent with findings in younger samples. Several cross-sectional studies have reported that general psychopathology, internalizing, and externalizing are associated with lower global and regional measures of gray matter structure from childhood to young adulthood (Kaczkurkin et al., 2019; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). These studies capture a critical period in which the brain undergoes substantial structural changes, with cortical thickness peaking in childhood and decreasing from childhood to adolescence and surface area peaking in preadolescence and decreasing slowly from adolescence to early adulthood (Tamnes et al., 2017; Wierenga et al., 2014). The majority of psychiatric disorders also tend to emerge between childhood and young adulthood (Solmi et al., 2022), perhaps driven by disruptions to normative maturational processes in the brain during this highly sensitive period of neurodevelopment. In contrast, the clinical picture of psychopathology in older adulthood may reflect: 1) symptoms that emerge early in development and persist or re-occur across the lifespan; 2) symptoms that first emerge in older adulthood; or 3) symptoms that specifically precede or follow from the onset of cognitive decline and dementia. Psychiatric symptoms that emerge in later life may be driven more strongly by environmental factors and physical comorbidities than genetic influences, which may exert less of an impact on brain structure. In the present study, measurement models predominantly included indicators of current symptom expression and may therefore be capturing late onset psychopathology. Future research should examine whether the relationship between transdiagnostic symptom dimensions and brain health in older adulthood differs as a function of age at symptom onset. Alternatively, potential associations between psychopathology and brain structure may be obscured by the impacts of age-related pathologies and neurodegeneration that emerge specifically in older adulthood. In either case, the inconsistency in results between this study and studies of younger samples underscores the importance of investigating these relationships across different age groups and highlights the complexities of doing so specifically in ageing populations.

It is also important to consider sample size limitations when interpreting the lack of significant associations in longitudinal analyses of gray matter structure. MRI data was only available in a subsample of participants at baseline (n = 532), with substantial attrition across waves (n = 417 at Wave 2 and n = 262 at Wave 4). It is possible that analyses in this study were not adequately powered to detect the effects of dimensional psychopathology on within-person changes in brain structure over time. This limitation was unavoidable given the reliance on secondary analysis of existing data and that there are few other large-scale studies of older adults that include the data necessary to address these research questions (i.e., broad measurement of psychopathology, repeated MRI measures). Furthermore, there were significant differences between those with complete vs. incomplete follow-up MRI data. Specifically, those with complete MRI data were younger and had larger total GMV at baseline. As noted, age was included as a covariate in all analyses to control for age-related variation in GMV and missing data on the outcome was handled using maximum likelihood within a mixed model framework, which is more valid than complete case analysis (Dong & Peng, 2013). However, the overrepresentation of participants with greater baseline GMV in the follow-up sample may have reduced variability in GMV change, further limiting statistical power to detect associations with psychopathology dimensions. Additionally, since participants with higher baseline GMV may experience a different rate of decline than those with lower baseline GMV, the findings of these analyses might not fully capture the broader relationship between psychopathology and intra-individual change in GMV over time in older adulthood.

4.5.2 Transdiagnostic symptom dimensions as predictors of all-cause incident dementia in older adulthood

There was no evidence that general and specific/lower-order transdiagnostic symptom dimensions predict all-cause incident dementia in the Sydney MAS sample. These findings are somewhat surprising given extensive evidence that dementia is associated with a range of psychiatric disorders (Becker et al., 2018; Cai & Huang, 2018; Mo et al., 2023; Richmond-Rakerd et al., 2022; Velosa et al., 2020). In the MAS sample specifically, previous studies have shown that baseline symptoms of depression, anxiety, apathy, and agitation are associated with mild cognitive impairment (Brodaty et al., 2012; Shahnawaz et al., 2013). However, the only indicators of psychopathology that have been found to predict incident dementia at follow-up in this sample are depressive symptoms (Brodaty et al., 2012). It may be that the relationship between current psychopathology and dementia risk is driven by specific symptoms (e.g., depressive symptoms) rather than transdiagnostic dimensions, perhaps indirectly through their association with certain physiological mechanisms and processes (e.g., increased cortisol levels, vascular risk factors, neuroinflammation) that are also implicated in dementia (Bennett & Thomas, 2014). Indeed, depressive symptoms are highly correlated with many other forms of psychopathology, which might account for the observed associations between dementia and a range of psychiatric disorders (Mo et al., 2023; Richmond-Rakerd et al., 2022). That said, further research (particularly in larger samples) is needed to more thoroughly examine whether transdiagnostic symptom dimensions can be used to predict incident dementia in older adults. As noted, psychopathology in older adulthood may reflect symptoms that emerged earlier in development or had their onset in later life. These presentations likely follow distinct etiological pathways and may confer different risks with respect to the onset of dementia in older adulthood. For example, transdiagnostic dimensions derived from symptoms that were present earlier in development may be more likely to predict incident dementia due to their longer-term impacts on brain health and other related risk factors that unfold across the lifespan. Transdiagnostic symptom dimensions may also show greater predictive utility for specific subtypes of dementia (e.g., those characterized by psychiatric and behavioral disturbances, such as frontotemporal dementia) than for general measures of dementia status. There may also be a threshold effect in which dementia is associated with clinically significant psychopathology but not with subthreshold symptom dimensions derived from general population samples, as in the current study. Finally, future research should also investigate the predictive utility of other symptom dimensions that are commonly investigated in younger samples (e.g., broad externalizing, thought disorder), which may show stronger associations with dementia.

4.5.3 Strengths and limitations

There are several strengths and limitations to the current study that are important to consider when interpreting these results. Firstly, a strength of this this study was the inclusion of repeated measures of both brain structure (over six years of follow-up) and consensus-diagnoses of dementia (across 12 years of follow-up). That said, future research in larger samples would benefit from re-examining these relationships and also examining potential associations with other neurobiological correlates (e.g., white matter microstructure, functional connectivity) and more nuanced examination of dementia (e.g., specific subtypes rather than a general binary outcome measure). In addition, this study used a rigorous and theory-driven approach to modeling the latent structure of psychopathology. However, measurement was somewhat limited by the lack of detailed psychiatric assessment in the Sydney MAS dataset. Specifically, the model was restricted to internalizing and two subdimensions of externalizing (i.e., disinhibited-externalizing and substance use) due to an insufficient number of indicators to specify broader or more commonly studied dimensions (e.g., broad externalizing, thought disorder). In addition, whilst there were a large number of indicators for internalizing there were substantially fewer indicators for the other lower-order factors. The disinhibited-externalizing factor was defined by only three indicators (all informant-report items from the NPI) and the substance use factor was defined entirely by indicators of alcohol and nicotine use. These factors limited the ability to comprehensively model the latent structure of psychopathology and impact the extent to which results can be compared to those found in younger samples. Future research would thus benefit from investigating these relationships using dimensional models derived from a more extensive set of psychiatric indicators.

It is also important to consider the selection criteria of the Sydney MAS when interpreting the results of this study. Whilst participants with mild cognitive impairment were eligible for inclusion and represented 36.7% of the sample at baseline (Tsang et al., 2013), those diagnosed with dementia or who scored below 24 on the Mini-Mental State Examination were excluded. This has the advantage of reducing potentially confounding effects of dementia and significant cognitive impairment, allowing for clearer examination of the extent to which psychopathology contributes to these outcomes in an otherwise healthy sample of older adults. However, these selection criteria also limit the representativeness of the Sydney MAS sample (Sachdev et al., 2010; Tsang et al., 2013). It is possible that these criteria selected for participants with a lower range of structural brain changes over time and a lower incidence of later onset dementia compared to the general population of those aged 70 years or older. The MAS sample is also relatively well-educated (average education = 11.6 years) and not racially or ethnically diverse (98.4% Caucasian), further limiting the generalizability of the results. Future research may therefore benefit from investigating these relationships in a more representative sample of older adults. However, few available large-scale longitudinal studies in community-dwelling older adults include detailed psychiatric assessment, as well as neuroimaging and dementia status data.

4.5.4 Conclusions

This is the first study to utilize hierarchical dimensional models of psychopathology to investigate the relationships between transdiagnostic symptom dimensions, brain structure, and dementia status in older adulthood. There was no evidence of an association between transdiagnostic symptom dimensions and gray matter structure or all-cause incident dementia in this sample. However, given that our current understanding of the neural correlates of transdiagnostic symptom dimensions comes almost exclusively from studies of youth, this study represents an important first step in determining the nature of these associations in an important and understudied age group. Future research would benefit from investigating these relationships in larger samples of older adults using hierarchical dimensional models derived from a more detailed set of psychiatric indicators. In addition, future studies should investigate whether age of symptom onset, normative brain ageing, and age-related pathologies impact the relationships between transdiagnostic symptom dimensions, brain structure, and dementia risk in later life.

Chapter 5

Investigating the relationships between transdiagnostic dimensions of psychopathology, cognitive dysfunction, all-cause incident dementia, and polygenetic risk for Alzheimer's disease in older adults from the UK Biobank

Preface

Chapter 2 identified that no studies have investigated the biological correlates of transdiagnostic dimensions specifically in older adulthood. **Chapter 3** first demonstrated that the latent hierarchical structure of psychopathology identified in younger samples is also evident in older adults and remains invariant throughout later life. Building on this finding, **Chapter 4** presented the first study to investigate the neurobiological correlates of transdiagnostic phenotypes (i.e., general psychopathology, internalizing, disinhibited-externalizing, substance use) derived from a hierarchical dimensional model of psychopathology. **Chapter 5** extends this research by first replicating the best-fitting higher-order model from **Chapter 3** in a subsample of older adults from the UK Biobank who were free of dementia at baseline and of European ancestry. The phenotypes derived from this model are then used to conduct the first investigation of *genomic* associations with transdiagnostic dimensions of psychopathology specifically in older adulthood. This chapter additionally re-examines associations with all-cause incident dementia, leveraging the larger UK Biobank sample in order to address the limited statistical power in **Chapter 4**, which may have constrained the ability to detect significant associations. Of note, **Chapter 2** identified two prior studies that investigated genomic associations with transdiagnostic dimensions of psychopathology in participants from midlife to older adulthood (i.e., 51 to 83 years old and

40 to 69 years old), one of which included participants from the UK Biobank (Gard et al., 2021; Grotzinger et al., 2019). The sample in **Chapter 5** includes participants aged 55 to 78 years old at baseline, which arguably spans both midlife (i.e., 55-59 years old) and older adulthood. However, analyses included in this study investigated genomic associations both in the full sample and individually across four age groups (i.e., 55-59, 60-64, 65-69, 70-78 years old) to examine these relationships specifically in later stages of life. Furthermore, **Chapter 5** extends upon prior research by examining associations with polygenetic risk for a neurocognitive disorder relevant to older adult populations (i.e., Alzheimer's disease) rather than polygenetic risk for psychiatric disorders and traits.

This study is currently formatted for submission to the *Journal of Psychopathology and Clinical Science*.

Supplementary materials for **Chapter 5** are provided in Appendix H.

5.1 Abstract

Aims This study aims to determine whether transdiagnostic symptom dimensions derived from a hierarchical dimensional model of psychopathology are associated with all-cause incident dementia and polygenic scores for Alzheimer's disease (AD-PGS) in older adults. **Methods** Participants included older adults of European ancestry from the UK Biobank who were free of dementia at baseline (N = 109,844; male = 55.5%; mean age = 65.09 years old). Confirmatory factor analysis was used to model a general higher-order dimension and four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, and cognitive dysfunction). Multigroup measurement invariance was examined across four age groups (i.e., 55-59, 60-64, 65-69, and 70-78 years old). Structural equation modeling (SEM) examined bivariate associations with incident dementia and the AD-PGS and whether latent dimensions mediate the relationship between the AD-PGS and incident dementia. All SEMs were re-estimated across age groups to investigate age-specific differences in these relationships. Benjamini-Hochberg False Discovery Rate (FDR) correction was used to account for multiple testing. **Results** The higher-order model demonstrated acceptable model-fit (CFI = 0.935; TLI = 0.931; RMSEA = 0.041) and invariance across age groups (change in CFI $\leq$ 0.002). All higher- and lower-order dimensions were significantly positively associated with incident dementia (all p's < 0.001). Cognitive dysfunction was also positively associated with the AD-PGS ($p < 0.001$) and partially mediated the relationship between the AD-PGS and dementia ($p < 0.001$). The general higher-order dimension and all lower-order dimensions of psychopathology predicted dementia across age groups (all p's < 0.05). Cognitive dysfunction was positively associated with incident dementia and the ADPGS in the three oldest age groups (all p's < 0.001) and partially mediated the relationship between the AD-PGS and incident dementia in the three oldest age groups (all p's < 0.005). **Conclusions** Transdiagnostic

dimensions of psychopathology and cognitive dysfunction may represent useful targets for prevention and intervention in the context of dementia. Targeting cognitive dysfunction may additionally help mitigate genetic risk for Alzheimer's disease.

5.2 Introduction

Epidemiological research indicates that the number and proportion of older adults will increase significantly by the year 2050 (World Health Organization, 2023). Improving our understanding of conditions that impact healthy ageing is thus an increasingly important public health challenge. One of the most significant conditions impacting healthy ageing is dementia, a set of diseases broadly characterized by a progressive deterioration of brain health, cognitive functioning, and the capacity for independent living (Arvanitakis et al., 2019). As the number of older adults continues to increase so too will the number of people living with dementia, with recent estimates suggesting that this condition will affect approximately 152.8 million people by 2050 (Nichols et al., 2022). There is currently no means of curing dementia and consequently, current priorities are largely focused on prevention, risk-reduction, and efforts to further our understanding of disease-related mechanisms (Shah et al., 2016).

One potential disease-mechanism underpinning dementia is mental illness. Several studies indicate that a range of putatively distinct psychiatric disorders (e.g., anxiety, depression, alcohol and other substance use, attention-deficit/hyperactivity disorder, schizophrenia, bipolar disorder) are individually associated with greater likelihood of dementia diagnoses (Aranda et al., 2023; Becker et al., 2018; Cai & Huang, 2018; Cherbuin et al., 2015; Dobrosavljevic et al., 2022; Velosa et al., 2020). A population-based study of over 1.7 million participants also reported that those with *any* psychiatric disorder were significantly more likely to develop dementia than those without (Richmond-Rakerd et al., 2022). These findings indicate that the relationship between mental illness and dementia is transdiagnostic in nature, rather than being driven by associations with specific diagnostic categories.

As outlined in **Chapter 1**, hierarchical dimensional models of psychopathology capture patterns of symptom co-occurrence that cut across traditional diagnostic boundaries and provide a framework for disentangling shared and unique associations between psychiatric phenotypes and a range of external outcomes. These models may hold utility in research examining the relationship between mental illness and dementia, supporting the simultaneous investigation of both broad transdiagnostic vulnerabilities (i.e., associations with general higher-order dimensions) and potentially dissociable patterns of association at lower levels of the structural hierarchy (e.g., associations that may be observed for some lower-order dimensions but not others). As highlighted in **Chapter 3**, there is also growing interest in whether dimensions capturing cognitive function can be incorporated into hierarchical dimensional models of psychopathology (Eadeh et al., 2021; Forbes et al., 2024b; Littlefield et al., 2021; Ringwald, 2024; Rotstein et al., 2023). Hierarchical models that include cognitive phenotypes may be particularly useful in the context of dementia research, given that deficits in cognitive function are also known to proceed the onset of dementia in later life (Belleville et al., 2017; Hayat et al., 2021).

5.2.1 Hierarchical dimensional models of psychopathology in older adulthood

Few studies have investigated the latent structure of psychopathology specifically in older adults (Kotov et al., 2017). In addition, existing research has largely focused on examining specific/lower-order dimensions (e.g., internalizing, externalizing) rather than hierarchical models that capture a broader spectrum of psychopathology (Buchan et al., 2014; Eaton et al., 2011; Hoertel et al., 2015; Sunderland et al., 2013). **Chapter 3** demonstrated that the structure of psychopathology can be organized hierarchically in older adulthood, identifying a higher-order model that included a general higher-order factor and four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, and cognitive dysfunction) in participants aged 55 to 78 years old from the UK Biobank (Hoy et al., 2025a). **Chapter 4** extended this research by identifying a higher-order model of psychopathology that included a general factor and three lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use) in participants aged 70 to 90 years old from the Sydney Memory and Ageing Study (MAS; Hoy et al., 2025b). These two studies indicate that the latent hierarchical structure of psychopathology identified in younger samples is also evident in older adulthood and further support the inclusion of latent cognitive phenotypes within that hierarchical structure in later life. However, the extent to which phenotypes derived from these models are associated with important age-specific outcomes (e.g., dementia) or with biological factors that are uniquely relevant to ageing populations (e.g., polygenetic risk for neurocognitive disorders) has not been thoroughly investigated.

5.2.2 Hierarchical dimensional models as a novel framework for investigating the relationships between mental illness, cognitive dysfunction, and all-cause incident dementia in older adulthood

Chapter 4 presented the first study to examine whether transdiagnostic dimensional phenotypes are associated with all-cause incident dementia in older adulthood (Hoy et al., 2025b). This study found no evidence that general or specific/lower-order transdiagnostic dimensions predicted incident dementia across 12 years of follow-up in older adults from the Sydney MAS (Sachdev et al., 2010). However, these null findings may be explained by certain methodological limitations. For instance, the Sydney MAS dataset includes a relatively small sample size (N = 1,037) and a limited number of dementia cases (n = 269) were identified across follow-ups. Therefore, analyses may not have been adequately powered to detect associations between transdiagnostic dimensions of psychopathology and dementia. Furthermore, the transdiagnostic dimensions investigated in **Chapter 4** were derived from a limited set of observed indicators, constraining the ability to comprehensively model the latent structure of psychopathology and potentially limiting sensitivity to detect associations with dementia.

Chapter 5 addresses these limitations by re-examining the relationship between transdiagnostic phenotypes and all-cause incident dementia in a much larger sample of older adults from the UK Biobank. To support this analysis, the best-fitting model of psychopathology from **Chapter 3** was replicated in a subsample of participants who were free of dementia at baseline. This model includes phenotypes derived from a broader and more diverse set of observed indicators. It also includes a more comprehensive set of transdiagnostic phenotypes, spanning both psychiatric (i.e., internalizing, addictions and substance use, thought disorder) and cognitive domains (i.e., cognitive dysfunction). This model therefore enables more detailed examination of the extent to which transdiagnostic dimensions contribute to dementia risk in later life. Moreover, it provides a framework for investigating whether psychiatric and cognitive phenotypes exert shared and unique influences on dementia risk in later life and may thus facilitate the identification of promising and novel targets for prevention and intervention. For example, if a general higher-order factor defined by the shared variance of lower-order psychiatric and cognitive phenotypes is associated with incident dementia, this would suggest the presence of shared mechanisms underpinning both mental illness and cognition that influence dementia risk. Furthermore, if the phenotypes derived from this model demonstrate utility in predicting dementia in older adulthood, identifying genetic influences on these relationships would further our understanding of disease-related biological pathways that contribute to dementia risk in later life.

5.2.3 Genomic associations with transdiagnostic dimensions of psychopathology and cognitive dysfunction and their relationship to dementia

The relationship between mental illness and dementia in older adulthood suggests that polygenetic risk for neurocognitive conditions (e.g., Alzheimer's disease) may also be linked to transdiagnostic dimensional phenotypes. Indeed, there is evidence of shared genetic associations between specific psychiatric disorders and subtypes of dementia (Li et al., 2022;

Lutz et al., 2020). If polygenic scores (PGSs) for neurocognitive conditions show positive associations with transdiagnostic dimensions in older adulthood, it is also possible that the genetic variants defining these scores are indirectly linked to dementia via their influence on levels of higher- and lower-order dimensions. Demonstrating this would identify novel disease-mechanisms underlying dementia (e.g., polygenetic risk for neurocognitive disorders increase levels of general and lower-order transdiagnostic dimensions, which in turn increase the likelihood of dementia diagnoses) and point towards new targets (e.g., transdiagnostic psychiatric expression) for mitigating genetic risk. However, no studies have focused on the genomic correlates of transdiagnostic dimensions specifically in older adulthood. The systematic review presented in **Chapter 2** (Hoy et al., 2023) found that two studies have investigated whether genetic risk for a range of psychiatric disorders and traits are associated with transdiagnostic dimensions in participants from midlife to older adulthood (i.e., 51 to 83 and 40 to 69 years old), including participants from the UK Biobank (Gard et al., 2021; Grotzinger et al., 2019; Hoy et al., 2023). These studies both reported that general psychopathology was associated with a wide range of disorder and trait-specific PGSs (i.e., for schizophrenia, bipolar disorder, major depressive disorder, anxiety, and post-traumatic stress disorder, and neuroticism) as well as transdiagnostic PGSs (i.e., internalizing, externalizing, and general PGSs; Gard et al., 2021; Grotzinger et al., 2019). The current study extends this research by investigating whether a PGS for Alzheimer's disease (AD) is also associated with transdiagnostic dimensions and by including age-stratified analyses to investigate these relationships specifically in later life. Furthermore, additional analyses are conducted to investigate the extent to which transdiagnostic dimensional phenotypes mediate the relationship between polygenetic risk for AD and incident dementia throughout later life.

One prior study examined whether polygenetic risk for AD (AD-PGS) was associated with a binary composite variable capturing various psychiatric disorder diagnoses (i.e., schizophrenia and other psychotic disorders, bipolar spectrum disorders and manic episode, depressive and other mood disorders, and anxiety disorders) in the full sample of participants from the UK Biobank (Freudenberg-Hua et al., 2024). The authors also tested whether this composite variable was associated with incident dementia and whether it mediated the relationship between the AD-PGS and incident dementia. Whilst the composite diagnostic variable was associated with incident dementia, it was not associated with the AD-PGS and did not mediate its relationship with dementia risk. The present study extends this prior research in several ways. First, this study examines associations with a general factor defined by the shared variance of lower-order psychiatric and cognitive phenotypes and with a range of narrower latent dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction), allowing for a detailed and differentiated understanding of how general and lower-order phenotypes relate to genetic risk and dementia outcomes in later life. Second, rather than using a binary composite variable this study examines associations with latent transdiagnostic dimensions of psychopathology in a structural equation modeling (SEM) framework, accounting for measurement error and providing more reliable estimates of these relationships (Tomarken & Waller, 2005). Third, transdiagnostic dimensions are estimated using symptom-level indicators of psychopathology that allow for more detailed examination of the latent structure of psychopathology and avoid the limitations of depending on dichotomous disorder-level indicators (e.g., reliance on diagnostic thresholds that do not reflect dimensional psychiatric expression; Forbes et al., 2021a). Fourth, it focuses specifically on older adulthood by conducting age-stratified analyses across four age groups (spanning 55 to 78 years old), allowing for more precise examination of age-specific associations in later life.

5.2.4 The current study

The primary aims of **Chapter 5** are to examine whether general and lower-order dimensions of psychopathology and cognitive dysfunction in older adulthood: 1) are associated with all-cause incident dementia; 2) are associated with polygenetic risk for AD; and 3) show evidence of mediating the relationship between polygenetic risk for AD and incident dementia. Secondary aims are to examine potential age-specific differences in the nature of these associations throughout older adulthood. Given the exploratory nature of the study, no hypotheses were specified a priori.

5.3 Methods

5.3.1 Participants and study design

Data were drawn from the UK Biobank, a large-scale population-based study of 502,536 participants in the United Kingdom (Bycroft et al., 2018). Participants were recruited between 2006 and 2010 and aged between 40 and 69 years old at baseline. Online assessments of cognitive function were completed by a subsample of participants (n = 110,995 to 209,817) between 2014 and 2015. Online assessments of mental health were completed by a subsample of participants (n = 157,366) between 2016 and 2017. Study procedures and sample characteristics are reported in detail elsewhere (Bycroft et al., 2018; Davis et al., 2020; Sudlow et al., 2015). Participants were included in the current study provided that they: 1) completed the online assessments of cognitive function and mental health; 2) were aged 55 years or older at the time they completed cognitive assessments; 3) were free of dementia at the time they completed the online cognitive and mental health assessments; and 4) were of European ancestry (N = 109,844; male = 44.5%; mean age = 65.09 years old). Participant characteristics are provided Table 5.1. Details regarding data access approvals, ethical approvals, participant consent, and data availability are provided in the supplementary material (Appendix J).

5.3.2 Observed indicators of cognitive function

The UK Biobank administered a series of cognitive tests as part of an online follow-up in a subsample of participants (n = 110,995 to 209,817) between 2014 and 2015. Indicators of cognition used in the current study were drawn from the following cognitive tests: Trail Making Task A (TMTA), Trail Making Task B (TMTB), Fluid Intelligence, Numeric Memory, and the Symbol Digit Substitution Test (SDST). Analyses involved raw cognitive scores (i.e., total scores or time to completion), with scores for certain tests (i.e., Fluid Intelligence, Numeric Memory, SDST) reverse coded to ensure that for all cognitive tests, higher scores reflected worse performance. All indicators of cognitive function were continuous. Cognitive indicators included in the current study are outlined in the Table 5.2 and are identical to those included in **Chapter 3**. Further details regarding cognitive tests, the specific outcome variables that were used, as well as any transformations that were performed, are reported in detail in the supplementary material for **Chapter 3** (Appendix F.1, Table S1).

5.3.3 Observed indicators of psychopathology

The UK Biobank also administered the Mental Health Questionnaire (MHQ) as part of an online follow-up in a subsample of participants (n = 157,366) between 2016 and 2017. Observed indicators of psychopathology included in the current study were drawn from these assessments, including 39 self-reported symptoms of depression, mania, anxiety, addictions, alcohol use, cannabis use, unusual or psychotic experiences, post-traumatic stress, and suicidality/self-harm. All indicators of psychopathology were either binary or ordinal categorical variables. The specific indicators of psychopathology included in the current study are reported in Table 5.2 and are identical to those included in the analyses for **Chapter 3**. Detailed information regarding symptom-level indicators included in the current study and any transformations performed on these data are reported in the supplementary material for **Chapter 3** (Appendix F.1, Table S1).

5.3.4 Demographic covariates

As in **Chapter 3**, covariates included in these analyses were age at baseline and years of education (Table 5.1). Age at baseline was defined as the age at which participants completed online cognitive follow-up assessments. Years of education was estimated from data capturing educational qualifications (Field ID: 6138). The highest level of education attained was coded according to the International Standard for Classification of Education to produce an estimate of years of education (continuous), as in several previous studies using the UK Biobank data (Wang et al., 2024; Xie et al., 2023; Zhao et al., 2024). Further details regarding the estimation of years of education are provided in the supplementary material for **Chapter 3** (Appendix F, Table S2).

5.3.5 Polygenic scores for Alzheimer's disease

The UK Biobank provides access to a range of PGSs for various diseases and quantitative traits (Category 300). The Standard PGS for Alzheimer's disease (Field ID: 26206) were selected for inclusion in subsequent analyses. This PGS was trained on external genome-wide association study (GWAS) data only (i.e., on GWAS data that did not include participants from the UK Biobank) and calculated in the full UK Biobank sample. The methodology used to derive the PGS for Alzheimer's disease (AD-PGS) is detailed extensively elsewhere (Thompson et al., 2024). Briefly, scores were calculated using the summary statistics of two case-control GWASs of Alzheimer's disease, totaling 42,588 cases and 573,011 controls (Thompson et al., 2024). A fixed-effect inverse variance meta-analysis was conducted to combine the external GWAS data, with corrections for sample overlap. Genetic variants included in the PGS were required to have INFO scores > 0.80, minor allele frequency (MAF) > 0.05, and no significant deviations from Hardy-Weinberg Equilibrium ($p > 1e\text{-}10$). The AD-PGS was calculated as the genome-wide sum of per-variant posterior effect size estimates, multiplied by allele dosage. PGSs were centered by subtracting the PGSs predicted from linear regressions against the first four principal components of genetic ancestry (fitted in the 1000 Genomes Project dataset). Centered PGSs were then divided by the standard deviation of the PGSs in the 10000 Genomes ancestry group with the closest match to an individual participant, allowing for centered and variance-standardized PGSs. Consistent with previous research (Topriceanu et al., 2024), genetic principal components were not included as covariates because these variables were already adjusted for in deriving the PGS.

5.3.6 All-cause incident dementia

Dementia status was determined from first occurrences reported (Category 1712) and algorithmically-defined dementia outcomes (Category 47), consistent with previous research (Zhang et al., 2023). First occurrences (Category 1712) included dementia diagnoses identified through self-reported medical conditions (Field ID: 20002) and linkage to primary care (Field ID: 3000), hospital inpatient data (Field ID: 2000), and death register records (Field ID: 40001-40002). Diagnoses were mapped to ICD-9 and ICD-10 codes, including: dementia in Alzheimer's disease (F00); vascular dementia (F02); dementia in other diseases classified elsewhere (F03); unspecified dementia (F03); and Alzheimer's disease (G30). These data were combined with algorithmically-defined dementia outcomes provided by the UK Biobank (Category 47). Algorithmically-defined outcomes were derived from a combination of self-reported medical condition codes, hospital admissions, diagnoses and procedures, and death registry records. This included outcomes for all-cause dementia (Field ID: 42019), Alzheimer's disease (Field ID: 42021), vascular dementia (Field ID: 42023), and frontotemporal dementia (Field ID: 42025). These data were used to construct a binary variable indicating the presence or absence of all-cause incident dementia (i.e., any participant who was coded as having dementia across any of these variables was coded as having dementia in the current study and all other participants were coded as not having dementia). Participants with dementia diagnoses indicated prior to the completion of online cognitive and mental health assessments were excluded from the study. This resulted in n = 788 participants being classified with all-cause incident dementia in the final sample.

5.3.7 Analytic plan

5.3.7.1 Primary analyses

*Re-estimating the higher-order dimensional model of psychopathology***.** The best-fitting higher-order model identified in **Chapter 3** was re-estimated in the current study, given differences in sample size and composition. Specifically, the starting sample was somewhat smaller due to participant dropout and withdrawal of study data (n = 51). In addition, the analytic sample for this study was restricted to participants of European ancestry who were free of dementia at the time they completed the online cognitive and mental health assessments (N = 109,844). Model-specifications for the higher-order model were identical to **Chapter 3** (see Appendix F.2). Briefly, the model included four lower-order factors (i.e., internalizing, addictions and substance use, thought disorder, and cognitive dysfunction) defined by the exact same set of observed indicators as in **Chapter 3** and a general higher-order factor defined by the shared variance of those lower-order factors. The first factor loading for each latent factor was fixed to 1 for model identification.

Sensitivity analyses in **Chapter 3** also found that the loadings of cognitive dysfunction on the general factor improved when the lower-order factors were regressed on age and years of education (see Appendix F.5). The lower-order factors were again regressed on these demographic covariates in the current study. It is not possible to regress both the lower- and higher-order factors from a higher-order model on covariates simultaneously because the higher-order factor is defined entirely by the loadings of the lower-order factors, making the higher- and lower-order factors perfectly collinear (Moore et al., 2020). Regressing the lower-order factors on covariates was preferred because it allows for more precise control of covariate effects on lower-order dimensions included in the measurement model. Details regarding the assessment of model-fit are provided in the supplementary material (Appendix H.1). The measurement model, multigroup measurement invariance models, and all subsequent SEMs included in this study were estimated in Mplus version 8.10 (Muthén & Muthén, 2017) using weighted least squares mean variance (WLSMV) estimation and DELTA parameterization. Mplus code for all models estimated in the current study is additionally provided on Open Science Framework (OSF; https://osf.io/wrk7c/files/osfstorage) and in Appendix I.

Structural equation models examining bivariate associations between latent dimensions of psychopathology, cognitive dysfunction, polygenetic risk for Alzheimer's disease, and dementia status. Primary analyses were conducted in a step-wise fashion via the estimation of 15 SEMs. In the first SEM, dementia status was treated as the outcome variable and regressed on the general higher-order dimension (Model 1). In the second SEM, the general higher-order dimension was treated as the outcome variable and regressed on the AD-PGS (Model 2). The third SEM examined whether scores on the general higher-order dimension mediated the relationship between the AD-PGS and dementia status (i.e., the AD-PGS was treated as the predictor, the general higher-order dimension was treated as the mediator, and dementia status was treated as the outcome; Model 3). The remaining SEMs examined associations with each of the four lower-order dimensions individually (i.e., internalizing, addictions and substance use, thought disorder, and then cognitive dysfunction; Models 4-15). In one set of SEMs, dementia was treated as the outcome variable and regressed on each of the four lower-order dimensions individually (Models 4-7). In the next set of SEMs, each of the four lower-order dimensions were individually regressed on the AD-PGS (Models 8-11). The final set of SEMs examined the indirect effects of the AD-PGS on dementia status via its influence on levels of each lower-order dimension (i.e., the AD-PGS entered as the exposure variable, lower-order dimensions entered individually as mediators, and dementia status entered as the outcome variable; Models 12-15). In all models, age and years of education were controlled for by simultaneously regressing the four lower-order dimensions on both covariates. In relevant models, the dementia status outcome variable was additionally regressed on age and years of education (Model 1, Model 3, Models 4-7, Models 12-15).

In mediation models, the relationship between the exposure (X) and outcome (Y) is posited to be influenced at least in part by a mediating variable (M). Simple mediation models include three paths: the path between the exposure (e.g., the AD-PGS) and mediator (e.g., the latent factor; path *a*); the path between the mediator and outcome (e.g., incident dementia; path *b*); and the path between the exposure and outcome (path *c*'). The product of paths *a* and *b* represent the indirect effect, which quantifies the extent to which the exposure influences the outcome through the mediating variable. Traditional approaches to mediation require that all individual paths are significant (i.e., X → Y, X → M, and M → Y) before testing for mediation or indirect effects (Baron & Kenny, 1986). However, contemporary mediation frameworks emphasize that it is possible to have a significant indirect effect even when paths *a* or *b* (e.g., X → M or M → Y) are non-significant but non-zero because the *product* of these paths drives the indirect effect (Hayes, 2009). Analyses in the current study thus tested for indirect effects regardless of the significance of individual paths.

5.3.7.2 Secondary analyses

Multigroup measurement invariance of the higher-order model across age groups. Multigroup measurement invariance of the higher-order model across four age groups (i.e., 55-59, 60-64, 65-69, and 70-78 years old) was re-examined in this study following the exact same procedures and specifications as in **Chapter 3**. Briefly, for models including binary indicators and WLSMV estimation, metric invariance models are not identified and it is recommended to test for metric and scalar invariance simultaneously (Muthén & Muthén, 2018). For higher-order models, it is also necessary to examine metric/scalar invariance of the lower- and higher-order factors separately (Chen et al., 2005; Rudnev et al., 2018). Measurement invariance was thus tested in three steps (i.e., configural invariance, first-order metric/scalar invariance, second-order metric/scalar invariance). All models controlled for years of education but age was dropped as a covariate given that the focus was on investigating invariance across age groups. Complete details regarding model-specification for each invariance model are presented in the supplementary materials for **Chapter 3** (see Appendix F.4). As in **Chapter 3**, chi-square testing was not used to assesses invariance due to its sensitivity to large sample sizes (Cheung & Rensvold, 2002; Meade et al., 2008) and changes in CFI values of ≤ 0.01 (Cheung & Rensvold, 2002) and the more conservative threshold of ≤ 0.002 (Meade et al., 2008) were considered as evidence of invariance.

Bivariate analyses of age-specific differences in association with polygenetic risk for Alzheimer's disease and dementia status. Each of the SEMs conducted in the main analysis were re-estimated across the four different age groups to examine potential age-specific differences in the nature of associations between transdiagnostic dimensions, all-cause incident dementia, and polygenetic risk for Alzheimer's Disease. For SEMs examining associations with the general higher-order dimension, the second-order metric/scalar invariant model (in which higher-order means were free to vary) was used. For SEMs examining associations with the lower-order dimensions, the first-order metric/scalar invariance model (in which lower-order means were free to vary) was used.

Multivariable analyses of associations between transdiagnostic dimensions, AD-PGS, and incident dementia in the full sample and across age groups. To complement the primary and secondary analyses, a series of multivariable tests were conducted to examine whether associations between lower-order dimensions and external criteria (i.e., all-cause incident dementia, AD-PGSs) differed when controlling for the influence of the other lower-order dimensions. Specifically, SEMs from the primary and secondary analyses examining associations with lower-order dimensions (i.e., Models 4-15 and Models 19-30) were re-estimated with all lower-order dimensions entered simultaneously instead of individually. As previously mentioned, it is not possible to examine associations with higher- and lower-order factors simultaneously because the higher-order factor is defined entirely by the shared variance of the lower-order factors (Moore et al., 2020). For these reasons, multivariable analyses examined associations with lower-order dimensions only. Aside from including all four lower-order dimensions simultaneously in each SEM, model-specifications were identical to the primary and secondary analyses. All supplemental models in the full sample controlled for age and years of education and all models conducted across age groups controlled for years of education only.

5.3.8 Handling of missing data

The WLSMV estimator in Mplus handles missing data via pairwise deletion when estimating correlations among observed indicators. Mplus additionally excludes all participants with missing data on a given external predictor. There were n = 9 participants with missing data on all observed indicators and n = 539 participants with missing data on years of education removed from the analysis, reducing the analytic sample size to N = 109,296. A number of participants were additionally excluded due to missing genomic data (n = 2,245), resulting in a final analytic sample size of N = 107,051 for all analyses specifically involving the AD-PGS (i.e., all models examining direct associations with the AD-PGS and all mediation models).

5.3.9 False discovery rate corrections

Benjamini-Hochberg false discovery rate (FDR) was used to correct for multiple testing across sets of analyses, with an FDR threshold of 5% ($\alpha = 0.05$). Specifically, corrections were applied for all tests conducted in the full sample (i.e., 27 tests) and all tests conducted in each age-stratified subsample (i.e., 27 tests in participants aged 55-59; 27 tests in participants aged 60-64; 27 tests in participants aged 65-69; and 27 tests in participants aged 70-78 years old).

5.4 Results

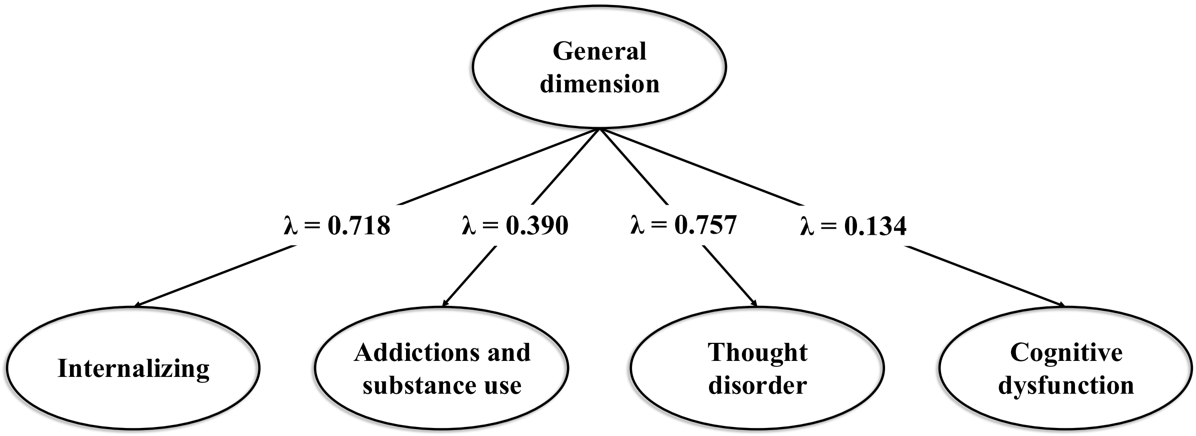
5.4.1 Primary analyses

5.4.1.1 Structural validity

The higher-order model (Figure 5.1) demonstrated acceptable absolute and incremental model-fit (CFI = 0.935; TLI = 0.931; RMSEA = 0.041), comparable to the previous analyses in **Chapter 3** (Hoy et al., 2025a). Model-based reliability estimates were also comparable to this previous analysis, with evidence of sufficient reliability for the internalizing (H = 0.975), addictions and substance use (H = 0.943), thought disorder (H = 0.850), and cognitive dysfunction (H = 0.829) dimensions (Hancock and Mueller, 2001). The thought disorder dimension demonstrated the strongest loading on the general factor ($\lambda = 0.757$), followed by internalizing ($\lambda = 0.718$), addictions and substance use ($\lambda = 0.390$), and cognitive dysfunction ($\lambda = 0.134$). Standardized factor loadings and standard errors for the higher-order factor model estimated in the full sample are presented in Table 5.2. Absolute and incremental model-fit statistics for the measurement model (Model 0) and all bivariate SEMs estimated in the full sample (Models 1-15) are provided in Table 5.3.

Figure 5.1

Simplified path diagram of the higher-order measurement model estimated in the full sample of older adults from the UK Biobank who were of European ancestry and free of dementia at baseline



Note. This figure depicts the higher-order measurement model estimated in the full sample of older adults from the UK Biobank, replicating the best-fitting factor model from **Chapter 3** in participants of European ancestry and free of dementia at baseline. Latent factors are represented as ellipses, including a general higher-order factor defined by the shared variance of four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction). Standardized factor loadings of lower-order dimensions on the general higher-order factor are shown. Observed indicators that defined the lower-order dimensions are omitted, as are paths to covariates (i.e., age and years of education). The higher-order model was estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017).

Table 5.1

Participant characteristics for the full sample and the four age-stratified subsamples

		Full sample		55-59 years old		60-64 years old		65-69 years old		70-78 years old	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age		65.09	5.18	57.47	1.19	62.08	1.41	66.92	1.34	72.02	1.74
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male		60,914	55.5	12,131	61.4	16,894	58.0	19,628	54.4	12,261	49.3
Female		48,930	44.5	7,642	38.6	12,244	42.0	16,454	45.6	12,590	50.7
Education		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	7 years	9,162	8.3	711	3.6	1,593	5.5	3,565	9.9	3,293	13.3
	10 years	15,729	14.3	2,662	13.5	3,825	13.1	5,422	15.0	3,820	15.4
	13 years	6,663	6.1	1,345	6.8	1,885	6.5	2,068	5.7	1,365	5.5

		Full sample		55-59 years old		60-64 years old		65-69 years old		70-78 years old	
	15 years	15,340	14.0	2,249	11.4	3,808	13.1	5,272	14.6	4,011	16.1
	19 years	14,125	12.9	3,002	15.2	3,965	13.6	4,413	12.2	2,745	11.0
	20 years	48,286	44.0	9,713	49.1	13,924	47.8	15,183	42.1	9,466	38.1
Dementia		788	0.7	19	0.1	60	0.2	249	0.7	460	1.9

Note. This table presents participant characteristics for the full sample (N = 109,844) and for each of the four age-stratified subsamples. Final analytic sample sizes varied slightly due to model-specific exclusions relating to missing data on certain external predictors (e.g., the AD-PGS, years of education). Descriptive statistics are thus presented for the full and age-stratified samples only. Baseline age was determined as the age at which participants completed the online cognitive assessments.

Table 5.2

Standardized factor loadings and standard errors for the higher-order model

Indicators of psychopathology and cognitive function	λ	SE
Internalizing		
Indicators of depression		
Recent feelings of depression	**0.875**	0.001
Recent lack of interest/pleasure in doing things	**0.853**	0.002
Recent changes in speed/amount of moving or speaking	**0.695**	0.004
Recent feelings of inadequacy	**0.786**	0.002
Recent tiredness or low energy	**0.686**	0.002
Recent poor appetite or overeating	**0.655**	0.003
Recent trouble concentrating	**0.737**	0.003
Recent trouble falling/staying asleep or sleeping too much	**0.592**	0.003
Indicators of anxiety		
Recent feelings of nervousness or anxiety	**0.867**	0.001
Ever worried more than most would in similar situation	**0.639**	0.004
Recent ease of annoyance or irritability	**0.728**	0.002
Recent feelings of foreboding	**0.803**	0.002
Recent inability to stop or control worrying	**0.938**	0.001
Recent restlessness	**0.734**	0.003
Recent trouble relaxing	**0.841**	0.002
Recent worrying too much about different things	**0.906**	0.001
Indicators of suicidality/self-harm		
Recent thoughts of suicide or self-harm	**0.767**	0.004
Self-harmed in past year	**0.536**	0.020
Indicators of post-traumatic stress		
Repeated disturbing thoughts of past stressful experience	**0.693**	0.002
Felt very upset when reminded of past stressful experience	**0.694**	0.002
Avoided activities/situations because of past stressful experience	**0.623**	0.003
Addictions and substance use		
Indicators of alcohol use		

Indicators of psychopathology and cognitive function	λ	SE
Frequency of inability to cease drinking	**0.858**	0.004
Frequency of failure to fulfil normal expectations due to drinking	**0.818**	0.006
Frequency of guilt/remorse after drinking	**0.839**	0.004
Frequency of needing a morning drink after heavy drinking session	**0.783**	0.018
Frequency of memory loss due to drinking	**0.781**	0.005
Been injured or injured someone else through drinking	**0.580**	0.009
Known person ever concerned about/recommend a reduction in drinking	**0.707**	0.005
Indicators of addiction		
Ever addicted to a behavior or miscellaneous	**0.539**	0.016
Ever addicted to alcohol	**0.818**	0.007
Ever addicted to illicit or recreational drugs	**0.761**	0.023
Ever addicted to prescription or over-the-counter medication	**0.612**	0.018
Indicators of cannabis use		
Frequency of taking cannabis	**0.364**	0.007
Thought disorder		
Indicators of psychosis		
Ever believed an un-real conspiracy against self	**0.718**	0.017
Ever believed in un-real communications or signs	**0.590**	0.017
Ever heard an un-real voice	**0.609**	0.013
Ever seen an un-real vision	**0.507**	0.011
Indicators of Mania		
Ever had a prolonged period of mania/excitability	**0.837**	0.009
Ever had a period of extreme irritability	**0.660**	0.010
Cognitive dysfunction		
Indicators of cognitive dysfunction		
Fluid Intelligence	**0.516**	0.004
Symbol Digit Substitution	**0.683**	0.003
Numeric Memory	**0.376**	0.004
Trail Making Task A	**0.672**	0.003
Trail Making Task B	**0.851**	0.003
Lower-order dimensions		

Indicators of psychopathology and cognitive function	λ	SE
Loadings on the general factor		
Internalizing	**0.718**	0.009
Addictions and substance use	**0.390**	0.007
Thought disorder	**0.757**	0.011
Cognition	0.134	0.006

Note. This table presents the standardized factor loadings and standard errors for the higher-order model estimated in the full sample. The model was estimated via confirmatory factor analysis, using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). All participants were aged 55-78 years old at the time of completing online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. Factor loadings that are positive in direction and substantial in magnitude (i.e., $\lambda > 0.3$) are denoted in bold text.

Table 5.3

Model-fit statistics for the higher-order measurement model and structural equation models estimated in the full sample

	CFI	TLI	RMSEA
Measurement model			
Model 0	**0.935**	**0.931**	**0.041**
Structural equation models			
Model 1	**0.935**	**0.932**	**0.040**
Model 2	**0.935**	**0.932**	**0.040**
Model 3	**0.936**	**0.932**	**0.039**
Model 4	**0.935**	**0.932**	**0.040**
Model 5	**0.936**	**0.932**	**0.040**
Model 6	**0.935**	**0.932**	**0.040**
Model 7	**0.936**	**0.933**	**0.040**
Model 8	**0.936**	**0.932**	**0.040**
Model 9	**0.937**	**0.933**	**0.040**
Model 10	**0.937**	**0.933**	**0.040**
Model 11	**0.937**	**0.933**	**0.040**
Model 12	**0.936**	**0.932**	**0.039**
Model 13	**0.937**	**0.934**	**0.039**
Model 14	**0.937**	**0.933**	**0.039**
Model 15	**0.938**	**0.935**	**0.039**

Note. CFI, Comparative Fit Index; TLI, Tucker Lewis Index; RMSEA, Root Mean Square Error of Approximation. This table presents the model-fit statistics for the measurement model and the 15 structural equation models (SEMs) estimated to examine associations with polygenic scores for Alzheimer's Disease (AD-PGS) and all-cause incident dementia in the full sample of older adults from the UK Biobank. Model 0 is the higher-order measurement model. Model 1 is the SEM regressing the binary all-cause incident dementia variable on the general higher-order factor. Model 2 is the SEM regressing the general higher-order factor on the AD-PGS. Model 3 is the SEM examining indirect effects of the AD-PGS on dementia status via the general higher-order factor. Models 4-7 are the SEMs regressing incident dementia on internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. Models 8-11 are the SEMs regressing internalizing, addictions and substance use, thought disorder, and cognitive dysfunction on the AD-PGS, respectively. Models 12-15 are the SEMs examining indirect effects of the AD-PGS on dementia status via internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. All models were estimated in Mplus version 8.10 (Muthén & Muthén, 2017) using weighted least squares mean variance (WLSMV) estimation and DELTA parameterization. All SEMs controlled for age and years of education.

5.4.1.2 Bivariate associations with the general higher-order factor estimated in the full sample

The results of SEMs examining bivariate associations between the higher-order general dimension, the AD-PGS, and all-cause incident dementia in the full sample are presented in Table 5.4 (Models 1-3). The general higher-order dimension was significantly positively associated with all-cause incident dementia but showed no association with the AD-PGS in the full sample. There was a significant direct effect of the AD-PGS on incident dementia but no evidence that the general higher-order dimension mediated this relationship.

5.4.1.3 Bivariate associations with lower-order dimensions of psychopathology and cognitive dysfunction estimated in the full sample

The results of SEMs examining bivariate associations between lower-order dimensions, the AD-PGS, and all-cause incident dementia in the full sample are presented in Table 5.4 (Models 4-15). The lower-order dimensions of internalizing, addictions and substance use, thought disorder, and cognitive dysfunction were all significantly positively associated with incident dementia in the full sample. The AD-PGS was significantly positively associated with cognitive dysfunction but showed no association with internalizing, addictions and substance use, or thought disorder dimensions. There was a significant direct effect of the AD-PGS on incident dementia in all SEMs examining indirect effects via lower-order dimensions. Cognitive dysfunction partially mediated the relationship between the AD-PGS and incident dementia (i.e., the AD-PGS was indirectly positively associated with incident dementia via its positive association with cognitive dysfunction), accounting for 4.52% of the total effect (Figure 5.2) in the full sample. There was no evidence that internalizing, addictions and substance use, or thought disorder mediated the relationship between the AD-PGS and incident dementia in the full sample.

Table 5.4

Bivariate associations between transdiagnostic dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia examined in the full sample

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Bivariate associations with the general higher-order dimension							
Model 1	Main effect	General factor	-	Incident dementia	**0.183**	**0.018**	**< 0.001**
Model 2	Main effect	AD-PGS	-	General factor	0.005	0.004	0.236
Bivariate mediation model with the general higher-order dimension							
Model 3	Direct effect	AD-PGS	-	Incident dementia	**0.198**	**0.010**	**< 0.001**
	Indirect effect	AD-PGS	General psychopathology	Incident dementia	0.001	0.001	0.239
	Total effect	AD-PGS	General psychopathology	Incident dementia	**0.199**	**0.010**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Bivariate associations with lower-order dimensions							
Model 4	Main effect	Internalizing	-	Incident dementia	**0.139**	**0.014**	**< 0.001**
Model 5	Main effect	Addictions and substance use	-	Incident dementia	**0.219**	**0.025**	**< 0.001**
Model 6	Main effect	Thought disorder	-	Incident dementia	**0.215**	**0.022**	**< 0.001**
Model 7	Main effect	Cognitive dysfunction	-	Incident dementia	**0.284**	**0.022**	**< 0.001**
Model 8	Main effect	AD-PGS	-	Internalizing	0.004	0.003	0.275
Model 9	Main effect	AD-PGS	-	Addictions and substance use	-0.002	0.005	0.626
Model 10	Main effect	AD-PGS	-	Thought disorder	-0.011	0.005	0.062
Model 11	Main effect	AD-PGS	-	Cognitive dysfunction	**0.034**	**0.004**	**< 0.001**

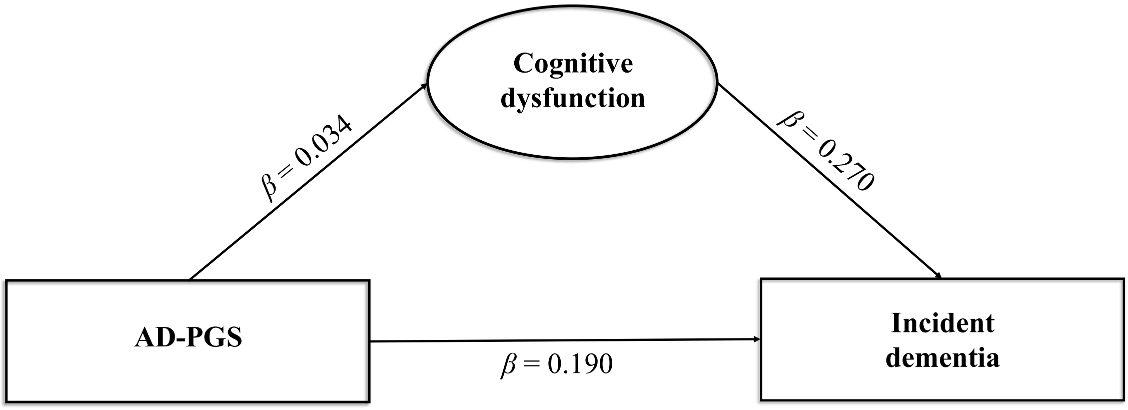
SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Bivariate mediation models with lower-order dimensions							
Models 12	Direct effect	AD-PGS	-	Incident dementia	**0.198**	**0.010**	**< 0.001**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.001	0.0008	0.275
	Total effect	AD-PGS	Internalizing	Incident dementia	**0.199**	**0.010**	**< 0.001**
Model 13	Direct effect	AD-PGS	-	Incident dementia	**0.199**	**0.010**	**< 0.001**
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	-0.001	0.001	0.626
	Total effect	AD-PGS	Addictions and substance use	Incident dementia	**0.199**	**0.010**	**< 0.001**
Model 14	Direct effect	AD-PGS	-	Incident dementia	**0.201**	**0.010**	**< 0.001**
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	-0.002	0.001	0.064
	Total effect	AD-PGS	Thought disorder	Incident dementia	**0.199**	**0.010**	**< 0.001**
Model 15	Direct effect	AD-PGS	-	Incident dementia	**0.190**	**0.001**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.009**	**0.001**	**< 0.001**
	Total effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.199**	**0.010**	**< 0.001**

Note. AD-PGS, Alzheimer's disease polygenic scores; SEM, Structural equation model. This table presents the standardized results from SEMs examining bivariate associations between transdiagnostic dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia, in the full sample of participants aged 55-78 years old from the UK Biobank. Model 1 is the SEM regressing the binary all-cause incident dementia variable on the general higher-order factor. Model 2 is the SEM regressing the general higher-order factor on the AD-PGS. Model 3 is the SEM examining indirect effects of the AD-PGS on dementia status via the general higher-order factor. Models 4-7 are the SEMs regressing incident dementia on internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. Models 8-11 are the SEMs regressing internalizing, addictions and substance use, thought disorder, and cognitive dysfunction on the AD-PGS, respectively. Models 12-15 are the SEMs examining indirect effects of the AD-PGS on dementia status via internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. All models were estimated in Mplus version 8.10 (Muthén & Muthén, 2017) using weighted-least squares (WLSMV) estimation and DELTA parameterization. All SEMs controlled for age and years of education. All p-values for main and indirect effects are False Discovery Rate (FDR) corrected. Significant associations are reported in bold text. Effect sizes for binary dementia outcomes are presented as probit regression coefficients rather than odds ratios, as WLSMV estimation in Mplus models categorical outcomes using a probit link function.

Figure 5.2

Simplified path diagram for the bivariate model examining whether cognitive dysfunction mediates the relationship between the AD-PGS and all-cause incident dementia in the full sample



Indirect effect: β = 0.009

Proportion of total effect mediated by cognitive dysfunction: 4.52%

Note. AD-PGS, Alzheimer's disease polygenic score. This figure presents a simplified path diagram illustrating the bivariate structural equation model in which cognitive dysfunction was found to significantly mediate the relationship between the AD-PGS and incident dementia in the full sample. Standardized estimates are presented for the direct path from the AD-PGS to cognitive dysfunction, from cognitive dysfunction to incident dementia, and from the AD-PGS to incident dementia. The standardized indirect effects and the proportion of the total effect mediated by cognitive dysfunction are also shown. The general higher-order dimension and lower-order dimensions of psychopathology included in the full measurement model are omitted to improve visual interpretability. Age and years of education were included as covariates in the model but are also not depicted in the figure. This model was estimated using weighted least squares mean variance (WLSMV) and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017).

5.4.2 Secondary analyses

5.4.2.1 Multigroup measurement invariance testing

As in **Chapter 3**, an alcohol use indicator (i.e., needing a morning drink after a heavy drinking session) and an internalizing indicator (i.e., self-harmed past year) had zero-cells in their bivariate correlation tables with several other indicators in participants aged 70-78 years old and were thus dropped from the models prior to invariance testing (Hoy et al., 2025a). Results from multigroup measurement invariance testing were consistent with **Chapter 3** and are presented in the supplementary material (Appendix H, Table S1). The configural invariance model demonstrated acceptable model-fit (CFI = 0.934; RMSEA = 0.044). The lower-order scalar invariance model also demonstrated acceptable model-fit (CFI = 0.940; RMSEA = 0.040) and a slight increase in CFI values compared to the configural invariance model (i.e., CFI increased by 0.06). The higher-order scalar invariance model also demonstrated acceptable model-fit (CFI = 0.940; RMSEA = 0.040) and no change in CFI value relative to the lower-order scalar invariance model. Changes in CFI values were within the two recommended thresholds (Cheung & Rensvold, 2002; Meade et al., 2008), indicating that the higher-order model was invariant across age groups. Differences in the latent means were consistent with the results from **Chapter 3** and are presented in the supplementary material (Appendix H, Table S1).

5.4.2.2 Age-specific differences in associations with the general higher-order factor

Model-fit statistics for all SEMs examining bivariate associations with the general higher-order dimension across the four age groups are provided in the supplementary material (Appendix, H, Table S2; Models 16-18). The results of SEMs examining bivariate associations between the general higher-order dimension, the AD-PGS, and incident dementia across each of the four age groups are presented in Table 5.5 (Models 16-18). The general higher-order factor was significantly positively associated with incident dementia in all age groups (i.e., 55-59, 60-64, 65-69, and 70-78 years old). There was no evidence of an association between the AD-PGS and the general factor across any age group. There was a significant direct effect of the AD-PGS on incident dementia across age groups but the general factor did not mediate this relationship in any age group.

5.4.2.3 Age-specific differences in bivariate associations with the lower-order dimensions of psychopathology and cognitive dysfunction

Model-fit statistics for all SEMs examining bivariate associations with lower-order dimensions across the four age groups are provided in the supplementary material (Appendix H, Table S2; Models 19-30). The results of SEMs examining bivariate associations between lower-order dimensions, the AD-PGS, and incident dementia across each age group are presented in Table 5.5 (Models 19-30). The internalizing, addictions and substance use, and thought disorder dimensions were significantly positively associated with incident dementia across all age groups. The cognitive dysfunction dimension showed no evidence of an association with incident dementia in the youngest age group (i.e., 55-59 years old) but was significantly positively associated with incident dementia in the three oldest age groups (i.e., 60-64, 65-69, and 70-78 years old). The AD-PGS was also not associated with cognitive dysfunction in the youngest age group (i.e., 55-59 years old) but was significantly positively associated with incident dementia in the three oldest age groups. The AD-PGS was not significantly associated with internalizing, addictions and substance use, or thought disorder across any age group. There was a significant direct effect of the AD-PGS on incident dementia in all SEMs examining indirect effects via lower-order dimensions across age groups. There was evidence that cognitive dysfunction partially mediated the relationship between the AD-PGS and incident dementia (i.e., the AD-PGS was indirectly positively associated with incident dementia via its positive association with cognitive dysfunction) in the three oldest age groups but not in the youngest age group. Across the three oldest age groups, cognitive dysfunction accounted for 10.53% (ages 60-64 years old), 5.21% (ages 65-69 years old), and 6.50% (ages 70-78 years old) of the total effect (Figure 5.3). There was no evidence that internalizing, addictions and substance use, or thought disorder mediated the relationship between the AD-PGS and incident dementia across any age group.

Table 5.5

Bivariate associations between transdiagnostic dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia examined across the four age-stratified subsamples

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Bivariate associations with the general higher-order dimension							
Model 16							
55-59 years old	Main effect	General factor	-	Incident dementia	**0.254**	**0.075**	**0.009**
60-64 years old	Main effect	General factor	-	Incident dementia	**0.157**	**0.055**	**0.018**
65-69 years old	Main effect	General factor	-	Incident dementia	**0.202**	**0.033**	**< 0.001**
70-78 years old	Main effect	General factor	-	Incident dementia	**0.195**	**0.028**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Model 17							
55-59 years old	Main effect	AD-PGS	-	General factor	0.014	0.010	0.175
60-64 years old	Main effect	AD-PGS	-	General factor	0.001	0.009	0.930
65-69 years old	Main effect	AD-PGS	-	General factor	0.003	0.008	0.742
70-78 years old	Main effect	AD-PGS	-	General factor	0.008	0.010	0.389
Bivariate mediation model with general higher-order dimension							
Model 18							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.133**	**0.048**	**0.006**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Indirect effect	AD-PGS	General psychopathology	Incident dementia	0.003	0.003	0.430
	Total effect	AD-PGS	General psychopathology	Incident dementia	**0.136**	**0.048**	**0.005**
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.114**	**0.033**	**0.001**
	Indirect effect	AD-PGS	General psychopathology	Incident dementia	0.0001	0.001	0.758
	Total effect	AD-PGS	General psychopathology	Incident dementia	**0.114**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.192**	**0.019**	**< 0.001**
	Indirect effect	AD-PGS	General psychopathology	Incident dementia	0.001	0.002	0.871
	Total effect	AD-PGS	General psychopathology	Incident dementia	**0.193**	**0.019**	**< 0.001**
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.244**	**0.015**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Indirect effect	AD-PGS	General psychopathology	Incident dementia	0.002	0.002	0.461
	Total effect	AD-PGS	General psychopathology	Incident dementia	**0.246**	**0.015**	**< 0.001**
Bivariate associations with lower-order dimensions							
Model 19							
55-59 years old	Main effect	Internalizing	-	Incident dementia	**0.181**	**0.063**	**0.023**
60-64 years old	Main effect	Internalizing	-	Incident dementia	**0.117**	**0.042**	**0.018**
65-69 years old	Main effect	Internalizing	-	Incident dementia	**0.153**	**0.025**	**< 0.001**
70-78 years old	Main effect	Internalizing	-	Incident dementia	**0.146**	**0.021**	**< 0.001**
Model 20							

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
55-59 years old	Main effect	Addictions and substance use	-	Incident dementia	**0.294**	**0.073**	**0.014**
60-64 years old	Main effect	Addictions and substance use	-	Incident dementia	**0.190**	**0.072**	**0.024**
65-69 years old	Main effect	Addictions and substance use	-	Incident dementia	**0.221**	**0.043**	**< 0.001**
70-78 years old	Main effect	Addictions and substance use	-	Incident dementia	**0.212**	**0.035**	**< 0.001**
Model 21							
55-59 years old	Main effect	Thought disorder	-	Incident dementia	**0.282**	**0.076**	**0.003**
60-64 years old	Main effect	Thought disorder	-	Incident dementia	**0.178**	**0.065**	**0.018**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
65-69 years old	Main effect	Thought disorder	-	Incident dementia	**0.237**	**0.039**	**< 0.001**
70-78 years old	Main effect	Thought disorder	-	Incident dementia	**0.223**	**0.034**	**< 0.001**
Model 22							
55-59 years old	Main effect	Cognitive dysfunction	-	Incident dementia	0.255	0.103	0.059
60-64 years old	Main effect	Cognitive dysfunction	-	Incident dementia	**0.357**	**0.056**	**< 0.001**
65-69 years old	Main effect	Cognitive dysfunction	-	Incident dementia	**0.258**	**0.036**	**< 0.001**
70-78 years old	Main effect	Cognitive dysfunction	-	Incident dementia	**0.302**	**0.031**	**< 0.001**
Model 23							

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
55-59 years old	Main effect	AD-PGS	-	Internalizing	0.009	0.008	0.479
60-64 years old	Main effect	AD-PGS	-	Internalizing	0.003	0.007	0.758
65-69 years old	Main effect	AD-PGS	-	Internalizing	0.002	0.006	0.871
70-78 years old	Main effect	AD-PGS	-	Internalizing	0.006	0.007	0.461
Model 24							
55-59 years old	Main effect	AD-PGS	-	Addictions and substance use	0.010	0.011	0.537
60-64 years old	Main effect	AD-PGS	-	Addictions and substance use	-0.018	0.009	0.113

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
65-69 years old	Main effect	AD-PGS	-	Addictions and substance use	0.004	0.009	0.871
70-78 years old	Main effect	AD-PGS	-	Addictions and substance use	-0.005	0.011	0.719
Model 25							
55-59 years old	Main effect	AD-PGS	-	Thought disorder	0.008	0.011	0.550
60-64 years old	Main effect	AD-PGS	-	Thought disorder	-0.014	0.010	0.249
65-69 years old	Main effect	AD-PGS	-	Thought disorder	-0.020	0.009	0.058
70-78 years old	Main effect	AD-PGS	-	Thought disorder	-0.015	0.011	0.364
Model 26							

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
55-59 years old	Main effect	AD-PGS	-	Cognitive dysfunction	0.021	0.011	0.138
60-64 years old	Main effect	AD-PGS	-	Cognitive dysfunction	**0.034**	**0.008**	**< 0.001**
65-69 years old	Main effect	AD-PGS	-	Cognitive dysfunction	**0.039**	**0.008**	**< 0.001**
70-78 years old	Main effect	AD-PGS	-	Cognitive dysfunction	**0.055**	**0.009**	**< 0.001**
Bivariate mediation models with lower-order dimensions							
Model 27							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.134**	**0.048**	**0.005**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.001	0.001	0.535

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Total effect	AD-PGS	Internalizing	Incident dementia	**0.136**	**0.048**	**0.005**
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.114**	**0.033**	**0.001**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.0004	0.001	0.758
	Total effect	AD-PGS	Internalizing	Incident dementia	**0.1144**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.193**	**0.019**	**< 0.001**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.0003	0.001	0.871
	Total effect	AD-PGS	Internalizing	Incident dementia	**0.1933**	**0.019**	**< 0.001**
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.244**	**0.015**	**< 0.001**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.001	0.001	0.461

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Total effect	AD-PGS	Internalizing	Incident dementia	**0.245**	**0.015**	**< 0.001**
Model 28							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.133**	**0.048**	**0.006**
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	0.003	0.003	0.539
	Total effect	AD-PGS	Addictions and substance use	Incident dementia	**0.136**	**0.048**	**0.005**
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.117**	**0.034**	**< 0.001**
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	-0.003	0.002	0.249
	Total effect	AD-PGS	Addictions and substance use	Incident dementia	**0.113**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.192**	**0.019**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	0.001	0.002	0.871
	Total effect	AD-PGS	Addictions and substance use	Incident dementia	**0.193**	**0.019**	**< 0.001**
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.247**	**0.015**	**< 0.001**
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	-0.001	0.002	0.718
	Total effect	AD-PGS	Addictions and substance use	Incident dementia	**0.246**	**0.015**	**< 0.001**
Model 29							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.134**	**0.048**	**0.006**
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	0.002	0.003	0.550
	Total effect	AD-PGS	Thought disorder	Incident dementia	**0.136**	**0.048**	**0.005**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.116**	**0.034**	**0.001**
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	-0.002	0.002	0.334
	Total effect	AD-PGS	Thought disorder	Incident dementia	**0.114**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.197**	**0.019**	**< 0.001**
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	-0.005	0.002	0.069
	Total effect	AD-PGS	Thought disorder	Incident dementia	**0.193**	**0.019**	**< 0.001**
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.249**	**0.015**	**< 0.001**
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	-0.003	0.002	0.364
	Total effect	AD-PGS	Thought disorder	Incident dementia	**0.245**	**0.015**	**< 0.001**

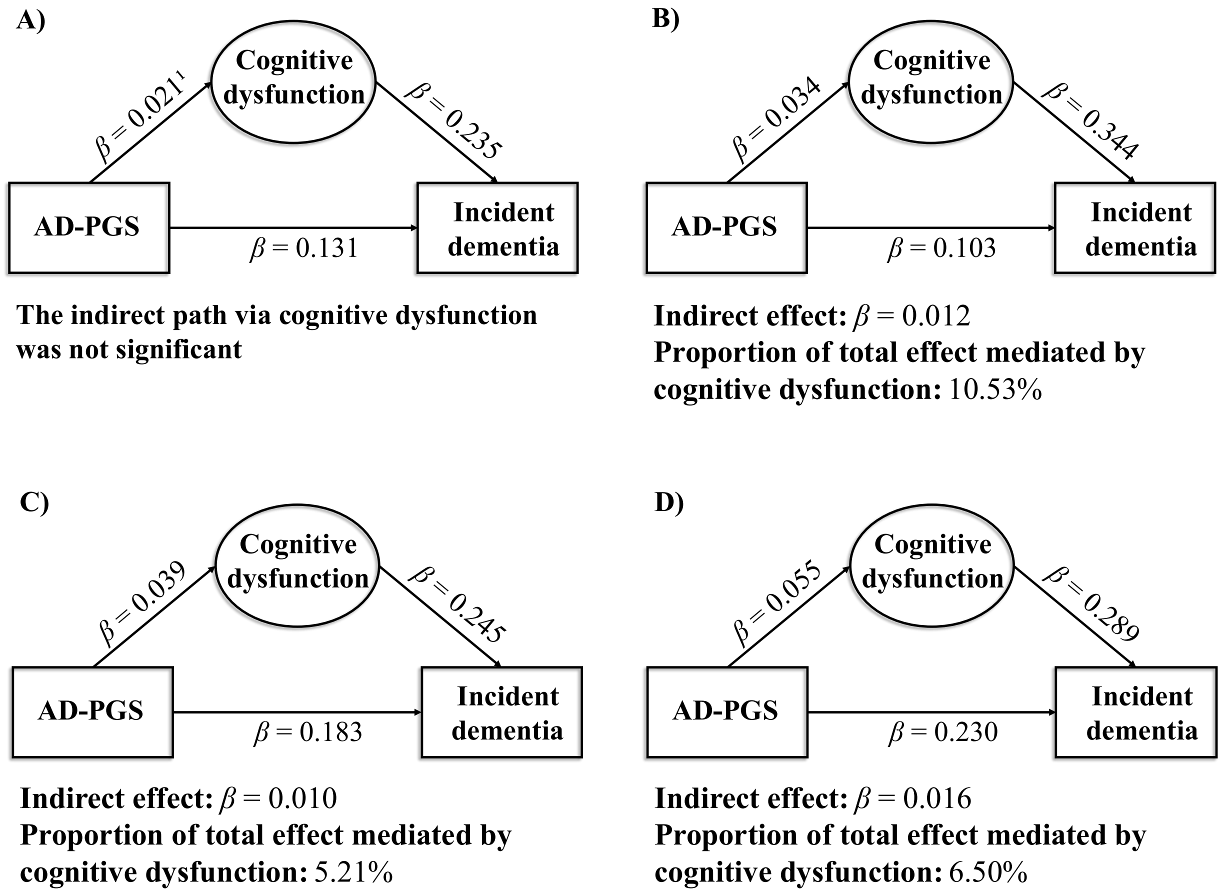
SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Model 30							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.131**	**0.048**	**0.007**
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	0.005	0.003	0.354
	Total effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.136**	**0.048**	**0.005**
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.103**	**0.034**	**0.002**
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.012**	**0.003**	**0.005**
	Total effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.114**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.183**	**0.019**	**< 0.001**
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.010**	**0.002**	**< 0.001**
	Total effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.192**	**0.019**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.230**	**0.015**	**< 0.001**
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.016**	**0.003**	**< 0.001**
	Total effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.246**	**0.015**	**< 0.001**

Note. AD-PGS, Alzheimer's disease polygenic scores; SEM, Structural equation model This table presents the standardized results of bivariate analyses examining associations between lower-order dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia across age groups. Participants were stratified by age into four categories, including: 55-59 years old, 60-64 years old, 65-69 years old, and 70-78 years old. SEMs examining associations with the general factor were estimated using the higher-order metric/scalar invariance model from secondary analyses. SEMs examining associations with lower-order factors were estimated using the lower-order metric/scalar invariance model from secondary analyses. Model 16 is the SEM regressing the binary all-cause incident dementia variable on the general higher-order factor across age groups. Model 17 is the SEM regressing the general higher-order factor on the AD-PGS on across age groups. Model 18 is the SEM examining indirect effects of the AD-PGS on dementia status via the general higher-order factor across age groups. Models 19-22 are the SEMs regressing incident dementia on internalizing, addictions and substance use, thought disorder, and cognitive dysfunction across age groups, respectively. Models 23-26 are the SEMs regressing internalizing, addictions and substance use, thought disorder, and cognitive dysfunction on the AD-PGS across age groups, respectively. Models 27-30 are the SEMs examining indirect effects of the AD-PGS on incident dementia via internalizing, addictions and substance use, thought disorder, and cognitive dysfunction across age groups, respectively. All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). Analyses were restricted to participants that were aged 55-78 years old at the time of completing the online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. All models controlled for years of education. There were n = 788 participants with dementia in the full sample, which included: n = 19 in those aged 55-59 years old; n = 60 in those aged 60-64 years old; n = 249 in those aged 65-69 years old; and n = 460 in those aged 70-78 years old. All p-values for main and indirect effects are false discovery rate (FDR) corrected. Significant associations are denoted in bold text. Effect sizes for binary dementia outcomes are presented as probit regression coefficients rather than odds ratios, as WLSMV estimation in Mplus models categorical outcomes using a probit link function.

Figure 5.3

Simplified path diagrams for bivariate models examining whether cognitive dysfunction mediates the relationship between the AD-PGS and all-cause incident dementia across the four age-stratified subsamples



Note. AD-PGS, Alzheimer's disease polygenic score. This figure presents simplified path diagrams illustrating structural equation models examining whether cognitive dysfunction mediates the relationship between the AD-PGS and incident dementia across the four age-stratified subsamples: A) 55–59 years old; B) 60–64 years old; C) 65–69 years old; and D) 70–78 years old. Standardized estimates are presented for the direct paths from the AD-PGS to cognitive dysfunction, from cognitive dysfunction to incident dementia, and from the AD-PGS to incident dementia. Standardized indirect effects and the proportion of the total effect mediated by cognitive dysfunction are also shown. The general higher-order dimension and lower-order dimensions of psychopathology included in the full measurement model are omitted to improve visual interpretability. Years of education was included as a covariate in all models but is not depicted in the figure. All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017).

[1] This path was not significant following Benjamini-Hochberg false discovery rate (FDR) correction.

5.4.2.4 Multivariable associations with lower-order dimensions of psychopathology and cognitive dysfunction in the full sample

Model-fit statistics for all multivariable SEMs are provided in the supplementary material (Appendix H, Table S3; Models S1-S6). The results of multivariable analyses examining associations between lower-order dimensions, the AD-PGS, and incident dementia in the full sample are presented in Appendix H (Table S4; Models S1-S3). The lower-order dimensions of internalizing and cognitive dysfunction were significantly positively associated with all-cause incident dementia, whilst the addictions and substance use and thought disorder dimensions no longer showed evidence of an association when other lower-order factors were included in the model. The AD-PGS remained significantly positively associated with cognitive dysfunction and again showed no association with internalizing, addictions and substance use, or thought disorder dimensions. As in the primary analysis, there was a significant direct effect of the AD-PGS on all-cause incident dementia and a significant indirect effect on this relationship via cognitive dysfunction (i.e., the AD-PGS was indirectly positively associated with incident dementia via its positive association with cognitive dysfunction). There was no evidence that internalizing, addictions and substance use, or thought disorder mediated the relationship between the AD-PGS and incident dementia.

5.4.2.5 Age-specific differences in multivariable associations with lower-order dimensions of psychopathology and cognitive dysfunction

The results of multivariable analyses examining associations between lower-order dimensions, the AD-PGS, and incident dementia across the four age groups (i.e., 55-59, 60-64, 65-69, and 70-78 years old) are presented in Appendix H (Table S5; Models S4-S6). The internalizing dimension was not associated with incident dementia in the two youngest age groups (i.e., 55-59 and 60-64 years old) but was significantly positively associated with incident dementia in the two oldest age groups (i.e., 65-69 and 70-78 years old). The addictions and substance use dimension was not associated with incident dementia across any age group. The thought disorder dimension was significantly positively associated with incident dementia in the youngest age group (i.e., 55-59 years old) and significantly *negatively* associated with incident dementia in the oldest age group (i.e., 70-78 years old) but showed no association in the remaining two age groups. The cognitive dysfunction dimension was not associated with incident dementia in the youngest age group (i.e., 55-59 years old) but was significantly positively associated with incident dementia in the three oldest age groups. The AD-PGS was significantly positively associated with cognitive dysfunction in the three oldest age groups (i.e., 60-64, 65-69, and 70-78 years old) but showed no association with cognitive dysfunction in the youngest age group. The AD-PGS was not significantly associated with internalizing, addictions and substance use, or thought disorder in any age group. Cognitive dysfunction partially mediated the relationship between the AD-PGS and incident dementia (i.e., that AD-PGS was indirectly positively associated with incident dementia via its positive association with cognitive dysfunction) in participants aged 60-64, 65-69, and 70-78 years old but not in participants aged 55-59 years old. There was no evidence that internalizing, addictions and substance use, or thought disorder dimensions mediated the relationship between the AD-PGS and incident dementia across any age group.

5.5 Discussion

This study examined the relationships between transdiagnostic dimensions of psychopathology, cognitive dysfunction, all-cause incident dementia, and polygenetic risk for AD in a large sample of older adults from the UK Biobank. A higher-order model of psychopathology demonstrated acceptable model-fit in participants aged 55-78 years old who were free of dementia and of European ancestry. Several novel results emerged from this study, including: 1) that general and lower-order dimensions of psychopathology and cognitive dysfunction are positively associated with all-cause incident dementia in older adulthood; 2) that polygenetic risk for AD is associated with cognitive dysfunction but not with transdiagnostic dimensions of psychopathology or with a general higher-order factor capturing the shared variance between psychopathology and cognitive dysfunction; 3) that cognitive dysfunction mediates the relationship between polygenetic risk for AD and incident dementia; 4) that there are age-specific differences in the nature of these relationship throughout older adulthood; and 5) that some relationships between lower-order dimensions, incident dementia, and polygenetic risk for AD are maintained even when controlling for the effects of other lower-order psychiatric and cognitive phenotypes.

5.5.1 Relationships between transdiagnostic dimensions and all-cause incident dementia in the full sample

The general higher-order factor was significantly positively associated with all-cause incident dementia in the full sample. This finding adds to an extensive body of evidence indicating that general factors are associated with a range of adverse outcomes in younger samples (Conway et al., 2019a; Pettersson et al., 2018; Sallis et al., 2019; Smith et al., 2020), demonstrating that they are likewise associated with important age-specific outcomes in older adulthood. Importantly, the general factor in this study was defined by the shared variance of lower-order dimensions capturing both psychopathology *and* cognitive dysfunction. The observed positive relationship with incident dementia thus suggests the possibility of shared risk factors underlying mental illness and cognition that contribute to dementia risk in older adulthood; however, polygenetic risk for AD was not identified as a shared risk factor in the current study (discussed further below). The findings of this study also have important implications for strategies aiming to reduce the risk (or delay the onset) of dementia in older adulthood. Several studies have identified both cognition and mental illness as modifiable risk factors for dementia (Duffner et al., 2022; Gimson et al., 2018; Zhang et al., 2022) and meta-analytic evidence indicates that multiple risk factors can exert a cumulative impact the risk of subsequent dementia diagnoses (Peters et al., 2019). The observed association between the general higher-order factor and incident dementia suggests that transdiagnostic intervention strategies (i.e., simultaneously targeting broad psychopathology and cognitive function) may hold utility in reducing the risk of dementia in older adulthood.

Primary analyses further demonstrated that each of the lower-order latent dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction) were positively associated with all-cause incident dementia in the full sample. The observed association between cognitive dysfunction and incident dementia in this study is consistent with prior research indicating that poorer performance on neurocognitive tests is associated with subsequent dementia diagnoses in the general population (Calvin et al., 2019; Hayat et al., 2021). The results of this study are further consistent with several well-powered population-based studies indicating that multiple psychiatric disorders are non-specifically associated with increased risk of subsequent dementia diagnoses. For instance, one recent study found that a range of psychiatric disorders (including substance use, psychotic, mood, personality, and developmental disorders) were associated with increased risk of dementia in over 1.7 million people from New Zealand over a 30 year follow-up period (Richmond-Rakerd et al., 2022), consistent with the non-specificity of associations between transdiagnostic dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) and incident dementia in the current study. This study extends these findings by demonstrating a transdiagnostic association between psychopathology and incident dementia based on symptom-level phenotypes in the general population (as opposed to clinical diagnoses) and by demonstrating this predictive relationship over a much shorter period of observation.

It is important to note that the dimensions of psychopathology in this study were derived from a higher-order model, in which the lower-order factors were allowed to correlate with one another. One criticism of higher-order models is that this shared variance among lower-order factors can mask the extent to which identified associations with external criteria represent unique relationships with a given phenotype. To address these limitations, multivariable analyses were conducted in which all lower-order dimensions were simultaneously entered into SEMs examining associations with incident dementia and the AD-PGS. These analyses found that internalizing and cognitive dysfunction were positively associated with incident dementia even when controlling for the variance shared with other lower-order factors. The relationship between cognitive dysfunction and incident dementia is well-established (Calvin et al., 2019; Hayat et al., 2021); however, the current study extends this research by demonstrating that the relationship exists over and above the influence of several transdiagnostic dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder). The unique relationship between internalizing and incident dementia in the current study is also consistent with several studies indicating that internalizing-related psychopathologies (e.g., depression, anxiety) are associated with subsequent dementia diagnoses (Gulpers et al., 2016; Saczynski et al., 2010; Singh-Manoux et al., 2017; Skogen et al., 2015; Yaffe, 2012). The present study adds to this literature by demonstrating that the association with internalizing exists over and above the influence of not only other dimensions of psychopathology but also of cognitive dysfunction. This finding points to a robust association between internalizing and incident dementia in older adulthood and further highlights the utility of hierarchical dimensional models in disentangling the relationships between psychopathology, cognitive function, and dementia in later life. Collectively, these findings also have important clinical implications, suggesting that all forms of psychopathology, but particularly internalizing and cognitive dysfunction, represent promising targets for interventions aiming to reduce the risk of dementia in older adulthood.

5.5.2 Age-specific differences in the relationship between transdiagnostic dimensions of psychopathology, cognitive dysfunction, and all-cause incident dementia throughout older adulthood

The positive relationship between the general higher-order factor and all-cause incident dementia was found across all age groups, demonstrating its utility in predicting dementia throughout older adulthood (i.e., from ages 55-78). In bivariate analyses, lower-order transdiagnostic dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) were also consistently positively associated with incident dementia across all age groups. However, multivariable analyses indicated that the relationship between internalizing and incident dementia that exists when controlling for other psychopathology dimensions and cognitive dysfunction emerges at a later stage of older adulthood and persists throughout later life (i.e., ages 65-78). The likelihood of dementia diagnoses increases with increasing age and there is some evidence to suggest that internalizing-related psychopathology (e.g., depression, anxiety) may reflect a prodromal stage of the condition, rather than an independent risk factor (Bennett & Thomas, 2014; Brommelhoff et al., 2009; Gatz et al., 2005; Li, 2011; Mendez, 2021). For instance, a population-based study in participants aged 65 and older that included a 5-year follow-up period found that baseline symptoms of depression predicted dementia but not self-reported history of depression or duration of previous depressive symptoms (Gatz et al., 2005). Similarly, another population-based study reported that depression onset occurring within 10 years of dementia diagnoses was associated with greater risk of dementia but found no evidence of an association with depression onset that occurred 10 years prior to dementia diagnoses (Brommelhoff et al., 2009). The fact that multivariable analyses revealed a relationship between internalizing and incident dementia only in the two oldest age groups (i.e., ages 65-78) may reflect that internalizing psychopathology is a prodromal stage of dementia, which is more likely to emerge in these later age groups.

Multivariable analyses across age groups also revealed that higher thought disorder psychopathology at ages 55-59 was positively associated with the subsequent development of dementia but negatively associated with dementia at ages 70-78. This result is counter-intuitive and further research is needed before any meaningful interpretations can be made. One potential explanation for the negative association observed in the oldest age group is survival bias, wherein individuals with higher thought disorder symptoms and elevated risk of dementia are less likely to survive into older age. Those with higher thought disorder symptoms at age 70-78 may represent a more resilient or cognitively preserved subgroup due to other unobserved protective factors, which could make it falsely appear as though thought disorder is protective of dementia in this age group.

Finally, cognitive dysfunction was found in both bivariate and multivariable analyses to be positively associated with incident dementia only in the three oldest age groups (i.e., ages 60-64, 65-69, and 70-78 years old) and not in the youngest age group (i.e., ages 55-59 years old). Importantly, higher scores on the cognitive dysfunction dimension reflect worse performance on neurocognitive tests but not necessarily impairment in cognitive function. Analyses of latent mean differences also revealed that mean levels of cognitive dysfunction were significantly higher in all age groups relative to the 55-59 year old age group. It is possible that there is a threshold effect, wherein cognitive dysfunction becomes predictive of subsequent dementia diagnoses at a certain degree of severity that is not present in this younger age group. Furthermore, analyses were restricted to participants free of dementia at the time they completed both the online cognitive and mental health assessments (i.e., between 2016 and 2017) and follow-up data on dementia was only available up to seven years (i.e., the year 2023). Future research should investigate whether scores on this cognitive dimension at ages 55-59 years old is predictive of incident dementia over a longer follow-up period.

5.5.3 Relationships between polygenetic risk for Alzheimer's disease and transdiagnostic dimensions of psychopathology and cognitive dysfunction

There was no evidence that polygenetic risk for AD predicted the general higher-order factor or the lower-order dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder). There was also no evidence that levels of the general factor or lower-order psychopathology dimensions mediated the relationship between the AD-PGS and incident dementia, which is consistent with the absence of associations between the AD-PGS and each of these phenotypes. One prior study has examined direct relationships between an AD-PGS and transdiagnostic dimensions of psychopathology (i.e., general psychopathology, internalizing, externalizing, neurodevelopmental, somatoform, and detachment) in preadolescents from the Adolescent Brain and Cognitive Development (ABCD) study (Waszczuk et al., 2021). Consistent with the results of this study, the authors also found no evidence that these psychopathology-specific transdiagnostic dimensions were associated with polygenetic risk for AD.

A point of difference and novel feature to the current study is the inclusion of a latent cognitive dysfunction dimension, which in contrast to the psychopathology-specific dimensions, was significantly positively associated with the AD-PGS in the full sample and was additionally found to mediate the relationship between the AD-PGS and incident dementia. When examining associations across age groups, the direct association between the AD-PGS and cognitive dysfunction and the role of cognitive dysfunction in mediating the relationship between the AD-PGS and incident dementia emerged at ages 60-64 and persisted until ages 70-78. Each of these associations held in both bivariate analyses and in multivariable analyses controlling for the presence of lower-order psychopathology dimensions. Collectively, the findings of this study indicate that polygenetic risk for AD represents a unique biological risk factor for cognitive dysfunction and the subsequent development of dementia but not for different dimensions of psychopathology.

The identification of cognitive dysfunction as a mediator represents a novel contribution of this study. Whilst prior research has not examined latent cognitive dysfunction directly as a mediator of polygenetic risk for clinical outcomes, adjacent studies in younger populations have identified other intermediary mechanisms (i.e., total gray matter volume and impulsivity) that mediate the relationship between psychiatric PGSs and transdiagnostic dimensions of psychopathology (Lahey et al., 2022, 2024). Although the constructs and developmental periods differ, these studies collectively underscore the value of modeling intermediary mechanisms to understand how genetic risk contributes to clinical outcomes, whether related to psychopathology in youth or age-specific outcomes like dementia in later life. Whereas prior work has identified structural brain features or psychiatric traits (e.g., impulsivity) as mediators of genetic risk, the current study introduces a dimensional cognitive phenotype as a mediator of genetic risk for dementia, extending this framework into later life and highlighting cognitive dysfunction as a distinct pathway to neurodegenerative disease. These findings also have important clinical implications, suggesting that interventions targeting cognitive dysfunction may mitigate genetic vulnerability to AD in ageing populations.

A recent study by Freudenberg-Hua and colleagues (2024) similarly examined whether polygenetic risk for AD was associated with psychopathology and incident dementia in the UK Biobank. Although not focused specifically on older adults, their study tested whether a general composite variable capturing multiple psychiatric diagnoses (e.g., psychotic disorders, bipolar disorder, depression, anxiety) mediated the relationship between polygenetic risk for AD and incident dementia. Consistent with the findings of this study, they observed independent associations between the composite variable and dementia, as well as between the AD-PGS and dementia, but no evidence of mediation. Whilst the general factor in the current study also captured transdiagnostic variance in psychopathology, it extends the approach taken in this previous study by modeling a broader latent phenotype that incorporates both psychiatric and cognitive indicators. Another novel contribution of this study was the use of a higher-order model that included both general and lower-order dimensions, allowing for more precise examination of the pathways through which polygenetic risk for AD influences dementia. This approach revealed a specific mediating role for cognitive dysfunction in the absence of any mediating effects for transdiagnostic psychopathology, highlighting the added value of hierarchical dimensional modeling in uncovering distinct mechanisms of genetic risk and underscoring the importance of including cognitive dysfunction in transdiagnostic frameworks when investigating dementia risk in older adulthood.

Whilst polygenetic risk for AD was not associated with general psychopathology in the current study, the association between the general higher-order factor and all-cause incident dementia still suggests the presence of shared mechanisms that underly psychopathology and cognitive function and contribute to dementia risk. Several other pathophysiological mechanisms have been implicated in dementia and demonstrate shared associations with both mental illness and cognition. For example, recent research identified shared causal proteins and molecular processes underlying psychiatric and neurodegenerative diseases and suggested a central role of synaptic transmission, immune function, and mitochondrial processes (Wingo et al., 2022). Further research is needed to probe for potential mechanisms that influence dementia risk via both psychopathology and cognition, as well as biological mechanisms that may be uniquely predictive of dementia via psychopathology.

5.5.4 Strengths and limitations

There are several strengths and limitations to the current study that are important to consider. Most existing literature examining the biological correlates of transdiagnostic dimensions of psychopathology has focused on samples ranging from childhood to adulthood (Hoy et al., 2023). This study represents one of only two studies to examine biological associations with transdiagnostic phenotypes specifically in older adulthood (**Chapter 4**; Hoy, et al., 2025b), addressing a critical gap in the current evidence-base. That said, analyses focused solely on polygenetic risk for AD and future research would benefit from examining associations with a wider range of PGSs (e.g., capturing genetic risk for other neurocognitive conditions, subtypes of dementia, and psychopathology). In particular, future research should examine whether there are differences in associations when multiple PGSs are entered simultaneously as predictors in a given model. Indeed, **Chapter 2** found that associations between psychiatric PGSs and transdiagnostic dimensions varied between studies that did and did not control for the effects of other PGSs. Prior research has also found support for a general PGS that captures genetic risk for multiple psychiatric disorders (Selzam et al., 2018) and which has consistently been associated with general psychopathology across different samples and developmental periods (Allegrini et al., 2020; Gard et al., 2021; Grotzinger et al., 2019). Future research should examine whether a general PGSs capturing genetic risk for multiple neurocognitive disorders or a PGS capturing genetic risk for both neurocognitive *and* psychiatric conditions is associated with the phenotypes included in this study. The latter approach may be particularly informative when investigating associations with general dimensions that capture variance in psychopathology and cognitive dysfunction.

Few studies have examined dimensional models of psychopathology that include cognitive dimensions (Eadeh et al., 2021; Forbes et al., 2024b; Littlefield et al., 2021; Ringwald, 2024; Rotstein et al., 2023) and the extant literature has thus far focused on establishing the structural validity of these models rather than their utility in predicting important external criteria. This is the first study to demonstrate the predictive utility of general factors derived from higher-order dimensional models comprising both psychiatric and cognitive phenotypes. However, it was not possible to control for the general factor when examining associations with lower-order dimensions due to the collinearity between higher- and lower-order dimensions included in the higher-order model. Future research may benefit from the use of alternative modeling approaches (e.g., bi-factor models) that allow for simultaneously controlling for both general and specific factors; however, analyses in **Chapter 3** found that the higher-order model used in the current study demonstrated greater model-based reliability and interpretability compared to a bi-factor model defined by the same set of indicators (Hoy et al., 2025a).

It is also important to note that the observed indicators of psychopathology and cognition included in the measurement model were derived from different measurement approaches (e.g., performance-based measures of cognition v. self-report measures of psychopathology) and assessed at different time points, which likely impact the strength of association between cognitive dysfunction and the general higher-order factor. The implications of this for the measurement model are addressed extensively in **Chapter 3**; however, it is also possible that this methodological variance impacted the observed relationships between the general factor and external criteria in the current study.

Finally, a major strength of this study is that associated were examined in a large (N > 100,000) and thus well-powered sample of older adults from the general population. However, analyses were restricted to participants of European ancestry from the United Kingdom and may not generalize to participants from other racial or ethnic backgrounds or to those from low- to middle-income countries. Future research should investigate whether these associations are maintained when examined in more diverse samples of older adults.

5.5.4 Conclusions

This is the first study to investigate the utility of hierarchical dimensional models in examining the relationships between transdiagnostic dimensions of psychopathology, cognitive dysfunction, incident dementia, and polygenetic risk for AD in older adulthood. A general higher-order factor (capturing the shared variance between psychopathology and cognitive dysfunction) was found to predict incident dementia, identifying a novel marker of dementia risk that persists throughout older adulthood. Analyses further demonstrated that lower-order dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) and cognitive dysfunction are similarly associated with greater likelihood of dementia in older adulthood. These findings have important implications for prevention and risk-reduction approaches, suggesting that interventions addressing both mental illness and cognition may be particularly useful in preventing or delaying subsequent dementia diagnoses. Secondary analyses revealed age-specific patterns in the nature of these relationships and robust associations between internalizing, cognitive dysfunction, and incident dementia that exist over and above the influence of other lower-order phenotypes, which may further inform the development of transdiagnostic intervention strategies. The results of this study also highlight that polygenetic risk for AD is uniquely associated with cognitive dysfunction and incident dementia and not with other dimensions of psychopathology or with a general factor defined by their shared variance. These findings have important implications for research investigating shared mechanisms underlying psychopathology and cognitive function and for research investigating biological pathways to dementia. Overall, this study highlights the value of hierarchical dimensional models in uncovering complex relationships between mental illness, cognition, dementia, and genetic risk.

Chapter 6

General Discussion

6.1 Broad overview

The overarching aim of this thesis was to investigate the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan using hierarchical dimensional models, with a particular focus on identifying and addressing key age-specific gaps in the existing evidence-base. **Chapter 1** provides an in-depth review of hierarchical dimensional models of psychopathology, focusing particularly on their utility in biological research and the importance of adopting a lifespan approach. This chapter also outlined several methodological limitations and recommendations for best-practice approaches to investigating the latent structure of psychopathology prior to testing for associations with external criteria, which were carefully followed throughout the remaining empirical studies (**Chapters 3-5**). **Chapter 2** presents a systematic review examining existing evidence from studies investigating the biological correlates of transdiagnostic dimensions of psychopathology, identifying that not a single study had focused specifically on older adults. **Chapter 3** first investigated the latent hierarchical structure of psychopathology in older adulthood and **Chapters 4** and **5** subsequently examined whether transdiagnostic phenotypes derived from hierarchical dimensional models are associated with brain structure and polygenetic risk in this population. Given the specific focus of later chapters on older adults, additional analyses examined whether a dimension capturing cognitive dysfunction could be incorporated into the latent hierarchical structure of psychopathology and whether transdiagnostic dimensional phenotypes hold utility in predicting important age-specific outcomes (i.e., all-cause incident dementia) in later life (**Chapters 4-5**).

To address the aims of this thesis, each empirical chapter follows a multidisciplinary approach that integrates several diverse fields, including: psychiatric epidemiology, cognitive science, neuroscience, genomics, ageing, and dementia research. The included studies additionally combine large-scale data analysis with a range of sophisticated statistical techniques, including: confirmatory factor analysis, structural equation modeling, measurement invariance testing, mediation analysis, Bayesian methods, linear mixed-models, and logistic regression. Finally, each empirical chapter draws on expertise from national and international teams of collaborators from Australia, the United States, and Canada. Together, the findings of this thesis provide critical and novel insights into our understanding of the latent structure and biological correlates of psychopathology across the lifespan, addressing critical gaps in this field of research with respect to ageing populations.

The included studies were specifically designed to address the following eight research questions, as outlined in **Chapter 1**:

1) What are the biological correlates (i.e., genomic, brain structural, and brain functional) of general and specific/lower-order dimensions of psychopathology in general population samples across the lifespan?
2) What is the symptom-level latent hierarchical structure of psychopathology in the general population of older adults?
3) Is there evidence that a dimension capturing cognitive dysfunction can be incorporated into the latent hierarchical structure of psychopathology in older adulthood?
4) Is the latent hierarchical structure of psychopathology invariant across different age groups throughout older adulthood?
5) Are general and specific/lower-order transdiagnostic symptom dimensions associated with global and regional measures of gray matter structure in older adults?

6) Does polygenetic risk for Alzheimer's disease predict variations in higher- and lower-order transdiagnostic dimensions in older adulthood?
7) Are general and specific/lower-order transdiagnostic dimensions associated with all-cause incident dementia in older adulthood?
8) Do biological predictors mediate the relationship between transdiagnostic dimensions and all-cause incident dementia in older adults?

The following section of this concluding chapter presents an overview of the key findings from this thesis in relation to each of these research questions (6.2). The strengths and limitations of this thesis are then discussed (6.3), followed by the implications of findings for research and clinical practice (6.4), suggested directions for future research (6.5), and final conclusions (6.6).

6.2 Overview of key findings

6.2.1 What are the biological correlates (i.e., genomic, brain structural, and brain functional) of general and specific/lower-order dimensions of psychopathology in general population samples across the lifespan?

Chapter 2 presents the first systematic review of studies investigating the biological (i.e., genomic, brain structural, brain functional) correlates of general and specific/lower-order dimensions of psychopathology across the lifespan and in the general population. The review offers an exhaustive overview of the current evidence-base; however, only notable findings and patterns are highlighted in this section. In the genomics literature, general psychopathology was consistently positively associated with polygenic scores (PGSs) for a range of psychiatric disorders and traits (e.g., attention-deficit/hyperactivity disorder, neuroticism, depression, schizophrenia, anxiety, post-traumatic stress disorder) and with general PGSs (i.e., individual PGSs that capture genetic risk for multiple psychiatric disorders and traits simultaneously) across multiple age groups and developmental periods. In the structural neuroimaging literature, general psychopathology was also consistently associated with lower global and regional measures of gray matter structure (i.e., gray matter volume, cortical surface area) across multiple studies spanning childhood to midlife. Several specific/lower-order dimensions (i.e., internalizing, externalizing, thought disorder) demonstrated similar associations with a range of genomic and structural neuroimaging variables across multiple studies. There was some evidence of dimension-specific associations reported *within* several studies but limited evidence of dimension-specific associations that were consistently reported *across* studies. Functional neuroimaging studies predominantly examined associations with functional connectivity in participants from the Adolescent Brain and Cognitive Development (ABCD) study, with multiple studies indicating that general psychopathology is associated with lower connectivity *within* the Default Mode Network (DMN) and Dorsal Attention Network (DAN) and greater connectivity *between* the DMN and DAN.

Overall, the findings from included studies indicate that general and specific/lower-order dimensions of psychopathology are associated with a wide range of biological mechanisms and processes across various age groups and developmental periods. However, the review identified that most studies have focused on samples of youth (i.e., childhood to young adulthood) and that studies in older age groups tended to include wide age ranges (e.g., adulthood to older adulthood or midlife to older adulthood). The existing literature has predominantly focused on cross-sectional analyses; however, some longitudinal analyses indicate age-specific differences in biological associations over relatively short periods of observation. There was also some evidence of age-specific differences across studies that investigated similar relationships in different age groups. For example, the ADHD-PGS was consistently associated with general psychopathology across six studies spanning childhood to adolescence but showed no association in one study of midlife to older adult participants (i.e., 51 to 83 years old). In addition, multiple neuroimaging studies reported negative associations between general psychopathology and global surface area and no evidence of an association with cortical thickness; however, the inverse pattern of associations was reported in a single study of participants at midlife (i.e., age 45 years old). The most salient gap identified in the current literature was that not a single study focused on investigating the biological correlates of transdiagnostic dimensions specifically in older adulthood. This finding formed the foundation of the remaining chapters of this thesis, which present three empirical studies designed to improve our understanding of the latent structure and biological correlates of psychopathology in this population.

6.2.2 What is the symptom-level latent hierarchical structure of psychopathology in the general population of older adults?

Chapters 3-5 of this thesis are the first studies to investigate the latent *hierarchical* structure of psychopathology in older adulthood. Following the rigorous model-selection and evaluation procedures outlined in **Chapter 1** (Figure 1.3), **Chapters 3-4** both found that a higher-order model provided the best fit to the data when compared to a variety of competing structural models (i.e., one-factor, correlated-factor, and bi-factor models). All models followed a confirmatory approach, were tested in general populations samples, and included either symptom-level indicators of psychopathology (**Chapter 4**) or a combination of symptom-level psychiatric indicators and performance-based indicators of cognitive function (**Chapters 3** and **5**). **Chapter 3** demonstrated that a higher-order model comprising a general factor and four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction) provided acceptable fit to the data in older adults aged 55 to 78 years old from the UK Biobank. **Chapter 4** examined the latent structure of psychopathology in a later stage of life, demonstrating that a higher-order model including a general factor and three lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use) provided acceptable fit to the data in a general population sample of older adults aged 70 to 90 years old from the Sydney Memory and Ageing Study (MAS). Finally, **Chapter 5** replicated the best-fitting higher-order model from **Chapter 3** in a subsample of UK Biobank participants aged 55 to 78 years old who were of European ancestry and free of dementia.

6.2.3 Is there evidence that a dimension capturing cognitive dysfunction can be incorporated into the latent hierarchical structure of psychopathology in older adulthood?

Chapters 3 and **5** of this thesis present the first studies to investigate whether a dimension capturing cognitive dysfunction can be incorporated into hierarchical dimensional models of psychopathology in older adults. **Chapter 3** examined multiple competing structural models (i.e., one-factor, correlated-factor, higher-order, and bi-factor) in a large general population sample of older adults aged 55 to 78 years old from the UK Biobank. This study found support for a higher-order model, including a general higher-order dimension defined by the shared variance of three lower-order dimensions comprising symptom-level indicators of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) and a lower-order dimension comprising performance-based indicators of cognitive function (i.e., cognitive dysfunction). The loadings of cognition on the general factor were relatively weak compared to the loadings of other lower-order dimensions, which was possibly due to differences in the timing of psychiatric and cognitive assessments and differences in approaches to the measurement of these constructs (i.e., self-report indicators of psychopathology and performance-based indicators of cognition). Importantly, secondary analyses revealed that the magnitude of this loading improved substantially when controlling for method variance, demographic covariates (i.e., age and years of education), and both method variance and demographic covariates simultaneously. As noted, **Chapter 5** subsequently replicated this model in a subsample of older adults from the UK Biobank who were of European ancestry and free of dementia.

6.2.4 Is the latent hierarchical structure of psychopathology invariant across different age groups throughout older adulthood?

Chapters 3 and **5** present the first studies to examine whether hierarchical dimensional models of psychopathology are invariant across age groups in older adulthood. Following a rigorous and step-wise approach to invariance testing, these studies demonstrated configural, lower-order metric/scalar and higher-order metric/scalar invariance of a higher-order model comprising a general higher-order dimension and four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction) across four age groups throughout older adulthood (i.e., 55 to 59, 60 to 64, 65 to 69, and 70 to 78 years old). This age-invariant higher-order model was first demonstrated in a large sample of older adults from the UK Biobank (**Chapter 3**) and then replicated in a subsample of older adults from the UK Biobank that were of European ancestry and free of dementia (**Chapter 5**). Secondary analyses in both studies (**Chapter 3** and **5**) additionally examined whether there were differences in the latent means of each dimension across age groups. These secondary analyses demonstrated that the general higher-order factor and lower-order dimensions of psychopathology were significantly lower across all age groups compared to participants in the youngest age group (i.e., 55-59 years old). Conversely, latent means for the cognitive dysfunction dimension were significantly higher in all age groups compared to this youngest age group. These findings provided the necessary foundation for subsequent analyses investigating age-specific differences in genomic associations with latent dimensions of psychopathology and cognitive dysfunction in **Chapter 5**.

6.2.5 Are general and specific/lower-order transdiagnostic symptom dimensions associated with global and regional measures of gray matter structure in older adults?

Chapter 4 presents the first study to investigate the relationship between transdiagnostic dimensions and brain structure in older adults, aged 70 to 90 years old from the Sydney MAS. As previously noted, a higher-order model including a general dimension and three lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use) was identified as the best-fitting model following recommended approaches to model selection and evaluation outlined in **Chapter 1**. The results of **Chapter 4** indicated that general and specific/lower-order dimensions of psychopathology were not associated with gray matter structure in older adulthood. Specifically, general and lower-order dimensions were not associated with global measures of GMV or cortical thickness. There was also no evidence that any transdiagnostic dimension was associated with regional GMV or cortical thickness in the frontal, parietal, occipital, or temporal lobes, or with GMV in the cerebellum and hippocampus. These null findings were found in cross-sectional analyses at baseline and in longitudinal analyses that examined whether transdiagnostic dimensions predict intra-individual change in each of these outcome measures over six years of follow-up. These findings were also consistent with secondary analyses that examined the same relationships using general and specific factors derived from a bi-factor model.

6.2.6 Does polygenetic risk for Alzheimer's disease predict variations in higher- and lower-order transdiagnostic dimensions in older adulthood?

Chapter 5 presents the first study to investigate genomic associations with transdiagnostic dimensions of psychopathology specifically in older adults. As previously mentioned, the best-fitting higher-order model from **Chapter 3** (i.e., the higher-order model including a general higher-order factor and lower-order dimensions of internalizing, addictions and substance use, thought disorder, and cognitive dysfunction) was first replicated in a subsample of participants aged 55 to 78 years old from the UK Biobank who were of European ancestry and free of dementia. Additional analyses replicated the multigroup measurement invariant model from

Chapter 3 in this subsample, again demonstrating configural, lower-order metric/scalar, and higher-order metric/scalar invariance across the four age groups (i.e., 55-59, 60-64, 65-69, 70-78 years old). The Alzheimer's disease polygenic score (AD-PGS) was not associated with the general higher-order factor or with any lower-order dimension of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) in the full sample or across any of the four age groups. These null findings were maintained in multivariable analyses that controlled for the effects of other lower-order dimensions. In contrast, the AD-PGS was significantly positively associated with the cognitive dysfunction dimension in the full sample and age-specific analyses indicated that this association was present in participants from the three oldest age groups (i.e., 60-78). These findings were also maintained in multivariable analyses controlling for the effects of other lower-order dimensions.

6.2.7 Are general and specific/lower-order transdiagnostic dimensions associated with all-cause incident dementia in older adulthood?

Chapters 4-5 present the first studies to investigate whether transdiagnostic dimensions are associated with all-cause incident dementia in older adulthood. There was no evidence that general or specific/lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use) predicted all-cause incident dementia over 12 years of follow-up in participants aged 70 to 90 years old from the Sydney MAS (**Chapter 4**). These null findings were consistent regardless of whether transdiagnostic phenotypes were derived from the best-fitting higher-order model or from a bi-factor model. In contrast, a general higher-order factor and four lower-order dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction) were significantly positively associated with all-cause incident dementia in a larger sample of participants aged 55 to 78 years old from the UK Biobank (**Chapter 5**). Bivariate analyses found that the general factor and lower-order dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder) were positively associated with incident dementia in the full sample and across four age groups throughout older adulthood (i.e., 55-59, 60-64, 65-69, 70-78 years old). The lower-order cognitive dysfunction dimension was positively associated with incident dementia in the full sample and in the three oldest age groups (spanning 60 to 78 years old). Multivariable analyses found that internalizing was associated with incident dementia when controlling for the effects of other lower-order dimensions in the full sample and that this association emerged specifically in the two oldest age groups (spanning 65 to 78 years old). Multivariable analyses also found that cognitive dysfunction was associated with incident dementia when controlling for other lower-order dimensions in the full sample and in the three oldest age groups (spanning 60 to 78 years old).

6.2.8 Do biological predictors mediate the relationship between transdiagnostic dimensions and all-cause incident dementia in older adults?

Chapter 5 additionally examined whether transdiagnostic dimensions mediate the relationship between polygenetic risk for AD and all-cause incident dementia in older adults. This study found that cognitive dysfunction significantly mediated the relationship between the AD-PGS and all-cause incident dementia in the full sample and specifically in the three oldest age groups (i.e., 60-78 years old), indicating that part of the genetic contribution to incident dementia is driven by its impact on cognitive functioning. This relationship was maintained in multivariable analyses controlling for the effects of other lower-order dimensions of psychopathology (i.e., internalizing, addictions and substance use, thought disorder). In contrast, there was no evidence that the general higher-order factor or any lower-order dimension of psychopathology mediated this relationship in the full sample or across any age group throughout older adulthood (in both bivariate and multivariable analyses).

6.3 Strengths and limitations

Overall, the findings of this thesis advance our understanding of the latent hierarchical structure and biological underpinnings of psychopathology across the lifespan, particularly with respect to ageing populations. Each empirical chapter further highlights the utility of hierarchical dimensional models in investigating the relationships between mental illness, cognitive dysfunction, and incident dementia in later life. However, there are several strengths and limitations that are important to consider when interpreting these findings and evaluating the broader implications of this research. These include strengths and limitations relating to the generalizability of research findings (Section 6.3.1), approaches to model-selection and evaluation (Section 6.3.2), methods to account for uncertainty in single-point estimates of factor scores (Section 6.3.3), reliance on secondary analysis of existing data (Section 6.3.5) study design (Section 6.3.6), and sample size and statistical power (6.5.7).

6.3.1 Generalizability

Firstly, the three empirical chapters of this thesis were conducted using participants drawn from two datasets, the UK Biobank and the Sydney MAS. Both datasets include large-scale general population samples of older adults, with **Chapters 3** and **5** including over 100,000 participants aged 55 to 78 years old (from the UK Biobank) and **Chapter 4** including over 1000 participants aged 70 to 90 years old (from the Sydney MAS). Large-scale general population datasets are better able to capture the true distribution of psychopathology and offer greater generalizability compared to studies of more narrowly defined subpopulations (e.g., clinical samples). Collectively, these two datasets also span a broad segment of the older adult population (i.e., from ages 55 to 90 years old). However, it is important to acknowledge that both cohorts comprise predominantly Caucasian participants and that all included participants reside in high-income countries (i.e., Australia, England, Scotland, Wales, and Northern Ireland).

Therefore, the extent to which findings from this thesis generalize to people of other racial or ethnic backgrounds or to populations living in low- to middle-income countries is currently unclear. Whilst there is evidence to support the generalizability of hierarchical dimensional models of psychopathology across diverse subpopulations (e.g., racial, ethnic, age-related, sexual orientation; Balling et al., 2024), limited research has been conducted to examine the latent structure and biological correlates of psychopathology in older adults and by extension in diverse subpopulations of older adults.

6.3.2 Approaches to model-selection and evaluation

A major strength of this thesis was the use of a rigorous and multi-faceted approach to model-selection and evaluation prior to testing associations with external criteria (i.e., brain structure, genomics, and incident dementia). The studies in **Chapters 3-4** compare multiple competing models of psychopathology (i.e., one-factor, correlated-factors, higher-order, and bi-factor models) and determine the best-fitting model on the basis of traditional indices of absolute and incremental model-fit (e.g., CFI, TLI, and RMSEA values), model-based estimates of reliability (e.g., ECV, PUC, Omega H/Hs, H coefficients), and thorough evaluation of model parameters and interpretability (e.g., the magnitude, direction, and significance of standardized factor loadings and the magnitude of standard errors). This approach follows the evidence-based recommendations for model-selection and evaluation that were outlined in **Chapter 1** (Forbes et al., 2021b; Rodriguez et al., 2016a, 2016b; Watts et al., 2019), addressing several limitations identified in prior research investigating the biological correlates of transdiagnostic dimensions of psychopathology. All structural models in this thesis are additionally estimated in general population samples using either symptom-level indicators of psychopathology (**Chapter 4**) or a combination of symptom-level psychiatric indicators and performance-based cognitive indicators (**Chapters 3** and **5**), which allow for more detailed examination of the latent structure of psychopathology and avoid the limitations of depending on dichotomous disorder-level indicators (e.g., loss of information regarding within-disorder heterogeneity and severity, shared symptoms across categorical disorders; Forbes et al., 2021a). Importantly, these more stringent and detailed approaches to modeling the structure of psychopathology strengthen the validity of subsequent analyses, ensuring that associations with biological variables and incident dementia are tested with phenotypes derived from more optimal, psychometrically robust, and theoretically consistent models of psychopathology.

6.3.3 Methods to account for the uncertainty of factor score estimates

Another major strength of this thesis was the use of advanced statistical methods to account for uncertainty around factor score estimates when examining associations with external criteria (i.e., brain structure, genomics, incident dementia). Most prior studies investigating associations with external criteria (including biological associations) have relied on the use of single-point estimates of latent factor scores (as evident in **Chapter 2**), which are highly skewed when derived from categorical indicators and prone to random error (Wu, 2005). In **Chapter 4**, this limitation was addressed by generating 100 Bayesian Plausible Values (BPVs) for each transdiagnostic dimension (i.e., latent factor) from the posterior end of the distribution of possible factor scores. Subsequent analyses were then run over each imputed value for each latent factor and results were pooled into a final set of estimates within a multiple imputation framework, producing more reliable estimates of associations with gray matter structure and incident dementia. In **Chapter 5**, associations between transdiagnostic dimensions external criteria (i.e., the AD-PGS, incident dementia) were estimated using structural equation modeling (SEM). This approach simultaneously models latent variables and their paths to external criteria (e.g., the AD-PGS) within a single framework, directly accounting for measurement error and providing more accurate and unbiased estimates of these relationships compared to analyses that rely on single-point estimates (Tomarken & Waller, 2005).

6.3.4 Reliance on secondary analysis of existing data

A consistent limitation across the studies included in this thesis is that they each relied on secondary analysis of existing datasets, none of which were designed to capture the full breadth of psychopathology. This constraint limited the ability to comprehensively model the latent structure of mental illness in older adulthood, which further limited the extent to which relationships between transdiagnostic dimensions, biology, and incident dementia could be examined. Studies modeling the latent structure of psychopathology (**Chapters 3-5**) incorporated a range of psychiatric indicators, spanning multiple domains of mental illness (i.e., depression, anxiety, self-harm, suicidality, disinhibition, aggression, hostility, psychosis, mania, alcohol use, nicotine use, addictions to prescription medication, illicit substances, behavioral addictions, delusions, hallucinations, mania, agitation/aggression, disinhibition, irritability/lability). Indicators used to model cognitive dysfunction in **Chapters 3** and **5** covered a similarly broad range of cognitive domains (e.g., processing speed, visual attention, verbal and numeric reasoning, problem-solving skills, numerical working memory, short-term memory, processing speed, attention, and visuospatial working memory). The psychiatric indicators allowed for modeling several commonly studied specific/lower-order dimensions in both the UK Biobank (i.e., internalizing, addictions and substance use, thought disorder; **Chapters 3** and **5**) and Sydney MAS (i.e., internalizing, substance use, and disinhibited-externalizing; **Chapter 4**) samples. The cognitive indicators further allowed for investigating a novel cognitive dysfunction dimension and its incorporation within hierarchical dimensional models of psychopathology.

However, it was not possible to model broad externalizing in either dataset due to limited phenotyping of this construct. Externalizing is a widely studied transdiagnostic dimension of psychopathology, which has consistently been associated with a range of important outcomes and biological variables in younger samples (Krueger et al., 2021). Indeed, several studies identified in **Chapter 2** have demonstrated neurobiological and genomic associations with broad dimensions of externalizing across multiple age groups and developmental periods (Hoy et al., 2023). In the UK Biobank sample, externalizing-related symptoms were largely restricted to indicators of substance use and addiction. Externalizing symptoms were somewhat better represented in the Sydney MAS but due to poor coverage of other domains of psychopathology (e.g., psychosis) and the need to include three lower-order factors for identification when estimating higher-order factor models, it was necessary to model two subdimensions of this phenotype (i.e., disinhibited-externalizing and substance use). The disinhibited-externalizing dimension was further limited to only three indicators (i.e., agitation/aggression, disinhibition, irritability/lability) and the substance use dimension was restricted to indicators of alcohol and nicotine use. These limitations precluded examining whether broad externalizing was associated with gray matter structure, polygenetic risk for AD, and incident dementia in **Chapters 4-5**. Due to limited coverage of psychosis-related symptoms (e.g., delusions, hallucinations) in the Sydney MAS, it was also not possible to examine whether thought disorder was associated with gray matter structure in **Chapter 4**. Importantly, an extensive search was conducted to identify datasets with sufficiently large samples of older adults that included deep phenotyping of psychopathology and other relevant domains (e.g., cognition, neuroimaging, genomics) prior to conducting these studies. The difficulty in locating such datasets reflects a broader limitation in the resources currently available to researchers seeking to examine the latent structure and correlates of psychopathology in later life, which often lack comprehensive assessments of mental illness.

6.3.5 Study design considerations

There were additional limitations arising from the use of secondary data, particularly the lack of control over study design. Across both datasets, psychopathology was assessed either at a single point in time (**Chapters 3** and **5**) or the measurement of psychopathology was inconsistent across waves of data collection (**Chapter 4**). These limitations precluded *longitudinal* measurement invariance testing, which would have enabled more thorough assessment of whether hierarchical structure of psychopathology remained stable within individuals over time. They also prevented the ability to move beyond simple baseline-prediction models and address more genuinely developmental questions (e.g., whether changes in one symptom domain dynamically predict subsequent changes in another or whether there were bi-directional relationships between transdiagnostic dimensions and brain structure over time). Furthermore, analyses in **Chapters 3** and **5** required the inclusion of indicators of psychopathology and cognitive function that were collected at different time points in, which may have influenced the strength of association between cognitive dysfunction and the general factor in both studies (as detailed in **Chapter 3**).

6.3.6 Sample size considerations and statistical power

Finally, whilst the three empirical studies reported in **Chapters 3-5** drew from large general population samples there were still considerable differences in the size of these samples that may have impacted power to detect associations with external criteria. **Chapter 5** benefitted from a very large sample (N > 100,000), which enabled the detection of subtle genomic associations and age-stratified analyses of associations across four subsamples of older adults. In contrast, associations in **Chapter 4** were examined in a comparatively smaller sample, comprising N = 1,037 participants in the full sample and n = 532 participants with neuroimaging data at baseline, which declined substantially over follow-up waves (i.e., n = 417 at the second wave and n = 262 at the fourth wave). This smaller sample size may have limited statistical power to detect associations with gray matter structure, particularly longitudinal associations with intra-individual changes in gray matter structure over time (potentially accounting for the null findings of this study). Notably, there was also no evidence of an association with incident dementia in **Chapter 4** but consistent significant associations identified when examining this relationship using the much larger sample of participants from the UK Biobank in **Chapter 5**.

6.4 Implications of this thesis

The findings of this thesis have several important implications for research investigating the latent structure of psychopathology across the lifespan and specifically in older adulthood (Section 6.4.1), methodological approaches to modeling the latent structure of psychopathology (Section 6.4.2), research investigating the neurobiological (Section 6.4.3) and genomic (Section 6.4.4) correlates of transdiagnostic dimensions, and research investigating the relationships between transdiagnostic dimensional phenotypes and dementia in older adulthood (Section 6.4.5).

6.4.1 Implications for research investigating the latent structure of psychopathology across the lifespan and specifically in older adulthood

An extensive body of research in younger samples indicates that the structure of psychopathology can be organized hierarchically into a set of transdiagnostic dimensions, including a general dimension and several specific/lower-order dimensions (e.g., internalizing, externalizing, thought disorder; Kotov et al., 2017, 2021). However, the extent to which hierarchical dimensional models hold in later life has not been thoroughly investigated, limiting our understanding of how psychopathology is organized across the lifespan. The empirical chapters of this thesis demonstrate that the latent hierarchical structure of psychopathology is also evident in older adulthood, a finding which was consistently reported across two large general population samples spanning ages 55 to 78 and 70 to 90 years old (**Chapters 3-5**). These findings provide compelling evidence to support the continuity of hierarchical dimensional models of psychopathology across the lifespan, suggesting that the overall structure of psychopathology in older adulthood is not qualitatively distinct from that observed in younger populations.

However, further research is needed to build on these findings by formally testing whether the hierarchical structure of psychopathology is age-invariant across the lifespan (i.e., from childhood to older adulthood). Establishing age-invariance is critical to determining whether the presumed latent structure of psychopathology is truly consistent across the lifespan or within age-stratified sub-populations (e.g., older adults). Invariance testing is also a necessary prerequisite for research aiming to identify group-specific differences (e.g., age differences) in associations between a given latent construct and external criteria (Putnick & Bornstein, 2016). Without evidence of invariance, any identified differences in associations with external criteria may reflect differences in measurement properties rather than meaningful age-related variation. Previous studies investigating the age-invariance of transdiagnostic dimensional models of psychopathology have been restricted to modeling lower-order dimensions and subdimensions (Eaton et al., 2011; Hoertel et al., 2015; Sunderland et al., 2013) rather than hierarchical dimensional models that capture a broader spectrum of psychopathology. Importantly, this research has found evidence to support the continuity of transdiagnostic dimensional models across the lifespan. For example, one study demonstrated that a model including externalizing and two subdimensions of internalizing (i.e., fear and distress) was invariant across seven age groups, from early adulthood (i.e., 18-24 years old) to older adulthood (i.e., 75+ years old; Hoertel et al., 2015). The empirical chapters of this thesis extend this research by demonstrating the invariance of hierarchical dimensional models of psychopathology across four age groups (spanning 55 to 78 years old) throughout later life (**Chapters 3** and **5**).

The findings of this thesis also have important implications for research investigating the placement of cognition within hierarchical dimensional models of psychopathology (**Chapters 3** and **5**). It is widely acknowledged that deficits in cognitive function represent a transdiagnostic feature of mental illness (Abramovitch et al., 2021; Forbes et al., 2024a); however, few studies have investigated the structural validity of hierarchical models that include cognitive indicators. The extant literature has so far produced inconsistent results in younger samples or in samples covering broad age ranges, with studies variably reporting: that cognitive dysfunction forms a separable dimension in latent structural models (Forbes et al., 2024b; Rotstein et al., 2023); that cognitive indicators load alongside other specific psychiatric indicators but do not form their own separate factor (Ringwald, 2024); and that there is no evidence to support the inclusion of cognitive indicators (Eadeh et al., 2021; Littlefield et al., 2021). The findings of this thesis extend this research by demonstrating that a separable dimension of cognitive dysfunction can be incorporated into hierarchical models of psychopathology in a large general population sample of older adults (**Chapters 3** and **5**). The inclusion of cognitive indicators facilitates more comprehensive modeling of the latent structure of psychopathology and identifying models with separable cognitive dimensions enables research aimed at examining the shared and unique contributions of psychiatric and cognitive phenotypes to relevant external criteria. This approach may hold particular utility in ageing populations, where cognitive dysfunction and co-occurring psychiatric symptoms are prevalent (Jeste et al., 2005; Lutz et al., 2018) and thus complicate efforts to isolate their respective biological associations (e.g., genomic) and contributions to various age-related outcomes (e.g., dementia).

6.4.2 Methodological implications for studies modeling the latent hierarchical structure of psychopathology

As outlined in **Chapter 1**, the extant literature has predominantly favored the use of bi-factor models due to their tendency to outperform competing structural models based on traditional indices of absolute and incremental model-fit (e.g., CFI, TLI, RMSEA). As a consequence, much of the literature examining associations between transdiagnostic dimensions and external criteria (e.g., genomic and neural correlates) has also been conducted using phenotypes derived from bi-factor models. However, bi-factor models are increasingly criticized for their tendency to over-fit the data and produce unstable parameter estimates (Bonifay et al., 2017; Bonifay & Cai, 2017). Indeed, simulation studies indicate that bi-factor models demonstrate good model-fit even when applied to data comprising invalid or random response patterns (Bonifay & Cai, 2017; Reise et al., 2016) and outperform competing models when the true underlying data structure is specified to not conform to a bi-factor structure (Greene et al., 2019; Morgan et al., 2015). Consistent with this research, the bi-factor models examined in **Chapters 3-4** of this thesis demonstrated superior absolute and incremental model-fit compared to other competing structural models (i.e., one-factor, correlated-factors, higher-order). However, these models also tended to reveal factor loadings that were non-significant, negative in direction, and/or small in magnitude (i.e., $\lambda < 0.3$). These parameters limit the interpretability of the model and do not align with theoretical assumptions that all indicators (e.g., depressive symptoms, anxious symptoms) of a given factor (e.g., internalizing) will load substantially and positively on that factor. In contrast, standardized factor loadings from the higher-order models in each study tended to be significant, positive, and substantial in magnitude (i.e., $\lambda > 0.3$). Evaluation of model-based reliability estimates further indicated that whilst there was evidence of multidimensionality in the data (e.g., appropriate ECV and PUC values), the lower-order factors from the higher-order model consistently demonstrated greater reliability and replicability (i.e., H coefficient values) compared to the specific factors of the bi-factor model. Several studies in younger samples have likewise demonstrated that higher-order models outperform bi-factor models when following similar approaches (Lees et al., 2021; Mewton et al., 2022; Sunderland et al., 2021). Collectively, these findings highlight the importance of following more stringent approaches to model-selection and evaluation and suggest that higher-order models may provide a more optimal approach to modeling the hierarchical structure of psychopathology.

6.4.3 Implications for research investigating relationships between transdiagnostic dimensions of psychopathology and brain structure

As previously noted, **Chapter 2** identified several studies that demonstrated significant associations between transdiagnostic dimensions and gray matter structure in samples ranging from childhood to midlife. However, **Chapter 4** found no evidence that general and specific/lower-order dimensions of psychopathology (i.e., internalizing, disinhibited-externalizing, substance use) were associated with global or regional measures of gray matter structure in older adulthood. These conflicting findings may reflect important age-specific differences in the underlying relationship between brain structure and psychopathology across the lifespan. Research in younger samples captures a critical and sensitive period of neurodevelopment in which the brain is still undergoing dynamic changes in maturation (e.g., cortical thinning, synaptic pruning, and myelination) that are highly sensitive to genetic, environmental, and psychological factors (Tamnes et al., 2017). This period also coincides with the onset of most forms of mental illness (Solmi et al., 2022), which likely arise from disruptions to these normative neurodevelopmental processes and result in measurable deviations in brain morphology that are relatively consistent across individuals and dimensions of psychopathology. Importantly, studies in youth typically report *global or widespread* reductions in gray matter that are associated with transdiagnostic dimensions of psychopathology, suggesting a diffuse neurobiological signature that spans multiple brain regions. In older adulthood, brain morphology is characterized by atrophy and neurodegeneration that relate to distinct age-related neurobiological processes (e.g., shrinking neurons, loss of synapses, and reductions in synaptic spines; Fjell & Walhovd, 2010). These processes exert a similarly diffuse impact on brain morphology, including widespread reductions in cortical and subcortical gray matter structure (Peters, 2006). This may mask additional variance in brain structure that is associated with transdiagnostic psychopathology in this population. That is, because global or widespread regional gray matter reductions are already prevalent in aging, any further structural alterations linked to psychopathology may be statistically diluted or neurobiologically less distinct.

Moreover, brain morphology in later life is shaped by a range of factors that accumulate over the lifespan (e.g., chronic stress, lifestyle factors, physical health conditions) and exert heterogeneous effects on brain structure, which may further weaken or obscure associations with transdiagnostic phenotypes. This problem is compounded by the fact that psychiatric symptoms in older adulthood can arise through diverse etiological pathways, including: 1) symptoms that emerge in early development and persist or re-occur across the lifespan; 2) symptoms that emerge specifically in older adulthood; and 3) symptoms that precede or co-occur with other age-related conditions (e.g., cognitive decline, dementia). These diverse etiological pathways may also dilute any consistent neuroanatomical signature of transdiagnostic psychopathology in older adults. These factors introduce substantial variability that may limit the ability to detect associations that are more commonly observed in younger populations.

There are several methodological factors that may also account for the null findings in **Chapter 4**, which have additional implications for research investigating the neurobiological correlates of transdiagnostic dimensions. First, **Chapter 4** used BPVs to account for the uncertainty inherent in relying upon single-point estimates of latent factor scores, which represents a more stringent approach compared to much of the prior literature. However, **Chapter 2** identified a previous study that also used BPVs derived from a higher-order model to examine associations between transdiagnostic dimensions and gray matter structure in preadolescents from the Adolescent Brain and Cognitive Development (ABCD) study (Mewton et al., 2022). In contrast to the null findings in **Chapter 4**, this study found that all transdiagnostic dimensions were significantly associated with lower global and regional gray matter structure. The conflicting results between these two studies may reflect differences in sample size between the ABCD cohort (i.e., N > 12,000 participants with neuroimaging data at baseline) and Sydney MAS cohort (i.e., N = 532 in the neuroimaging subsample at baseline). Furthermore, whereas some prior studies have employed voxel-wise analyses to detect fine-grained regional associations with brain structure, the modest size of the neuroimaging subsample in **Chapter 4** necessitated a focus on broader cortical regions of interest (i.e., frontal, parietal, occipital, and temporal lobes) and two subcortical structures (cerebellum and hippocampus). It is possible that transdiagnostic dimensions in older adulthood are associated with lower gray matter structure within more localized brain regions that were not investigated in **Chapter 4**. Future research in larger, well-characterized older adult samples using voxel-wise approaches will be important to more precisely map the structural neural correlates of transdiagnostic dimensions in later life. More broadly, these limitations underscore the importance of carefully aligning sample characteristics, measurement precision, and analytic approach with the specific aims of transdiagnostic research in aging populations, particularly when investigating subtle brain–behavior relationships.

6.4.4 Implications for research investigating the genomic correlates of transdiagnostic dimensions

The findings of this thesis also have several important implications for research investigating genomic associations with transdiagnostic dimensions of psychopathology across the lifespan and particularly in older adults. A key assumption underlying hierarchical dimensional models is that general psychopathology reflects broad genetic vulnerabilities and that increasingly specific genetic associations should emerge at lower levels of the structural hierarchy (Lahey et al., 2017a; Waszczuk et al., 2020). Evidence from genomic studies identified in **Chapter 2** partially supported these assumptions, indicating that genetic liability towards supposedly distinct psychiatric disorders contribute non-specifically to general psychopathology and demonstrate greater genetic coherence and specificity in associations with specific/lower-order dimensions.

An important distinction between **Chapter 5** and prior studies investigating genomic associations with transdiagnostic dimensions relates to differences in modeling approaches and the type of genetic risk that was examined. The studies identified in **Chapter 2** modeled dimensions of psychopathology only and predominantly examined associations with genetic risk for psychiatric disorders and traits. In contrast, the measurement model in **Chapter 5** incorporated both psychiatric (i.e., internalizing, addictions and substance use, thought disorder) and cognitive (i.e., cognitive dysfunction) phenotypes. Furthermore, **Chapter 5** examined associations with polygenetic risk for a neurocognitive condition (i.e., Alzheimer's disease) characterized more by deficits in cognitive function than psychiatric symptoms.

Importantly, the AD-PGS in **Chapter 5** was robustly associated with cognitive dysfunction but showed no evidence of an association with any lower-order dimension of psychopathology, which is consistent with theoretical assumptions of increasing genetic specificity at lower levels of the structural hierarchy (Waszczuk et al., 2020). This finding is also consistent with one prior study in preadolescents from the ABCD study (Waszczuk et al., 2021), which similarly found no associations between the AD-PGS and several dimensions of psychopathology (i.e., internalizing, externalizing, neurodevelopmental, somatoform, and detachment dimensions).

However, the absence of association between the AD-PGS and the general higher-order dimension in **Chapter 5** is notable. Given that the general factor captured shared variance across psychiatric *and* cognitive phenotypes, one would expect that observed genetic influences on cognitive dysfunction would also influence the general factor. The lack of association suggests that the genetic coherence of general factors may not extend to associations with neurocognitive disorders, even when the general factor is expanded to include variance from related phenotypes (i.e., cognitive dysfunction). This may indicate that cognitive dysfunction represents a distinct construct that co-occurs with psychopathology but is driven by separate underlying mechanisms rather than shared (i.e., transdiagnostic) mechanisms. Indeed, the cognitive dysfunction dimension demonstrated a relatively weak loading on the general factor in **Chapters 3** and **5**. This was interpreted as a methodological artifact stemming from differences in the timing of assessment (i.e., psychopathology and cognition were assessed at different time points) and measurement modality (i.e., self-report indicators of psychopathology and performance-based indicators of cognitive function); however, these weak loadings may instead reflect a meaningful dissociation between cognitive dysfunction and psychopathology.

Alternatively, these findings may not indicate a fundamental separation between cognitive dysfunction and psychopathology but rather, the specificity of genetic risk captured by the AD-PGS. That is, although cognitive dysfunction and psychopathology frequently co-occur and can be modeled within a coherent hierarchical framework, the genetic variants underlying AD risk may be distinct from that which contributes to the phenotypic overlap between psychiatric and cognitive phenotypes. Both interpretations have important implications for how general factors are defined and interpreted. In particular, they underscore the importance of empirically validating expanded transdiagnostic models against external biological criteria, rather than assuming genetic coherence based solely on model-fit. More broadly, these findings highlight the need for age-sensitive genomic research that evaluates how various forms of genetic liability differentially map onto psychiatric and cognitive dimensions across the lifespan.

Beyond identifying direct associations, **Chapter 5** also examined whether transdiagnostic phenotypes mediated the relationship between polygenic risk for Alzheimer's disease and incident dementia. The general factor and all lower-order dimensions significantly predicted dementia risk. However, only the cognitive dysfunction dimension mediated the relationship between the AD-PGS and incident dementia. These findings reinforce the interpretation that genetic risk for AD operates through pathways specific to cognitive dysfunction rather than broader transdiagnostic pathways and suggest that targeting cognitive dysfunction may be uniquely beneficial in mitigating genetic risk for AD. However, the observed associations between lower-order dimensions of psychopathology and dementia suggest that these phenotypes may mediate dementia risk via genetic variants that are not captured by the AD-PGS. Moreover, the positive association between the general higher-order factor and incident dementia further suggests the presence of genetic variants shared across psychiatric and cognitive phenotypes that likewise contribute to neurodegenerative outcomes in later life. Overall, these findings underscore the importance of further research to determine how shared and domain-specific genetic influences shape the pathways linking psychopathology and cognitive dysfunction to dementia risk in later life.

6.4.5 Implications for dementia research

The findings of this thesis have several implications for research investigating the relationships between mental illness, cognitive function, and all-cause incident dementia in older adulthood. To date, most studies have focused on examining associations between specific psychiatric disorders and dementia risk (Aranda et al., 2023; Becker et al., 2018; Cai & Huang, 2018; Cherbuin et al., 2015; Dobrosavljevic et al., 2022; Velosa et al., 2020). The findings from these studies suggest that a given psychiatric disorder represents an independent risk factor or prodromal form of dementia, despite collectively indicating a level of non-specificity in the relationship between mental illness and dementia risk. In contrast, the findings of this thesis explicitly demonstrate that the relationship between mental illness and all-cause incident dementia is transdiagnostic in nature (**Chapter 5**). For example, lower-order dimensions of internalizing, addictions and substance use, and thought disorder were all significantly positively associated with incident dementia in the full sample of participants aged 55 to 78 years old and across all four age groups investigated in secondary analyses (i.e., ages 55-59, 60-64, 65-69, and 70-78 years old). This research also challenges the conventional approach to examining psychopathology and cognition as independent predictors of dementia. By modeling both constructs in the context of a hierarchical dimensional model, a general higher-order factor defined by the shared variance of psychiatric and cognitive dimensions (i.e., internalizing, addictions and substance use, thought disorder, cognitive dysfunction) was identified as a robust predictor of incident dementia across the full sample and in each age group throughout older adulthood. These findings indicate that the covariance between psychiatric and cognitive phenotypes capture meaningful variance in all-cause incident dementia and suggest the presence of shared underlying mechanisms (e.g., biological, environmental). Identifying these common mechanisms may offer novel targets for early intervention and prevention efforts aimed at reducing dementia risk in older adulthood.

Importantly, the findings of **Chapter 5** do not preclude the possibility that more specific features of mental illness (e.g., signs, symptoms, or lower-order dimensions) or cognitive function will demonstrate unique associations with dementia risk. Rather, they underscore the importance of accounting for broader transdiagnostic phenotypes when investigating these relationships. Indeed, multivariable analyses in **Chapter 5** identified two lower-order dimensions that were significantly associated with incident dementia over and above the influence of other lower-order phenotypes. Internalizing remained a significant predictor of incident dementia even when controlling for the effects of other lower-order psychiatric *and* cognitive dimensions and this association appears to emerge specifically in the later stages of older adulthood (i.e., between the ages of 65 and 78 years old). This indicates a robust association between emotionally-focused psychopathology (e.g., symptoms of depression, anxiety, self-harm, and suicidality) and incident dementia in older adulthood. Similarly, the cognitive dysfunction dimension was associated with incident dementia over and above the effects of internalizing, addictions and substance use, and thought disorder and this relationship appears to emerge between the ages of 60 and 78 years old. Together, these findings highlight two promising targets (i.e., internalizing and cognitive dysfunction) for prevention and intervention efforts and highlight the value of hierarchical dimensional models in disentangling shared and unique contributions of psychiatric and cognitive phenotypes to dementia risk in later life. The age-specific patterns of association further suggest that the predictive utility of different symptom dimensions may vary across stages of later life, highlighting the importance of age-stratified analyses in future research.

It is important to note that analyses in **Chapter 4** found no evidence that general psychopathology or three lower-order dimensions (i.e., internalizing, disinhibited-externalizing, substance use) were associated with incident dementia over 12 years of follow-up in older adults from the Sydney MAS. However, these null findings should be interpreted in the context of several limitations related to the analytic sample. Firstly, the Sydney MAS cohort represents a relatively healthy segment of the older adult population in that participants were free of dementia at baseline despite their advanced age range (i.e., 70 to 90 years old) and were predominantly well-educated and of higher socio-economic status. Secondly, the sample size in **Chapter 4** was relatively modest (N = 1,037) and few cases of dementia were reported over the follow-up period, limiting power to detect significant associations. Together, the conflicting findings between **Chapters 4** and **5** highlight the importance of examining the relationship between transdiagnostic dimensions of psychopathology and dementia in large, well-powered, and representative samples of older adults.

6.4.6 Clinical implications

The findings of this thesis also have several important clinical implications. Firstly, as outlined in **Chapter 1**, a key limitation of existing research is that support for hierarchical dimensional models has largely focused on their utility in research contexts and limited progress has been made regarding their translation to clinical practice (Ruggero et al., 2019). For hierarchical dimensional models to demonstrate utility in clinical contexts, they must first be validated across diverse populations, including in older adulthood. **Chapters 3-5** present the first studies to demonstrate that the hierarchical dimensional structure of psychopathology identified in younger samples is also evident in older adulthood. This provides critical support for the generalizability of hierarchical diagnostic frameworks across different age groups and developmental periods. In demonstrating the structural validity and age-invariance of hierarchical dimensional models in later life, the findings of this thesis lay essential groundwork for future translational efforts in ageing populations and support the eventual development of diagnostic approaches and treatment strategies that can be applied across the lifespan.

Second, psychiatric symptoms and cognitive deficits often co-occur in ways that complicate diagnosis and impact treatment outcomes (Kim et al., 2018; Millan et al., 2012). This issue is particularly salient in older adults, where age-related cognitive changes can obscure the presentation of psychiatric symptoms and contribute to complex, overlapping clinical profiles (Jeste et al., 2005; Lutz et al., 2018). **Chapters 3** and **5** of this thesis demonstrate that cognitive dysfunction can be modeled as a distinct but structurally integrated dimension alongside other transdiagnostic dimensions of psychopathology in later life. These findings lay the groundwork for future efforts to improve the identification, differentiation, and management of co-occurring psychiatric and cognitive symptoms in older adulthood. They also provide the foundation for developing future clinical tools and approaches that could support more personalized care, facilitate collaboration between psychiatric and cognitive services, and improve outcomes for older adults with comorbid or diagnostically complex presentations.

Third, the findings of this thesis also have several implications for the interpretation and application of biological data in clinical settings, particularly in older adults. Whilst neuroimaging has advanced etiological research, it is currently not suitable for diagnostic or treatment decision-making in any age group (First et al., 2018). The findings in **Chapter 2** indicate that transdiagnostic dimensions are associated with largely overlapping neuroanatomical signatures in younger samples, with little evidence of dimension-specific associations. The lack of unique associations reported across included studies highlights current limitations in the ability of transdiagnostic dimensional phenotypes to support differential diagnoses based on neurobiological markers. The null findings in **Chapter 4** further suggest that efforts to identify clinically useful neurobiological markers may be especially challenging in ageing populations, where age-related neurodegeneration and etiological heterogeneity may further hinder the ability to identify meaningful brain-behavior associations. In contrast, **Chapter 5** demonstrated that polygenetic risk for AD was robustly associated with cognitive dysfunction but not with any transdiagnostic dimension of psychopathology or with a general factor capturing shared variance among psychiatric and cognitive phenotypes. Cognitive dysfunction alone also mediated the relationship between the AD-PGS and incident dementia, indicating a specific pathway from polygenetic risk for AD to cognitive decline and subsequent dementia. These findings reinforce the value of incorporating direct assessments of cognitive functioning into psychiatric evaluations of older adults and suggest that targeting cognitive dysfunction (rather than psychiatric symptoms) may offer a uniquely effective approach to mitigating the impact of genetic risk for AD. More broadly, they suggest that genetic markers currently hold greater promise than neuroimaging markers (particularly in older adults) for identifying clinically useful biological associations that are capable of distinguishing between transdiagnostic phenotypes.

Fourth, the findings in **Chapter 5** have important implications for improving the screening, early identification and prevention of dementia in older adulthood. The results indicated that all transdiagnostic dimensional phenotypes (i.e., general psychopathology, internalizing, addictions and substance use, thought disorder, and cognitive dysfunction) were prospectively associated with increased risk of dementia in later life. Hierarchical dimensional frameworks may thus be better suited for identifying those at risk of dementia compared to approaches focused on individual psychiatric disorders or cognitive profiles, allowing for more comprehensive assessment and capturing subclinical presentations that may otherwise be overlooked. **Chapter 5** further identified that cognitive dysfunction and internalizing remained significantly associated with dementia even when controlling for the effects of other lower-order dimensions, suggesting that these phenotypes may be particularly promising targets for prevention and intervention and further supporting the integration of psychiatric and cognitive assessments into routine evaluations of dementia risk in older adulthood. Finally, age-specific analyses revealed that internalizing was uniquely associated with dementia risk between ages 65 and 78, whilst cognitive dysfunction was uniquely associated between the ages of 60 and 78. These findings highlight the importance of age-sensitive screening and intervention strategies that account for heterogeneous pathways to dementia risk in later life. Overall, the findings of **Chapter 5** suggest that hierarchical dimensional models may serve as a clinically useful framework for improving the identification of individuals at increased risk of dementia in later life and guide the development of more targeted and age-sensitive intervention strategies.

6.5 Suggested directions for future research

The findings of this thesis highlight several directions for future research investigating the latent hierarchical structure of psychopathology (Section 6.5.1), the biological correlates of transdiagnostic dimensions (Section 6.5.2), and the relationship between transdiagnostic phenotypes and incident dementia (Section 6.5.3) across the lifespan and specifically in older adulthood.

6.5.1 Directions for future research investigating the hierarchical structure of psychopathology across the lifespan

Several studies included in this thesis demonstrate that the hierarchical dimensional structure of psychopathology identified in younger populations also emerges in general population samples of older adults (**Chapters 3-5**). Future research should attempt to identify this same hierarchical structure in specific subpopulations of older adults (e.g., clinical samples and samples with mild cognitive impairment or pre-existing diagnoses of dementia) and in participants from more diverse backgrounds (e.g., those from low- to middle-income countries and those of different racial and ethnic backgrounds). The measurement models examined in this thesis were also limited in their coverage of psychopathology and further research is needed to examine whether other commonly studied transdiagnostic dimensions (e.g., broad externalizing, psychosis) and subdimensions (e.g., fear, detachment) also emerge in later life.

The findings in **Chapters 3** and **5** also contribute to an emerging body of evidence indicating that dimensions capturing cognitive dysfunction can be incorporated into hierarchical dimensional models of psychopathology (Forbes et al., 2024b; Ringwald, 2024; Rotstein et al., 2023). Further research using confirmatory factor analysis should attempt to replicate this model in other general population samples of older adults, in specific subpopulations of older adults (e.g., clinical or more diverse), and more generally in samples covering other age groups and developmental periods. This research should also attempt to address some of the methodological limitations of these studies, particularly by examining whether the strength of association between cognitive dysfunction and general higher-order dimensions differs when psychiatric and cognitive assessments are conducted at the same time point and using the same modality (e.g., using self-report indicators of psychopathology and cognitive function; see Forbes et al., 2024b).

Finally, the measurement models included in this thesis examined the latent structure and age-invariance of psychopathology cross-sectionally. Future research should prioritize longitudinal designs that include consistent repeated measures of psychopathology to evaluate the temporal stability and developmental trajectories of hierarchical dimensional models in later life. In particular, *longitudinal* invariance testing in this population is needed to establish whether the underlying structure of psychopathology remains invariant across time within individuals. If longitudinal measurement non-invariance in older populations is supported, techniques such as latent growth curve modeling could be implemented, allowing for the estimation of intra-individual changes in symptom dimensions and the identification of risk and protective factors that influence baseline levels and rates of change in the levels of transdiagnostic phenotypes in later life. However, the ability to pursue such questions is currently limited by the lack of suitable longitudinal datasets in older populations. There is a clear need for large-scale data collection efforts in older adults that include detailed measurement of psychopathology across multiple dimensions and time points.

6.5.2 Directions for future research investigating the biological correlates of transdiagnostic dimensions of psychopathology across the lifespan and specifically in older adults

Further research is needed to more thoroughly examine the neurobiological correlates of transdiagnostic dimensions in older adulthood. Most importantly, this includes replicating the analyses from **Chapter 4** using larger samples of older adults and extending this research by employing more fine-grained approaches to measuring alterations in brain structure (e.g., whole-brain voxel-wise analyses). In addition to the dimensions already investigated, future research should also explore neurobiological associations with other commonly studied transdiagnostic phenotypes (e.g., thought disorder) and more novel dimensions (e.g., cognitive dysfunction) that were successfully incorporated into hierarchical dimensional models in **Chapters 3** and **5**. Future research should also investigate whether associations between transdiagnostic dimensions and neurobiology differ as a function of the timing of symptom onset (e.g., early developmental onset, late onset) and symptom severity (e.g., clinically-significant psychiatric expression), which may reflect distinct etiological pathways.

Furthermore, whilst **Chapter 4** examined whether transdiagnostic dimensions predicted intra-individual change in brain structure over time, future studies should also examine the inverse association (i.e., whether brain structure predicts changes in the levels of transdiagnostic dimensions) and explore potential bidirectional relationships in later life. However, this research hinges on the availability of large-scale longitudinal datasets that include both neuroimaging data and detailed repeated measures of psychopathology. As noted previously, such datasets are not currently available. Finally, future research should also incorporate alternative imaging modalities that may be associated with transdiagnostic psychopathology in later life. This includes functional magnetic resonance imaging (fMRI) to examine associations with patterns of functional connectivity and network-level dysfunction, as well as diffusion tensor imaging (DTI) to examine potential associations with white matter microstructure. Notably, further research employing the use of these imaging modalities (i.e., fMRI, DTI) was also identified in **Chapter 2** as an important direction for future research in younger cohorts.

In the context of genomic research, a key priority for future studies is to investigate associations between polygenetic risk and transdiagnostic phenotypes in older adulthood using a more comprehensive set of PGSs. This includes PGSs indexing genetic liability towards a broad range of psychiatric disorders and traits and PGSs for neurocognitive conditions (e.g., other subtypes of dementia). It will also be important for these studies to investigate whether patterns of association change when multiple PGSs are simultaneously included in a given model, as discussed in **Chapter 2**. More generally, future research is also needed to investigate associations with PGSs derived from genome-wide association studies (GWASs) of transdiagnostic phenotypes (e.g., PGSs for internalizing, externalizing, thought disorder), both in older adults and across other age groups and developmental periods. These studies will be critical to more precisely validating the genetic coherence of hierarchical dimensional models of psychopathology. However, only a limited number of GWASs have directly investigated transdiagnostic dimensional constructs to date (Jami et al., 2022; Karlsson Linnér et al., 2021). In parallel, studies incorporating cognitive phenotypes should examine associations with broader PGSs capturing genetic risk for multiple neurocognitive conditions and PGSs indexing combined risk for psychiatric and cognitive traits. The latter approach may be particularly informative in studies investigating associations with general factors defined by the shared variance of both psychiatric and cognitive indicators.

As noted, **Chapter 5** found that the AD-PGS was uniquely associated with cognitive dysfunction in older adulthood and not with any transdiagnostic dimension of psychopathology. Future studies should aim to replicate this finding in other cohorts, to determine the robustness and generalizability of these results. Furthermore, examining this association in younger samples would be useful to determine whether polygenetic risk for Alzheimer's disease predicts earlier manifestations of cognitive dysfunction or whether this relationship is specific to older adults. Indeed, if genetic risk for Alzheimer's disease is associated with cognitive dysfunction in youth this would suggest that early interventions targeting cognition may mitigate the long-term impact of genetic vulnerability to this condition.

Further building on the results of **Chapter 5**, future studies should aim to identify genetic variants that contribute to general dimensions defined by both psychiatric and cognitive indicators. This research would clarify whether shared genetic liability underlies co-occurring psychopathology and cognitive dysfunction in later life and potentially reveal common biological pathways to dementia in this population. Moreover, this research would strengthen the validity of hierarchical dimensional models incorporating psychiatric and cognitive phenotypes. Finally, future research should investigate potential mediating pathways linking genetic risk and dementia through transdiagnostic dimensions of psychopathology, rather than cognitive dimensions. For example, PGSs indexing liability to psychiatric disorders (e.g., depression, schizophrenia) may contribute to dementia risk indirectly via their influence on levels of transdiagnostic dimensions of psychopathology (e.g., internalizing, thought disorder).

6.5.3 Suggestions for future research examining the relationships between transdiagnostic dimensions and incident dementia in older adulthood

Other important directions for future research stemming from the findings of this thesis involve more thoroughly investigating the relationships between transdiagnostic dimensions and incident dementia. Firstly, it is necessary to replicate the findings of **Chapter 5** in independent samples of older adults to evaluate the generalizability of these findings (particularly given the null findings of **Chapter 4**). It would also be beneficial to examine whether transdiagnostic phenotypes predict incident dementia over longer follow-up periods (i.e., whether levels of general and specific/lower-order transdiagnostic dimensions in younger age groups predict dementia in later life). This would provide important insights into the long-term predictive utility of transdiagnostic dimensional phenotypes and inform the timing of preventative interventions across the lifespan. Another important priority for future research is to investigate the relationships between internalizing, cognitive dysfunction, and dementia in more detail, given that these phenotypes emerged as uniquely robust predictors in **Chapter 5**. In particular, future studies should examine the age periods during which associations between internalizing, cognitive dysfunction, and dementia are most pronounced, assess whether these associations vary by dementia subtypes, and assess potential moderation of these relationships by other factors (e.g., baseline cognitive status, symptom severity, biological vulnerabilities). A more detailed understanding of these patterns may improve the utility of transdiagnostic phenotypes in identifying individuals at elevated risk of dementia and inform the optimal timing of dementia risk screening and targeted preventative interventions.

A further priority for future research is to expand the range of transdiagnostic phenotypes and dementia outcomes examined. For example, studies should examine associations with broader transdiagnostic phenotypes (e.g., externalizing, psychosis) that capture variance not accounted for by more narrowly defined subdimensions (e.g., disinhibited-externalizing, addictions and substance use, thought disorder). Relatedly, studies should assess associations with specific subtypes of dementia (e.g., Alzheimer's disease, frontotemporal dementia, vascular dementia) and specifically investigate whether general and specific/lower-order dimensions are differentially associated with these subtypes. Identifying dissociable patterns of association would help to determine whether particular symptom dimensions are differentially relevant to specific neurodegenerative processes and could inform more tailored approaches to risk assessment and intervention.

Finally, future research should directly examine the clinical utility of hierarchical dimensional models of psychopathology in the early detection and prevention of dementia. This should include assessing whether the phenotypes derived from these models (particularly key dimensions e.g., internalizing, cognitive dysfunction) improve risk prediction beyond established clinical markers and whether they can feasibly be incorporated into screening tools used in clinical settings.

6.6 Conclusions

The findings of this thesis advance our understanding of psychopathology across the lifespan, addressing critical gaps in the existing literature with respect to ageing populations. The empirical chapters included herein represent the first attempt to comprehensively examine the underlying structure, biology, and clinical consequences of psychopathology specifically in older adulthood. These chapters draw on multidisciplinary and methodologically rigorous approaches, integrating insights from diverse but interrelated fields (e.g., psychiatric epidemiology, neuroscience, genetics, cognitive science, statistical modeling) to address complex questions at the intersection of mental health, biology, and ageing. Hierarchical dimensional models are identified as a novel and powerful framework for investigating psychiatric and cognitive health in older adulthood, offering a means of more precisely and effectively characterizing psychopathology and its associations with neurobiology, genetics, and clinical outcomes in this population.

Chapters 3-5 demonstrate the structural validity and age-invariance of hierarchical dimensional models of psychopathology in older adulthood and underscore the value of incorporating dimensions capturing cognitive dysfunction within that structure. **Chapter 4** highlights the complexity of identifying neurobiological correlates of transdiagnostic phenotypes in ageing populations and the need for future research using larger samples, finer-grained imaging approaches, and more detailed psychiatric phenotyping. **Chapter 5** demonstrates that hierarchical dimensional models can be applied to investigate the genetic architecture of psychopathology in later life and highlights the utility of extending these models to include both psychiatric and cognitive phenotypes in order to identify dimension-specific associations with genetic risk for non-psychiatric conditions (e.g., neurocognitive disorders) in older adulthood. Finally, the findings of this thesis provide support for the utility of hierarchical dimensional models in investigating the relationships between psychopathology, cognitive dysfunction, and all-cause incident dementia in later life. Taken together, these findings establish a new empirical foundation for advancing research into the underlying structure, biology, and clinical consequences of psychopathology in ageing populations. In doing so, they draw attention to an age group often neglected in psychiatric research and emphasize that research in this population is fundamentally important to developing a comprehensive understanding of mental illness across the lifespan.

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Appendix A

Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population

Preface

This systematic review was published as **Hoy, N**., Lynch, S.J., Waszczuk, M.A., Reppermund, S., & Mewton, L. Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population. *Neuroscience and Biobehavioural Reviews*, 155, 105431. https://doi.org/10.1016/j.neubiorev.2023.105431

NH conceptualized the study with support from LM, SR, and MW. NH screened 100% of the titles and abstracts identified by the search strategy and SL screened 25% of the titles and abstracts. NH and SL screened 100% of the full texts identified via title and abstract screening. NH completed 100% of data extraction and quality assessments, completed the narrative synthesis and drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Review article

Transdiagnostic biomarkers of mental illness across the lifespan: A systematic review examining the genetic and neural correlates of latent transdiagnostic dimensions of psychopathology in the general population

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ABSTRACT

This systematic review synthesizes evidence from research investigating the biological correlates of latent transdiagnostic dimensions of psychopathology (e.g., the p-factor, internalizing, externalizing) across the lifespan. Eligibility criteria captured genomic and neuroimaging studies investigating general and/or specific dimensions in general population samples across all age groups. MEDLINE, Embase, and PsycINFO were searched for relevant studies published up to March 2023 and 46 studies were selected for inclusion. The results revealed several biological correlates consistently associated with transdiagnostic dimensions of psychopathology, including polygenic scores for ADHD and neuroticism, global surface area and global gray matter volume. Shared and unique associations between symptom dimensions are highlighted, as are potential age-specific differences in biological associations. Findings are interpreted with reference to key methodological differences across studies. The included studies provide compelling evidence that the general dimension of psychopathology reflects common underlying genetic and neurobiological vulnerabilities that are shared across diverse manifestations of mental illness. Substantive interpretations of general psychopathology in the context of genetic and neurobiological evidence are discussed.

1. Introduction

Mental illness is a leading contributor to the global burden of disease (Anon, 2022). The most recent estimates indicate that mental illness affects approximately 970 million people worldwide, corresponding to a 48.1% increase in the prevalence of psychiatric disorders since 1990 (Anon, 2022). Effective strategies for the prevention, diagnosis, and treatment of psychopathology are needed to reduce the global burden of mental illness. Biological research plays a critical role in the development of these strategies by informing our understanding of the etiology, course, and consequences of psychopathology (Wilson and Olino, 2021; Glannon, 2022; Cuthbert, 2014). This research broadly aims to identify valid and reliable biological markers of mental illness, in order to facilitate the development of effective preventative interventions (e.g., identifying at-risk individuals) and treatment approaches (e.g., predicting illness course, informing decision-making, pharmacological interventions). Importantly, identifying the biological underpinnings of mental illness also helps to validate and distinguish between different psychiatric phenotypes, which is critical to improving diagnostic accuracy and disentangling the inherent heterogeneity of psychiatric expression (Michelini et al., 2021; Smoller et al., 2019a; Cuthbert and Insel, 2013).

1.1. The categorical model of psychopathology

Despite decades of research and significant advances in genetic and neuroimaging methods, little progress has been made in identifying

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disorder-specific biomarkers with demonstrated clinical significance (Venkatasubramanian and Keshavan, 2016). A growing number of researchers argue that this lack of progress is driven by reliance on the categorical model of psychopathology (Cuthbert and Insel, 2013; Waszczuk et al., 2020; Latzman and DeYoung, 2020), endorsed by both the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) and the International Classification of Diseases (ICD) (World Health Organization, 2016). Briefly, the categorical model of psychopathology organizes psychiatric symptoms into a set of discrete diagnostic categories, distinct from other forms of psychopathology and from normal functioning. However, research has consistently demonstrated that liability towards disorder follows a continuum, ranging from normal functioning to more severe expressions of mental illness (Markon et al., 2011; Krueger et al., 2018; Kotov et al., 2017a). Psychiatric disorders also frequently co-occur within the same individual (i.e., comorbidity) (Kessler, 1994; Caspi et al., 2020) and show marked heterogeneity in symptom presentation and severity between individuals (Caspi et al., 2020; Feczko et al., 2019). Overall, this research suggests that the structure of psychopathology is poorly aligned with the discrete categorical boundaries imposed by traditional classification systems. For this reason, the categorical approach is now widely considered to provide a suboptimal framework through which to investigate the biological underpinnings of mental illness.

1.2. Latent Dimensional Models of Psychopathology

Latent dimensional models offer a data-driven alternative to measuring psychiatric phenotypes. These models identify patterns of covariation across a range of observed psychiatric symptoms, traits, and/or disorders and typically organize the structure of psychopathology hierarchically (Kotov et al., 2017a, 2021; Wright, 2023). Psychiatric symptoms and traits (e.g., depression, anxiety, substance use, aggressive behavior) are positioned at the lowest level of the hierarchy and grouped into higher-order dimensions based on their patterns of covariation with one another (e.g., internalizing, externalizing) (Kotov et al., 2021, 2017b). Briefly, the internalizing dimension typically captures more emotionally-focused indicators of psychopathology (e.g., anxiety, depression, specific phobia), whilst the externalizing dimension captures those that are more behaviourally-focused (e.g., aggression, impulsivity, substance use). Other prominent transdiagnostic phenotypes include the thought disorder dimension (which typically captures indicators of psychoticism e.g., hallucinations, delusions, disorganized thought) and the neurodevelopmental dimension (which typically captures indicators of neurodevelopmental disorders e.g., autism spectrum, developmental co-ordination disorder, and attention-deficit/hyperactivity disorder symptoms). Importantly, a superordinate general dimension of psychopathology (often referred to as the p-factor) is positioned at the top of this hierarchical structure (Kotov et al., 2021). This general dimension accounts for the frequent co-occurrence of mental health problems and is thought to reflect an underlying liability towards the full spectrum of psychopathology (Caspi et al., 2014; Caspi and Moffitt, 2018a).

The most prominent model to emerge from structural research is the Hierarchical Taxonomy of Psychopathology (HiTOP), a data-driven, hierarchically based classification system for mental illness (Kotov et al., 2017a, 2021). Within the HiTOP model, a general dimension of psychopathology (i.e., the p-factor) is positioned at the top of a hierarchical framework. This higher-order dimension is subdivided into increasingly specific lower-order spectra (e.g., internalizing, externalizing, thought disorder) and sub-spectra (e.g., internalizing can be subdivided into distress and fear dimensions). The general dimension of psychopathology (i.e., the p-factor) is defined by patterns of covariation among specific/lower-order dimensions (e.g., internalizing, externalizing), which are in turn defined by patterns of covariation among individual symptoms, signs, and maladaptive traits (Kotov et al., 2017a). The hierarchical and dimensional structure of psychopathology captured by the HiTOP model has been extensively validated, as outlined in several previous reviews (Kotov et al., 2021, 2017b, 2020; Krueger et al., 2021; Watson et al., 2022).

Factor analytic methods are the most commonly used approaches to studying the latent structure of psychopathology, predominately including correlated-factor, higher-order, and bi-factor models. These models offer several advantages over traditional diagnostic categories in examining the biological basis of mental illness: 1) they directly model the observed correlational and dimensional structure of psychiatric symptoms and thereby provide more valid and reliable phenotypes; 2) they offer greater precision and increased statistical power; and 3) they enable investigating biological correlates at varying levels of specificity and across the entire spectrum of psychiatric expression (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Zald and Lahey, 2017). Recent decades have seen a proliferation of research investigating the latent dimensional structure and underlying biology of psychopathology. This research is facilitated by the collection of large-scale datasets, primarily involving general population samples. Prominent examples include the Adolescent Brain and Cognitive Development (ABCD) Study (Satterthwaite et al., 2016), the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2016), and the UK Biobank (Sudlow et al., 2015). These studies involve extensive multidimensional data collection, often including detailed psychiatric assessments, as well as both neuroimaging and genomic measures. They also recruit significantly large sample sizes, providing the necessary statistical power for analyses of high-dimensional (e.g., genomic, neuroimaging) data and increasing the generalizability of research findings.

1.3. Genetic and neuroscientific biomarkers of mental illness

The expression of psychopathology arises from a complex set of interactions between different biological mechanisms (e.g., genomic, brain structural, brain functional) and between biological and environmental factors more broadly. As such, both genetic and neuroscientific research are fundamentally important to understanding of the biological basis of mental illness and provide promising and widely explored avenues for the identification of psychiatric biomarkers. In recent years, molecular genetic research has shifted its focus from candidate gene studies to genome-wide approaches in aiming to identify the genetic architecture underlying complex traits and disorders (Duncan et al., 2019). For example, genome-wide association studies (GWASs) compare the frequencies of a large number (typically 500k-1 M) of common variants across the genome (e.g., single-nucleotide polymorphisms or SNPs) between cases of a given phenotype (e.g., depressed patients) and controls (Corvin et al., 2010; Tam et al., 2019). Summary statistics from these studies can then be used to calculate polygenic scores (PGSs) in independent samples, providing a single quantitative metric of genetic risk for a particular trait or disorder based on the aggregate effects of genetic variants found to be associated with that phenotype through the relevant GWAS (Lewis and Vassos, 2022). These approaches capture polygenetic influences on psychiatric phenotypes (i.e., the contribution of multiple genetic variants to a given disorder) and have consistently demonstrated evidence of widespread pleiotropy across different forms of mental illness (Lewis and Vassos, 2022; Smoller et al., 2019b; Lee et al., 2021). That is, genetic variants influencing the expression of psychopathology are largely shared across putatively distinct diagnostic categories (Waszczuk et al., 2020).

Psychiatric neuroscience offers a complementary and interrelated approach to investigating the biological basis of mental illness. Generally, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) are used to investigate whether alterations in macroscopic (e.g., gray matter) and microscopic (e.g., white matter) features of brain morphology (i.e., brain structure) contribute to the expression of psychopathology. Alternatively, functional MRI (fMRI) measures changes in blood oxygenation levels as a proxy for neural activity and allows for investigating the functional neural correlates of mental illness. Resting-state fMRI measures spontaneous fluctuations in neural activity in the absence of external stimulation whilst task-based fMRI measures changes in blood oxygen level dependent (BOLD) responses to an experimental task. Similar to genomic research, neuroscientific studies historically aimed to identify disorder-specific associations within discrete brain regions and have more recently begun to examine how psychopathology relates to the interactions between them and to the overall structural and functional architecture of the brain. Importantly, alterations in brain structure and function have also been implicated across a range of psychiatric disorders and evidence from meta-analytic research suggests that these associations are primarily shared across different diagnostic categories (Goodkind et al., 2015; McTeague et al., 2017; Sha et al., 2019). These findings indicate that the biological mechanisms associated with mental illness are consistent with the observed correlational structure of psychopathology identified through phenotypic research. Both genomic and neuroimaging studies also indicate that the biological mechanisms underlying different manifestations of psychopathology are associated with subclinical expressions of mental illness in the general population, which is further consistent with the observed dimensionality of psychiatric phenotypes (Martin et al., 2018; Besteher et al., 2020).

Whilst several previous reviews have examined the correlates of transdiagnostic dimensional phenotypes, most have not followed a systematic approach (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Kotov et al., 2017a, 2021; Perkins, 2020; Conway et al., 2019). Furthermore, those which focused specifically on genetic or neuroimaging research examined only a select number of studies (Waszczuk et al., 2020; Latzman and DeYoung, 2020; Perkins*** et al., 2020). Research investigating the biological correlates of transdiagnostic symptom dimensions is rapidly developing and as such, it is important to provide a comprehensive overview and synthesis of the current evidence. A single review has systematically explored risk and protective factors (including biological factors) associated with transdiagnostic symptom dimensions but the included studies were restricted to a narrow age range (i.e., 10–24 years old) (Lynch et al., 2021). Whilst this was an important first step, research has long demonstrated age- and developmentally-specific differences in the expression of mental illness that are driven by normative and non-normative changes in genetic, neurobiological, and environmental factors (Wilson and Olino, 2021). Research across the lifespan is therefore critical to accurately modelling the structure and underlying biology of mental illness (Lahey et al., 2017). The aforementioned advantages of latent symptom dimensions over traditional diagnostic categories suggests that they may provide new insights into the etiology of mental illness and the biological mechanisms and processes associated with changes in the expression of psychopathology across different age groups and developmental periods. Moreover, this research may guide biologically-informed preventative and early intervention efforts (e.g., by identifying biomarkers that predict the onset of psychopathology), as well as the development of effective treatment strategies (e.g., by identifying biomarkers associated with active psychopathology, or prolonged exposure to psychopathology, which provide targets for pharmacological intervention) (Beauchaine et al., 2008).

1.4. The present review

The present review aims to extend previous research by systematically evaluating evidence from studies investigating the biological correlates of latent transdiagnostic symptom dimensions in the general population, across the lifespan. The review covers a wide range of biological correlates (i.e., genomic, brain structural, and brain functional) at various levels of specificity (i.e., general and specific transdiagnostic symptom dimensions). Synthesizing this research will provide a comprehensive understanding of the current evidence base and identify promising and understudied directions for future research aiming to advance the field.

2. Methods

2.1. Study protocol

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A, Table S1). The study protocol was published prospectively (Hoy et al., 2022) and registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021262717). Deviations from the protocol are outlined in Appendix A.

2.2. Search strategy

A comprehensive search strategy was employed across Embase, MEDLINE, and PsycINFO (Appendix B, Table S2). An initial search was run in July 2021 and re-run in March 2023. The search strategy captured three broad domains, including: latent variable models of psychopathology, genetics, and neuroimaging. Specifically, the overall strategy functioned as follows: (latent variable model terms AND psychopathology terms) AND (molecular genetic OR genomic terms) OR (brain structural OR brain functional neuroimaging terms). Reference lists of included articles were manually searched for additional citations.

2.3. Study eligibility

Eligibility criteria were developed using the Population Exposure Comparator Outcome (PECOS) framework. No criteria were imposed for the comparator component because research investigating dimensional models of psychopathology does not require the use of control groups (Lynch et al., 2021). The following inclusion and exclusion criteria were applied:

2.3.1. Inclusion criteria

Population.

Only studies investigating general population samples were eligible for inclusion.
Studies investigating any age group were eligible.
Only studies investigating human participants were eligible.

Exposure.

Studies using any latent variable modelling technique (e.g., factor analysis, principal component analysis, structural equation modelling) to investigate symptom- or disorder-level latent transdiagnostic dimensions as the exposure were eligible for inclusion.
  Studies investigating any latent transdiagnostic dimension(s) of psychopathology (e.g., general psychopathology, externalizing, internalizing, thought disorder) were eligible.
  Studies investigating any latent structural model(s) of psychopathology (e.g., bifactor models, hierarchical models, correlated factor models) were eligible.
Studies using any technique to investigate molecular genetic or genomic variables as the exposure (with the exception of candidate gene studies) were eligible for inclusion.
Studies using any neuroimaging technique to investigate any brain structural or brain functional variable as the exposure were eligible for inclusion.
Both whole-brain and region of interest neuroimaging studies were eligible.

Outcomes.

For studies that treat psychiatric phenotypes (i.e., symptom- or disorder-level latent transdiagnostic dimensions) as the exposure, the outcome measure must include at least one biological variable (i.

e., molecular genetic, genomic, brain structural, and/or brain functional).
For studies that treat biological variables as the exposure, at least one symptom- or disorder-level latent transdiagnostic dimension (e.g., general psychopathology, externalizing, internalizing) must be measured as the outcome.
Only studies reporting empirical data were included.

Study characteristics.

Only peer-reviewed studies were included.
Both cross-sectional and longitudinal studies were eligible. For longitudinal studies, all timepoints were considered.
Studies including any sample size were eligible.
Studies written in any language were eligible.

2.3.2. *Exclusion criteria*

Population.

With the exception of severe psychopathology (e.g., schizophrenia, autism), studies in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or maltreatment) were not eligible for inclusion.
Studies of non-human animals were excluded.

Exposures/Outcomes.

Studies investigating individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories were excluded.
Studies in which psychopathology was not measured using latent variable techniques (e.g., total scores on transdiagnostic instruments) were excluded.
Studies that included biometric genetic measures (e.g., twin, family, and adoption studies) were excluded.
Candidate gene studies were excluded.
Neurophysiological studies (e.g., studies using electroencephalography to measure neural activity) were excluded.
Neuroscientific studies using techniques other than neuroimaging (e.g., post-mortem studies) were excluded.

Study characteristics.

Grey literature and conference abstracts were excluded.
Publications that did not report original empirical findings (e.g., reviews, opinion pieces, letters, books, or book chapters) were excluded.

2.4. *Selection procedure*

Two reviewers (i.e., NH and SL) were involved in screening and study selection procedures. Following de-duplication, reviewer one (NH) screened all titles and abstracts to identify eligible studies. Reviewer two (SL) independently screened a random selection of 25% of the titles and abstracts to ensure accuracy of study selection. Following title and abstract screening, the full-texts of all included articles were screened by both reviewers to further assess study eligibility. Cohen's kappa was calculated to measure inter-rater agreement (for title and abstract screening and full-text screening) between the two reviewers, with a high level of agreement defined as a Cohen's kappa of.80 or above (McHugh, 2012). Disagreements were resolved through consultation among the two reviewers. Where disagreements could not be resolved, a third member of the research team (i.e., LM, SR, or MW) was consulted to reach consensus.

2.5. *Data Extraction*

All citations were imported to Covidence (Veritas Health Innovation, 2023) for title, abstract and full-text screening. Study data were extracted by NH using a data extraction spreadsheet developed by the research team.

2.6. *Data synthesis and quality assessment*

The results of all included genomic and neuroscientific (i.e., brain structural, and brain functional) studies are reported separately. Sufficient data were not available for meta-analyses and as such, a narrative synthesis of the results from included studies was conducted. Following data extraction, the quality of each included study was assessed independently by NH using checklists from the Joanna Briggs Institute (Moola et al., 2020). Cross-sectional studies were evaluated using the Checklist for Analytical Cross-Sectional Studies and longitudinal studies were evaluated using the Checklist for Cohort Studies (Moola et al., 2020).

3. Results

3.1. *Selection of studies*

The search strategy returned 7010 studies (after de-duplication) across the three databases. Of these, 173 remained eligible for inclusion following title and abstract screening. After full-text screening and manual search of citations, 46 studies were selected for inclusion in the review. Cohen's kappa showed a moderate level of agreement for title and abstract screening (k = 0.56) and for full-text screening (k = 0.48). The PRISMA flow chart is provided in the supplementary material (Appendix A, Fig. S1). Quality assessments for each of the included studies are presented in Table S3 (Appendix B).

3.2. *Characteristics of included studies*

A broad overview of study characteristics is presented in Table 1. Briefly, the review included 18 genomic studies, 14 structural neuroimaging studies, 11 functional neuroimaging studies, one study that included both structural and functional neuroimaging measures, and two studies that included both genomic and brain structural measures. There were 16 unique datasets used across the included studies, most commonly from the ABCD Study (n = 13) and the PNC (n = 9; see Appendix B, Table S4). The majority of included studies investigated samples of youth (i.e., childhood to young adulthood). In the genomics literature, 13 out of the 18 studies included participants aged 7–22 years old. One study examined latent trajectories of externalizing between the ages of 18–32 and the remaining studies included wide age ranges, from adulthood to older adulthood (ages 18–64, 25–75) or midlife to older adulthood (ages 37–73, 40–69, 51–83). In the structural neuroimaging literature, 10 of the 14 studies examined participants aged 6–23 years old. Of the remaining studies, one examined latent disinhibition in the UK Biobank (ages 40–69) and three examined participants form the Dunedin Study (age 45) (age 45). The 11 included functional neuroimaging studies examined samples ranging from childhood to young adulthood (ages 9–23) and almost half used participants from the ABCD Study (n = 5). Not a single included study across any domain (i.e., genomic, neuroimaging) focused specifically on older adults (i.e., samples aged 60 +). In terms of study design, 32 of the included studies were cross-sectional and 14 were longitudinal. The following section synthesizes evidence for relationships between transdiagnostic symptom dimensions and biological variables that were investigated across two or more of the included studies, as well as any notable trends that emerged. Key findings from the genomics and structural neuroimaging literature are presented in Table 2 and Table 3, respectively. For detailed summaries of all included studies (including effect sizes, where available)

Table 1
Overview of studies included in the review.

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
1. Genomic Studies							
Allegrini et al. (2020)	TEDS	7 (T1); 9 (T2); 12 (T3); 16 (T4)	L	N = 7026	PCA	General psychopathology	Genomic p-factor (derived from PGSs for ASD, MDD, BIP, SCZ, ADHD, OCD, AN, PTSD)
Avinun et al. (2020)	DNS	18–22	CS	N = 522	Bi-factor model	General psychopathology, internalizing, externalizing, thought disorder	PGSs for vitamin D serum levels
Birkell et al. (2020)	CATSS	9–12	CS	N = 13,457	(1) Bi-factor model (2) Bi-factor model	(1) General psychopathology (2) General psychopathology	PGSs for ADHD
Chen et al. (2022)	CATSS	9–12 (T1), 15 (T2)	L	N = 3907	(1) Bi-factor (S-1) model (2) Bi-factor (S-1) model	(1) General psychopathology (T1) (2) General psychopathology, emotional symptoms (i.e., internalizing) (T2)	PGSs for SCZ, BIP, MDD, neuroticism, ANX, PTSD, eating disorder, ASD, ADHD, ADHD symptoms, education, intelligence
Cuevas et al. (2021)	MIDUS Biomarker Project	25–75	CS	N = 1146	Two-factor model	Anxiety/negative affect (i.e., anxious-misery)	PGSs for ANX, MDD, and neuroticism
Gard et al. (2021)	HRS	51–83	CS	N = 3001	One-factor model	General psychopathology	General PGSs, internalizing-specific PGSs and externalizing-specific PGSs, as well as PGSs for MDD, ANX, ADHD, alcohol dependence, antisocial behaviour, cannabis, neuroticism, and height
Grotzinger et al. (2019)	UK Biobank	40–69	CS	N = 332,050	Bi-factor model	General psychopathology	General PGSs and PGSs for SCZ, BIP, MDD, ANX, PTSD
Jermy et al. (2022)	UK Biobank	37–73	CS	N = 119,692	Higher-order model	Internalizing	PGSs for MDD and height
Jones (2018)	ALSPAC	16	CS	N = 2863	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology, psychotic experiences (i.e., thought disorder) (2) Psychotic experiences (i.e., thought disorder)	PGSs for SCZ, MDD, BIP, and neuroticism
Lahey et al. (2022)	ABCD	9–10 (T1), 10–11 (T2)	L	N = 4342	Bi-factor model	General psychopathology, internalizing	PGSs for ADHD
Li et al. (2019)	Add Health	18–26 (T1), 24–32 (T2)	L	N = 7674	LCG model	Normal (consistently low levels), high decreasing (high initial symptoms that decrease over time), moderate (consistently moderate levels), and low increasing (low initial symptoms that increase over time) trajectories of externalising.	PGSs for ADHD
Mollon et al. (2021)	PNC	8–22	CS	N = 4662	(1) Bi-factor model (2) Higher-order model	General psychopathology, anxious-misery, fear, externalizing, psychosis (i.e., thought disorder)	SNP-heritability; genetic correlations; and gene by age interactions
Neumann et al. (2016)	Generation R	6–8	L*	N = 2115	Bi-factor model	General psychopathology, internalizing, externalizing	SNP-heritability
Musci et al. (2016)	Community sample	11 (T1), 17 (T2)	L*	N = 488	LTSO model	Latent trait measure of internalizing	PGSs for MDD
Pat et al. (2022)	ABCD	9–10	CS	N = 4814	(1) Higher-order model (2) Correlated-factors model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatic, detachment	PGSs for MDD, ADHD, ANX, BIP, SCZ, and ASD
Quattrone et al. (2021)	EU-GEI (population-based control group)	18–64	CS	N = 1497	Bi-factor model	General psychotic symptoms (i.e., thought disorder)	PGSs for SCZ
Riglin et al. (2020)	ALSPAC	7 (T1), 13 (T2)	L	N = 5518	Bi-factor model	General psychopathology, emotional (i.e., internalizing), behavioural (i.e., externalizing), neurodevelopmental	PGSs for SCZ, ADHD, ASD, MDD
Waszczuk et al. (2022)	ABCD	9–10	CS	N = 4717	(1) One-factor model (2) Five-factor model	(1) General psychopathology (2) Internalizing, externalizing, neurodevelopmental, somatoform, detachment	PGSs for adventurousness, disinhibition, number of sexual partners, risk tolerance, drinks per week (1), drinks per week (2), ever smoked regularly, depression, neuroticism, PTSD, insomnia, BIP, SCZ, ADHD, ASD, knee pain, chronic multisite pain, chronic back pain, educational

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Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
							attainment, intelligence, Alzheimer's disease, BMI
2. Structural Neuroimaging Studies							
Cardenas-Iniguez et al. (2021)	ABCD	9–10	CS	N = 8588	Bi-factor model	General psychopathology, internalizing	FA and MD
Caspi et al. (2020)	Dunedin	45	L*	N = 875	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	Brain age derived from multiple structural measures (i.e., cortical thickness, cortical surface area, subcortical volume)
Durham et al. (2021)	ABCD	9–10	CS	N = 9607	Bi-factor model	General psychopathology, internalizing	GMV
Kaczkurkin et al. (2019)	PNC	8–21	CS	N = 1394	Bi-factor model	General psychopathology, anxious-misery, psychosis (i.e., thought disorder), behavioural (i.e., externalizing), and fear	CT and GMV
Mewton et al. (2022)	ABCD	9–10	CS	N = 10,868	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	CT, SA, and cortical and subcortical GMV
Moberget et al. (2019)	PNC	8–23	CS	N = 1401	PCA	General psychopathology	CT, cerebellar GMV, subcortical GMV
Neumann et al. (2020)	Generation R	6–10	L*	N = 3030	Bi-factor model (with correlated specific factors orthogonal to the general factor)	General psychopathology, internalizing, externalizing	FA, MD, AD, RD; ROI-based analyses of FA in the left pons, two regions in the right pons, the left and right lemniscus, and the medial peduncle (i.e., attempted replication of Romer et al., 2018)
Parkes et al. (2021)	PNC	8–22	CS	N = 1271	Bi-factor model	General psychopathology, anxious-misery, fear, externalizing, psychosis-positive, psychosis-negative	GMV measured as raw cortical volume and as deviations from normative cortical volume
Romer et al. (2018)	DNS	18–22	CS	MRI analysis: N = 1200 DTI analysis: N = 951	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	GMV and FA
Romer et al. (2019)	Dunedin	45	L*	N = 875	Bi-factor model	General psychopathology	GMV and FA
Romer et al. (2021)	Dunedin	45	L*	N = 875	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology (2) Internalizing, externalizing, thought disorder	CT, SA, GMV
Romer et al. (2023)	ABCD	9–10 (T1); 10–11 (T2); 11–12 (T3)	L	N = 9220	(1) Higher-order model (2) Bi-factor model	(1–2) General psychopathology, internalizing, externalizing, neurodevelopmental, somatic, and detachment	CT, SA, and cortical and subcortical GMV
Snyder et al. (2017)	Community sample	6–10	L*	N = 254	(1) Bi-factor model (2) Correlated-factor model	(1) General psychopathology, internalizing, externalizing (2) Internalizing, externalizing	GMV
van Rooij et al. (2021)	UK Biobank	40–69	CS	N = 15,258	PCA	Behavioural disinhibition	Independent components of GMV *Note.* characterised by high loadings in the temporal/parietal and frontal cortices (component 1), occipital and frontal cortices (component 2), temporal cortex and subcortical regions (component 3), and the temporal cortex (component 4).
3. Functional neuroimaging studies							
Cui et al. (2022)	PNC	8–23	CS	N = 790	(1) Correlated-factor model (2) Bi-factor model	(1) Fear, anxious-misery, externalizing, psychosis (2) General psychopathology, fear, anxious-misery, externalizing, psychosis (i.e., thought disorder)	Functional network topography
Elliot et al. (2018)	DNS	18–22	CS	N = 605	Bi-factor	General psychopathology	Connectome-wide intrinsic functional connectivity
Hong et al. (2023)	ABCD	9–10	CS	N = 6905	One-factor model	General psychopathology	Within- and between-network connectivity (AUD, CON, CPN, DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and 'unassigned' network)
Kaczkurkin et al. (2018)	PNC	11–23	CS	N = 833	Bi-factor model	General psychopathology, anxious-misery, fear, behavioural (i.e., externalizing), psychosis (i.e., thought disorder)	Regional cerebral blood flow and seed-based functional connectivity of the dorsal anterior cingulate
Karcher et al. (2021)	ABCD	9–10	CS	Discovery: N = 3790	Nested hierarchical linear models	(1) General psychopathology (2) internalizing and externalizing	Within- and between-network connectivity (AUD, CON, CPN,

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Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
				Replication: N = 3791	derived from EFA (using oblique rotation): (1) One-factor model (2) Two-factor model (3) Three-factor model (4) Four-factor model (5) Five-factor model	(3) internalizing, externalizing, neurodevelopmental (4) internalizing, externalizing, neurodevelopmental. somatoform (5) internalizing, externalizing, neurodevelopmental, somatoform, detachment	DMN, DAN, FPN, RST, SAL, SMM, SMH, VAN, VIS, and an 'unassigned' network)
Kim-Spoon et al. (2021)	Community sample	13–14 (T1), 14–15 (T2), 15–16 (T3), 16–17 (T4)	L	N = 167	LCSM	Substance use	ROI-based analysis of task-based (i.e., economic lottery choice task) neural activation in the insula cortex
Lees et al. (2021)	ABCD	9–10	CS	N = 9074	Higher-order model	General psychopathology, internalizing, externalizing, thought disorder	Within- and between-network functional connectivity (CON, CPN, DMN, DAN, FPN, RST, SAL, VAN, AUD, SMH, SMM, VIS) and connectivity between these networks and several subcortical ROIs (cerebellum, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, ventral diencephalon) Task-based (i.e., emotional n-back task) neural activation across large-scale functional networks
Shanmugan et al. (2016)	PNC	8–22	CS	N = 1129	Bi-factor model	General psychopathology, anxious-misery, fear, behavioural (i.e., externalizing), psychosis (i.e., thought disorder)	Task-based (i.e., fractal n-back task) neural activation across large-scale functional networks
Sripada et al. (2021)	ABCD	9–10	CS	N = 6593	Bi-factor	General psychopathology	Within- and between-network functional connectivity (DMN, VIS, FPN, SAL, VAN, DAN, CPN, RST, AUD, CON, SMM, SMH, the cerebellum, a subcortical network, and an 'unassigned' network)
Xia et al. (2018)	PNC	8–22	CS	Discovery: N = 663 Replication: N = 336	sCCA	Mood (i.e., anxious-misery), psychosis (i.e., thought disorder), fear, externalizing	Whole-brain resting state functional connectivity
Zhang et al. (2022)	UK Biobank	40–69	CS	N = 6389	CCA	General psychopathology	Amplitude and connectivity strength in the DMN, SAL, and CEN
3. Structural and functional neuroimaging studies							
Modabbernia et al. (2022)	ABCD	9–10	CS	MRI analysis: N = 8114 DTI analysis: N = 7171 fMRI analysis: N = 5484	(1) ICA (2) EFA (3) ICA (4) EFA	(1) Negative affect (i.e., internalizing), opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental) (2) Internalizing, externalizing, neurodevelopmental (3) Negative affect (i.e., internalizing), opposition-disinhibition (i.e., externalizing), cognitive dyscontrol (i.e., neurodevelopmental), somatic (4) Internalizing, externalizing, neurodevelopmental, somatic, detachment	CT, SA, GMV, FA, MD, RD, AD, within- and between-network functional connectivity
4. Genomic and structural neuroimaging studies							
Alnaes et al. (2018)	PNC	8–22	CS	Genomic analysis: N = 2946	ICA	General psychopathology	SNP-heritability; multimodal DTI measures of white matter microstructural and connectivity features (i.e., fractional

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Table 1 (*continued*)

Authors	Sample	Age	Design	Analytic Sample Size	Latent Dimensional Model (s)	Transdiagnostic symptom dimensions	Biological variable (s)
				DTI analysis: N = 748			anisotropy, the principal DTI eigen value, radial diffusivity, mean diffusivity, mode of anisotropy, dominant fiber population, secondary fiber population, and connectivity density) decomposed into independent components (using ICA)
Fernandez-Cabello et al. (2022)	ABCD	9–10	CS	N = 7124	CCA	Internalizing and externalizing	General PGSs (derived from PGSs for AN, ADHD, ASD, BIP, MDD, OCD, SCZ, and Tourette syndrome) and PGSs for ADHD, ASD, BIP, MDD, OCD, SCZ, educational attainment; Several brain structural measures (i.e., CT, SA, WMV, FA and several measures of diffusivity)

Note. The table above provides a broad overview of studies included in the review. Symptom dimensions that were measured within a given latent variable model but were not treated as transdiagnostic dimensions are not reported (for full description of structural models see Appendix B, Tables S5-7). ABCD: Adolescent Brain and Cognitive Development Study; AD: axial diffusivity; Add Health: The National Longitudinal Study of Adolescent to Adult Health; ADHD: attention-deficit/hyperactivity disorder; ALSPAC: Avon Longitudinal Study of Parents and Children; AN: anorexia nervosa; ANX: anxiety; ASD: autism spectrum disorder; AUD: auditory network; BIP: bipolar disorder; CATSS: Child and Adolescent Twins Study in Sweden; CS: cross-sectional; CT: cortical thickness; CON: cingulo-opercular network; CPN: cingulo-parietal network; CCA: canonical correlation analysis; CEN: central executive network; DAN: dorsal attention network; DMN: default mode network; DNS: Duke Neurogenetics Study; DTI: diffusion tensor imaging; EFA: exploratory factor analysis; EU-GEI: European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; FA: fractional anisotropy; FPN: frontoparietal network; fMRI: functional magnetic resonance imaging; GMV: gray matter volume; HRS: Health and Retirement Study; ICA: independent component analysis; L: longitudinal; LCSM: latent change score model; LGC: latent growth curve model; LTSO: latent state-trait-occasion model; MD: mean diffusivity; MDD: major depressive disorder; MIDUS: Midlife in the United States Study; MRI: magnetic resonance imaging; OCD: obsessive-compulsive disorder; PCA: principal component analysis; PGS: polygenic scores; PNC: Philadelphia Neurodevelopmental Cohort; PTSD: posttraumatic stress disorder; RD: radial diffusivity; ROI: region of interest; RST: retrosplenial-temporal network; SA: surface area; SAL: Salience Network; sCCA: sparse canonical correlation analysis; SCZ: schizophrenia; SMH: sensorimotor- hand network; SMM: sensorimotor-mouth network; SNP: single nucleotide polymorphism; T1-4: Time 1–4; TEDS: Twins Early Development Study; VAN: ventral attention network; VIS: visual network; WMV: white matter volume.

see Appendix B (Tables S5-7).

3.3. Genomic studies

3.3.1. Polygenic risk scores

General PGSs.

General Psychopathology.

A polygenic p-factor (i.e., defined as the first principal component extracted from PGSs for a range of psychiatric disorders) was positively associated with general psychopathology across childhood and early adolescence (ages 7–16) (Allegrini et al., 2020) and in two studies spanning midlife to older adulthood (ages 40–83) (Grotzinger et al., 2019; Gard et al., 2021).

ADHD-PGSs.

General Psychopathology.

ADHD-PGSs were associated with greater general psychopathology across six studies, spanning childhood to adolescence (ages 7–16) (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022) but showed no association with general psychopathology in one study of midlife and older adult participants (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. The internalizing dimension was negatively associated with ADHD-PGSs in children (age seven) (Riglin et al., 2020) and showed mixed results in preadolescents and adolescents. ADHD-PGSs were negatively associated with internalizing in two studies of preadolescents (ages 9–10) from the ABCD study (at baseline but not at first follow-up) after controlling for general (Waszczuk et al., 2021; Lahey et al., 2022) and specific symptom dimensions (Lahey et al., 2022). However, another study of ABCD participants found no evidence of association with ADHD-PGSs when controlling for other PGSs (Pat et al., 2022). Two studies found no association between internalizing and disorder-level ADHD-PGSs in adolescents (ages 13, 15) (Riglin et al., 2020; Chen et al., 2022) but a significant negative association was observed between internalizing and symptom-level ADHD-PGSs at age 15 (Chen et al., 2022).

Externalizing. ADHD-PGSs showed no association with externalizing in bivariate analyses of preadolescents (ages 9–10) (Waszczuk et al., 2021); however, there was evidence of a positive association in analyses of the same sample when controlling for general and specific symptom dimensions, as well as multiple PGSs (Pat et al., 2022). ADHD-PGSs were also associated with 'high decreasing' and 'moderate' (but not low increasing) trajectories of externalizing between the ages of 18 and 32 based on longitudinal analyses using latent growth curve models (Li, 2019).

Neurodevelopmental. The neurodevelopmental dimension was not associated with ADHD-PGSs in childhood (age 7) (Riglin et al., 2020) but was positively associated with ADHD-PGSs in two studies of preadolescents (ages 9–10) (Waszczuk et al., 2021; Pat et al., 2022) from the ABCD study and in one study of adolescents (age 13) (Riglin et al., 2020).

Depression-PGSs.

General Psychopathology.

Two studies found a positive association between depression-PGSs and general psychopathology at baseline in the ABCD cohort (using one-factor and higher-order models) (Waszczuk et al., 2021; Pat et al., 2022). Another study found no association in a different sample of preadolescents (ages 9–12) when general psychopathology was modelled using a bi-factor approach (Chen et al., 2022). Depression-PGSs were also not associated with general psychopathology in childhood (age 7) (Riglin et al., 2020) or across three studies of adolescents (ages 13–16) (Riglin et al., 2020; Chen et al., 2022; Jones et al., 2018). However, they were positively associated with general psychopathology across two studies in midlife and older adulthood (Grotzinger et al., 2019; Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Table 2
Associations between transdiagnostic symptom dimensions and polygenic scores investigated in two or more studies.

Authors	Age	Structural model(s)	G-PGS	ADHD				SCZ					DEP				NEUR		ASD				BIP	ANX	PTSD	INTEL		EDU	
			GP	GP	INT	EXT	ND	GP	INT	EXT	TD	ND	GP	INT	EXT	ND	GP	INT	GP	INT	EXT	ND	GP	GP	GP	GP	INT	GP	INT
Allegrini et al. (2020)	7 9 12 16	PCA																											
Riglin et al. (2020)[1,2,3]	7 13	B-F																											
Waszczuk et al. (2022)[1]	9-10	1-F, 5-F																											
Pat et al. (2022)[3]	9-10	H-O																											
Lahey et al. (2022)[1,2]	9-10 10-11	B-F																											
Chen et al. (2022)[1,2,3]	9-12 15	B-F (S-1)																											
Birkell et al. (2020)[1,2]	9-12	B-F																											
Jones (2018)[1,2]	16	B-F																											
Musci et al. (2016)	11-17	LTSO																											
Li et al. (2019)	18-32	LCG																											
Quattrone et al. (2021)	18-64	B-F																											
Cuevas et al. (2021)[3]	25-75	CF																											
Jermy et al. (2022)	37-73	H-O																											
Grotzinger et al. (2019)	40-69	B-F																											
Gard et al. (2021)	51-83	1-F																											

Note. This table details evidence of associations between polygenic scores and general/specific transdiagnostic symptom dimensions investigated in two or more included studies. Significant positive associations are highlighted in green, significant negative associations in blue, and non-significant associations in grey. Blank cells indicate that no association was tested. Cuevas et al. (2021) examined a latent anxiety/negative affect dimension (i.e., the anxious-misery subdimension of internalizing). 1-F: one-factor model; 5-F: five-factor model; ADHD: attention-deficit/hyperactivity disorder; ANX: anxiety; ASD: autism spectrum disorder; B-F: bi-factor model; BIP: bipolar; CF: confirmatory factor model; DEP: depression; EDUC: education; EXT: externalizing; GP: general psychopathology; G-PGS: general polygenic scores; H-O: higher-order model; INT: internalizing; INTEL: intelligence; LCG: latent growth curve model;; LTSO: latent trait-state-occasion model; ND: neurodevelopmental; NEUR: neuroticism; PCA: principal component analysis; PGS: polygenic scores; PTSD: posttraumatic stress disorder; SCZ: schizophrenia; TD: thought disorder.
[1]Study controlled for general psychopathology.
[2]Study controlled for other specific symptom dimensions.
[3]Study controlled for other PGSs.

Internalizing. Depression-PGSs showed no association with Internalizing in childhood (age 7), when modelled using a bi-factor approach and simultaneously regressing multiple PGSs (Riglin et al., 2020). Depression-PGSs were not associated with Internalizing in bivariate analyses of the ABCD cohort (after controlling for general psychopathology) (Waszczuk et al., 2021) but were positively associated in analyses controlling for general and specific symptom factors, as well as other PGSs (Pat et al., 2022). In a multivariate analysis of adolescents (age 13), Internalizing was positively associated with depression-PGSs but showed no association with five other polygenic exposures (Riglin et al., 2020). However, another study of adolescents at age 15 (controlling for general and specific symptom dimensions and other PGSS) found no evidence of association (Chen et al., 2022). Depression-PGSs also showed a positive association with a measure of Internalizing extracted from longitudinal assessment data across ages 11–17 (Musci et al., 2016). Depression-PGSs were not associated with a latent 'anxiety/negative affect' factor in a cross-sectional study of participants aged 25–75 (Cuevas et al., 2021) but were associated with a transdiagnostic measure of depressive and anxious symptoms in midlife to older adult participants from the UK Biobank (Jermy et al., 2022).

Table 3
Associations between transdiagnostic symptom dimensions and global/whole-brain measures of brain structure.

Authors	Age	Structural Model(s)	Neuroimaging: exposure/outcome	Brain Structural Associations								
				Cortical Thickness								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Mewton et al. (2022)	9-10	H-O	Outcome	x	x	x	x					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)											
	11-12 (T3)											
Kaczkurkin et al. (2019)	8-21	B-F	Outcome	-		x	-					
Moberget et al. (2019)	8-23	PCA; ICA	Exposure	-			-					
Romer et al. (2021)	45	B-F; CF	Outcome	--	--	--	--					
				Surface Area								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)			--								
	11-12 (T3)											
Romer et al. (2021)	45	B-F; CF	Outcome	x	x	x	x					
				Gray Matter Volume								
				GP	**INT**	**EXT**	**TD**	**ND**	**SOM**	**DET**	**A-M**	**FEAR**
Snyder et al. (2017)	6-10	B-F; C-F	Outcome	--	+	-						
Mewton et al. (2022)[1]	9-10	H-O	Outcome	--	--	--	--					
Durnham et al (2021)[1]	9-10	B-F	Outcome	--	x							
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2023)[1]	9-10 (T1)	H-O; B-F	Exposure									
	10-11 (T2)			--								
	11-12 (T3)											
Parkes et al. (2021)	8-22	B-F	Exposure	--		-	-				+	-
Kaczkurkin et al. (2019)[1]	8-22	B-F	Outcome	--		-	x				++	-
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								
Romer et al. (2021)[1]	45	B-F; CF	Outcome	-	-	-	-					

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Table 3 (*continued*)

Authors	Age	Structural Model(s)	Neuroimaging: exposure/outcome	Brain Structural Associations								
				Fractional Anisotropy								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)[1]	6-10	B-F	Exposure	-	x	+						
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x	x						
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
Romer et al. (2018)[1]	18-22	B-F; CF	Outcome	-								
				Mean Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Cardenas-Iniguez et al. (2021)	9-10	B-F	Exposure	x	x							
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
				Radial Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									
				Axial Diffusivity								
				GP	INT	EXT	TD	ND	SOM	DET	A-M	FEAR
Neumann et al. (2020)	6-10	B-F	Exposure									
Modabbernia et al. (2022)	9-10	ICA; EFA	Exposure									

Note. The table above provides a broad overview of evidence from two or more studies investigating the relationship between general and/or specific transdiagnostic symptom dimensions with global/whole-brain measures of brain structure. Coloured cells indicate whether associations with global brain structure were positive, negative, or non-significant (green, blue, and grey squares, respectively). For whole-brain analyses of regional associations, significant positive effects are indicated by a plus sign (+), significant negative effects by a minus sign (-), and analyses that found no evidence of significant associations are marked with an 'x'. One sign (e.g., +/-) indicates few regional associations and two signs (e.g., ++/–) indicates that associations were widespread. Blank cells indicate that no association was tested. Importantly, relationships between symptom dimensions and brain structure were counted as having been examined in more than one study regardless of differences in the construction of psychiatric phenotypes (e.g., psychiatric indicators, latent variable models), measurement of brain structure (e.g., global/whole-brain measures), or the direction of association investigated (e.g., whether neuroimaging variables were included as the exposure or outcome) across studies. In addition, some studies included analyses across multiple latent variable approaches and significant associations indicated here may refer only to one approach or both. A-M: anxious-misery; B-F: bi-factor model; CF: correlated-factors model; DET: detachment; EFA: exploratory factor analysis; EXT: externalizing; GP: general psychopathology; H-O: higher-order model; ICA: independent component analysis; INT: internalizing; ND: neurodevelopmental; PCA: principal component analysis; SOM: somatic; T1-2: time 1–2; TD: thought disorder.

[1]Study controlled for global effects (e.g., total GMV, total FA).

Neurodevelopmental. Depression-PGSs were not associated with the neurodevelopmental dimension in one study of the ABCD cohort (i.e., bivariate analyses controlling for general psychopathology) (Waszczuk et al., 2021) but were positively associated in another (i.e., multivariate analyses controlling for general and specific symptom dimensions as well as other PGSs) (Pat et al., 2022). One additional study found no evidence of an association between depression-PGSs and a neurodevelopmental dimension in childhood or adolescence (using a bi-factor model and controlling for other PGSs) (Riglin et al., 2020).

Externalizing, Somatic, and Detachment. In bivariate analyses (controlling for general psychopathology), there was no evidence of an association between depression-PGSs and externalizing, somatic, or detachment dimensions in preadolescents from the ABCD study. However, in multivariate analyses of the same sample, controlling for general and specific symptom factors, as well as other PGSs, all three symptom dimensions were positively associated with PGSs for depression (Pat et al., 2022).

Schizophrenia-PGSs.

General Psychopathology.

Schizophrenia-PGSs were associated with greater general psychopathology in childhood (age 7) (Pat et al., 2022) but showed no association across three studies of preadolescents (ages 9–12) (Waszczuk et al., 2021; Pat et al., 2022; Chen et al., 2022). Results were mixed for adolescents, with schizophrenia-PGSs associated with greater general psychopathology in two studies (ages 13–16) (Riglin et al., 2020; Jones et al., 2018) and showing no association in another (age 15) (Chen et al., 2022). General psychopathology was also positively associated with PGSs for schizophrenia in one study of midlife and older adults (ages 40–69) (Grotzinger et al., 2019).

Specific Transdiagnostic Symptom Factors.

Internalizing. Schizophrenia-PGSs were positively associated with Internalizing in children (Riglin et al., 2020) but showed no association across three studies spanning preadolescence (Waszczuk et al., 2021) and adolescence (Riglin et al., 2020; Chen et al., 2022).

Thought Disorder. PGSs for schizophrenia were positively associated with a positive psychosis dimension (when derived from a correlated-factors model but not a bi-factor model) and with a negative psychosis dimension (when derived from both a bi-factor and correlated-factors model) adolescents (age 16) (Jones et al., 2018). In addition, schizophrenia-PGSs were positively associated with positive, negative, and general psychotic dimensions in participants aged 18–64 (Quattrone et al., 2021).

Neurodevelopmental. There was no evidence of an association with schizophrenia-PGSs and a neurodevelopmental dimension across two studies, spanning childhood and adolescence (ages 7–13) (Riglin et al., 2020; Waszczuk et al., 2021).

Autism-PGSs.

General Psychopathology.

One study found a positive association between general psychopathology and autism-PGSs based on bivariate analyses in preadolescents from the ABCD study (Waszczuk et al., 2021). However, three other studies found no evidence of an association across childhood and adolescence (ages 7–15), including in ABCD participants, when simultaneously controlling for other PGSs and/or specific symptom factors (Riglin et al., 2020; Pat et al., 2022; Chen et al., 2022).

Specific Transdiagnostic Factors.

Internalizing. Autism-PGSs were not associated with Internalizing across three studies, spanning childhood and adolescence (ages 7–15), (Riglin et al., 2020; Waszczuk et al., 2021; Chen et al., 2022).

Neurodevelopmental. Autism-PGSs were not associated with the neurodevelopmental dimension in childhood or adolescence (ages 7, 13) (Riglin et al., 2020) or in preadolescents from the ABCD study (after controlling for general psychopathology) (Waszczuk et al., 2021).

Bipolar-PGSs.

General Psychopathology.

Bipolar-PGSs were not associated with general psychopathology across four studies spanning preadolescence and adolescence (ages 9–15) (Waszczuk et al., 2021; Pat et al., 2022; Chen et al., 2022; Jones et al., 2018) but were positively associated in one study of midlife and older adulthood (40−69) (Grotzinger et al., 2019).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Bipolar-PGSs were not associated Internalizing across two studies, in preadolescents (ages 9–10) and adolescents (age 15) (Waszczuk et al., 2021; Chen et al., 2022).

Other. Bipolar-PGSs were also not associated with any symptom dimension that was investigated in a single study (i.e., externalizing, psychosis positive, psychosis negative, neurodevelopmental, somatic, and detachment), spanning preadolescence and adolescence (ages 9–10 and 16) (Waszczuk et al., 2021; Jones et al., 2018).

Neuroticism-PGSs.

General psychopathology.

Neuroticism-PGSs were positively associated with general psychopathology in bivariate analyses of preadolescents from the ABCD study (Waszczuk et al., 2021) but showed no association in another preadolescent sample that controlled for specific symptom factors and multiple PGSs (Chen et al., 2022). Neuroticism-PGSs were also positively associated with general psychopathology across two adolescent samples (ages 15–16) (Chen et al., 2022; Jones et al., 2018) and in a single study of midlife and older adulthood (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Neuroticism-PGSs were not associated with Internalizing (after controlling for general psychopathology) in preadolescents (ages 9–10) (Waszczuk et al., 2021) but were positively associated in adolescents (age 15) when controlling for other PGSs and latent factors (Chen et al., 2022). In addition, neuroticism-PGSs were positively associated with a 'anxiety/negative affect factor' in a cross-sectional study of participants aged 25–75 years old (Cuevas et al., 2021).

PTSD-PGSs.

General Psychopathology.

PGSs for PTSD were positively associated with general psychopathology in one study of ABCD participants (i.e., bivariate analyses controlling for general psychopathology) (Waszczuk et al., 2021) but not in another longitudinal study of preadolescents (ages 9 and 12) and adolescents (age 15) (controlling for general and specific symptom factors, as well as other PGSs) (Chen et al., 2022). General psychopathology was positively associated with PGSs for PTSD in one study of midlife and older adults (ages 51–83) (Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. PTSD-PGSs were not associated with Internalizing in preadolescents (after controlling for general psychopathology) (Waszczuk et al., 2021) or in a sample of adolescents (age 15) (Chen et al., 2022).

Anxiety-PGSs.

General Psychopathology.

Anxiety-PGSs showed no association with general psychopathology across two studies spanning childhood and adolescence (ages 9–15) (Pat et al., 2022; Chen et al., 2022) but were positively associated in two studies of midlife and older adult participants (ages 40–83) (Grotzinger et al., 2019; Gard et al., 2021).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. PGSs for anxiety were not associated with Internalizing at age 15 (Chen et al., 2022) or with a 'anxiety/negative affect' factor in a cross-sectional study of participants aged 25–75 (Cuevas et al., 2021).

3.3.2. SNP-heritability

General Psychopathology.

Significant SNP-heritability was observed for general psychopathology in children (ages 6–8) from the Generation R cohort (Neumann et al., 2016). In youths from the PNC (ages 8–22), two studies found significant SNP heritability associated with general psychopathology; (Mollon et al., 2021; Alnæs et al., 2018) however, this association did not survive false discovery rate (FDR) correction in one study (Mollon et al., 2021).

3.4. Structural neuroimaging studies

3.4.1. Gray matter

Cortical thickness.

General Psychopathology.

Two studies found no evidence of an association between global cortical thickness and general psychopathology, either at baseline or across the first three waves of data collection, in preadolescents from ABCD study (ages 9–12) (Mewton et al., 2022a; Romer et al., 2023). In the PNC (ages 8–22), reduced cortical thickness was associated with greater general psychopathology in a single structural network (out of 18 brain-wide structural covariance networks) comprising the precuneus and temporoparietal junction; however, this association did not survive sensitivity analyses (i.e., controlling for maternal education and excluding participants on psychotropic medication) (Kaczkurkin et al., 2019). Another study of the PNC found no evidence of an association with global cortical thickness, whilst follow-up univariate analyses (not controlling for global thickness) found that general psychopathology was negatively associated with cortical thickness specifically within the cuneus, fusiform, postcentral, precentral, precuneus, superior parietal, and transverse temporal regions (Moberget et al., 2019). In contrast to research in youths, global cortical thickness was significantly negatively associated with general psychopathology in midlife participants (age 45) from the Dunedin study (Romer et al., 2021a).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD cohort at baseline (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) or longitudinally across the first two follow-ups (Romer et al., 2023). However, lower global cortical thickness at baseline did predict steeper reductions in Internalizing across the first three waves of the ABCD study (Romer et al., 2023). Follow-up analyses revealed that this association was driven by cortical thickness within 16 (of 68) parcellated brain regions (corrected for global cortical thickness). In the PNC (ages 8–21), anxious-misery showed no association with cortical thickness across 18 brain-wide structural networks in youths (ages 8–21)

(Kaczkurkin et al., 2019). In addition, the fear dimension was negatively associated with cortical thickness in 13 structural networks; however, these associations were no longer significant when controlling for global cortical thickness (Kaczkurkin et al., 2019). In contrast, Internalizing was significantly negatively associated with global cortical thickness at midlife (age 45) (Romer et al., 2021a).

Externalizing. Externalizing was not associated with global cortical thickness in three studies of preadolescents from the ABCD study at baseline (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) or longitudinally across the first three waves of data collection, (Romer et al., 2023) nor with any structural covariance network (across 18 brain-wide networks) in participants aged 8–22 from the PNC (Kaczkurkin et al., 2019). Global cortical thickness was, however, negatively associated with externalizing at midlife (age 45) in the Dunedin Study (Romer et al., 2021a).

Thought Disorder. Global cortical thickness was not associated with the thought disorder dimension in preadolescents (using baseline data from the ABCD study) (Mewton et al., 2022a). Similarly, a psychosis dimension showed no association with global cortical thickness (Moberget et al., 2019) or with regional cortical thickness across 18 brain-wide structural covariance networks (Kaczkurkin et al., 2019) in two studies of youths (ages 8–23) from the PNC. However, global cortical thickness was negatively associated with thought disorder symptoms in midlife participants from the Dunedin study (Romer et al., 2021a).

Neurodevelopmental. The neurodevelopmental dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) or across the first two follow-ups (Romer et al., 2023).

Detachment. The detachment dimension was not associated with global cortical thickness in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) and across the first two follow-ups (Romer et al., 2023).

Somatic. The somatic dimension showed no association with global cortical thickness at baseline (or across the first two follow-ups) in ABCD participants, when derived from a higher-order model (Romer et al., 2023) and a correlated-factors model (Modabbernia et al., 2022) but was *positively* associated when derived from ICA (Modabbernia et al., 2022).

Surface area.

General Psychopathology.

Higher general psychopathology predicted lower global surface area (SA) at baseline in preadolescents from the ABCD study (ages 9–10) (Mewton et al., 2022b). Likewise, lower global SA predicted greater levels of general psychopathology at baseline and across the first two follow-up waves of the ABCD study (ages 9–12) (Romer et al., 2023). In contrast, global SA was not associated with general psychopathology at midlife (age 45) (Romer et al., 2021a).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing predicted lower global SA at baseline in preadolescents from the ABCD cohort, when derived from higher-order and correlated-factor models (Mewton et al., 2022a; Modabbernia et al., 2022) but not when derived from ICA (Modabbernia et al., 2022). In addition, when global SA was included as a predictor (in another study of ABCD participants), there was no evidence of an association with Internalizing at baseline or across the first two follow-ups (ages 9–12) (Romer et al., 2023). There was also no evidence of an association between global SA and Internalizing at midlife (age 45) (Romer et al., 2021a).

Externalizing. Global SA was negatively associated with externalizing in three studies of preadolescents from the ABCD cohort (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022) and in midlife participants from the Dunedin study (Romer et al., 2021a).

Thought Disorder. The thought disorder dimension was negatively associated with global SA in one study of preadolescents (ages 9–10) (Mewton et al., 2022a) but showed no association in midlife (age 45) (Romer et al., 2021a).

Neurodevelopmental. The neurodevelopmental dimension was negatively associated with global SA in ABCD participants when derived from a higher-order model (across the first three waves of data collection) (Romer et al., 2023) and correlated-factors model (at baseline) (Modabbernia et al., 2022) but showed no association when derived from ICA (at baseline) (Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global SA in two studies of preadolescents from the ABCD cohort, at baseline (Modabbernia et al., 2022) and across the first three waves of data collection (Romer et al., 2023).

Somatic. The somatic symptom dimension was not associated with global SA in two studies of ABCD participants, at baseline (Romer et al., 2023; Modabbernia et al., 2022) or across the first three follow-up waves (Romer et al., 2023).

Gray matter volume.

General Psychopathology.

In preadolescents from the ABCD cohort, general psychopathology predicted lower global GMV at baseline (ages 9–10) (Mewton et al., 2022a) and lower baseline global GMV predicted greater levels (but not the trajectories) of general psychopathology across the first three waves of data collection (ages 9–12) (Romer et al., 2023). In youths from the PNC (ages 8–22), general psychopathology was associated with lower global GMV in one study (Kaczkurkin et al., 2019) and with greater negative deviations from normative cortical volume (but not raw global cortical volume) in another (Parkes et al., 2021). Exploratory whole-brain analyses found that general psychopathology was associated with widespread regionally-specific reductions in GMV across six studies spanning childhood to early adulthood (ages 6–23) (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021; Snyder et al., 2017; Durham et al., 2021).

In contrast, whole-brain analyses in young adults from the DNS (ages 18–22) found that greater general psychopathology was associated with lower GMV in the bilateral lingual gyrus and right intracalcarine regions (of the visual cortex), as well as the left posterior cerebellum, after controlling for total GMV (Romer et al., 2018). Whole-brain analyses (not controlling for global GMV) in midlife participants (age 45) also found that general psychopathology was negatively associated with GMV in relatively few regions (Romer et al., 2021a). Of note, a ROI-based study of participants at midlife (age 45) replicated the negative association between general psychopathology and GMV in the visual cortex but not in the cerebellum (Romer et al., 2021b) (Romer et al., 2018). Similarly, general psychopathology was negatively associated with cerebellar GMV in ROI-based analyses of youths from the PNC (ages 8–22) (Moberget et al., 2019) but failed to replicate in participants at midlife (age 45) (Romer et al., 2021b).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Internalizing showed few (predominately positive) significant regional associations with GMV in exploratory whole-brain analyses of children (age 6–10) (Snyder et al., 2017). Internalizing predicted lower global GMV at baseline in ABCD participants (ages 9–10), when derived from a higher-order model (Mewton et al., 2022a) but not when derived from ICA or a correlated-factor model (Modabbernia et al., 2022). In whole-brain analyses of ABCD participants (at baseline), Internalizing was associated with widespread reductions in GMV when derived from a higher-order model (none of which remained significant after controlling for global GMV) (Mewton et al., 2022a) and was not associated with any region when derived from a bi-factor model (Durham et al., 2021). In addition, global cortical and subcortical volume did not predict Internalizing (higher-order model) at baseline or across the first two follow-ups (ages 9–12) in a subsequent study of ABCD participants (Romer et al., 2023). In the PNC (ages 8–22), lower global cortical volume (i.e., raw volume and deviations from normative cortical volume) did not predict the anxious-misery dimension and whole-brain analyses revealed relatively few (predominately positive) associations with regional GMV (Parkes et al., 2021). In contrast, the anxious-misery dimension predicted increased global GMV and was positively associated with GMV in 17 (out of 18) brain-wide structural networks (none of which remained significant after controlling for global GMV) in another study of the same sample (Kaczkurkin et al., 2019). Also in the PNC, lower global cortical volume and greater negative deviations from normative cortical volume predicted higher scores on the fear dimension (Parkes et al., 2021). Follow-up whole-brain analyses (not controlling for global GMV) also found that the fear dimension was associated with lower GMV in relatively few regions. Similarly, the fear dimension (when included as a predictor) was negatively associated with GMV in only eight out of 18 brain-wide structural covariance networks (none of which remained significant after controlling for global GMV) in the PNC (Kaczkurkin et al., 2019). In midlife (age 45), whole-brain analyses (not controlling for global GMV) revealed associations between Internalizing and only four anatomical regions (all of which were shared across other symptom factors) (Romer et al., 2021a).

Externalizing. Externalizing showed relatively few regional associations with GMV based on whole-brain analyses of a childhood community sample (ages 6–10) (Snyder et al., 2017). When derived from a higher-order model, externalizing predicted lower global GMV at baseline in ABCD participants (ages 9–10) (Mewton et al., 2022a) and lower global GMV predicted greater externalizing at baseline and across the first two follow-ups (ages 9–12) (Romer et al., 2023). However, there was no evidence of association with global GMV when externalizing was derived from ICA or a correlated-factors model in baseline ABCD data (Modabbernia et al., 2022). In addition, whole-brain analyses of ABCD participants (at baseline) found that externalizing predicted widespread regional reductions in GMV; however, no associations remained significant after controlling for global GMV (Mewton et al., 2022b). In the PNC (ages 8–22), global cortical volume (i.e., raw cortical volume and deviations from normative cortical volume) did not predict externalizing (Parkes et al., 2021). Follow-up whole-brain analyses found negative associations between externalizing and GMV in relatively few regions. Similarly, another study of the PNC found that externalizing predicted lower cortical volume in only two (i.e., superior parietal and fusiform cortices) of 18 brain-wide structural networks and these associations did not survive sensitivity analyses (controlling for maternal education and psychotropic medication use) (Kaczkurkin et al., 2019). Lastly, whole-brain analyses of midlife participants (age 45) also found relatively few associations between externalizing and regional GMV (Romer et al., 2021a).

Thought Disorder. The thought disorder dimension was negatively associated with global cortical volume in preadolescents from the ABCD study (ages 9–10) (Mewton et al., 2022b). Follow-up analyses revealed widespread reductions in regional GMV, none of which remained significant after controlling for global GMV. In the PNC (ages 8–22), lower global cortical volume (i.e., lower raw volume and greater negative deviations from normative cortical volume) predicted greater scores on a psychosis-positive (but not psychosis-negative) dimension (Parkes et al., 2021). Follow-up whole-brain analyses revealed few associations between psychosis-positive or psychosis-negative dimensions. Also in the PNC, a general psychosis dimension did not predict GMV in any of 18 brain-wide structural networks. Similarly, whole-brain analyses of participants at midlife (age 45) found few associations between thought disorder symptoms and regional GMV (Romer et al., 2021a).

Neurodevelopmental. When derived from a higher-order model, the neurodevelopmental dimension predicted lower global GMV at baseline in ABCD participants (ages 9–10) (Mewton et al., 2022a) and lower global cortical and subcortical GMV predicted higher scores on the neurodevelopmental dimension at baseline and across the first two follow-ups (ages 9–12) (Romer et al., 2023). However, there was no evidence of association with global GMV when the neurodevelopmental dimension was derived from ICA or a correlated-factors model using baseline ABCD data (Modabbernia et al., 2022).

Detachment. The detachment dimension was negatively associated with global cortical and subcortical volume across the first three waves of the ABCD study when derived from a higher-order model (Romer et al., 2023) but showed no association at baseline when derived from a correlated-factor model or ICA (Modabbernia et al., 2022).

Somatic. Two studies found no association between the somatic dimension and global GMV in ABCD participants at baseline (Romer et al., 2023; Modabbernia et al., 2022), or across the first two follow-up waves (Romer et al., 2023).

3.4.2. White matter microstructure

General Psychopathology.

Lower global fractional anisotropy (FA) (i.e., average fractional anisotropy across 12 white matter tracts) was associated with higher general psychopathology in children (ages 6–10) from the Generation R cohort (Neumann et al., 2016). In ABCD participants (ages 9–10), there were no significant associations between general psychopathology and FA in any of 17 bilateral white matter (WM) tracts following FDR correction (Cardenas-Iniguez et al., 2022). In contrast, exploratory whole-brain analyses in young adults from the DNS (ages 18–22) found that general psychopathology predicted lower FA specifically within the bilateral pons, when controlling for global FA (Romer et al., 2018). Follow-up ROI analyses (of white matter tracts within the pons and cerebellum) found that greater general psychopathology predicted lower FA in the right and left lemniscus, as well as the left superior peduncle (again controlling for whole-brain FA). The association between general psychopathology and lower FA in the pons (but not the cerebellum) when controlling for global FA, was subsequently replicated in participants at midlife (age 45) (Romer et al., 2021b). Analyses using an alternative model (not controlling for global FA) found that general psychopathology predicted lower FA in the medial peduncle of the cerebellum (Neumann et al., 2020). Lastly, general psychopathology showed no evidence of association with global medial diffusivity in children (ages 6–10) (Neumann et al., 2020) or with any of 17 bilateral WM tracts in preadolescents (ages 9–10) (Cardenas-Iniguez et al., 2022).

Specific Transdiagnostic Symptom Dimensions.

Internalizing. Global FA was not associated with Internalizing in children (ages 6–10) from the Generation R cohort (Neumann et al., 2020). In ABCD participants (ages 9–10), Internalizing was negatively associated with global FA when derived from a correlated-factor model but not from ICA (Modabbernia et al., 2022) and showed no association with any of 17 WM tracts when measured using a bi-factor model (Cardenas-Iniguez et al., 2022). ROI-based analyses in young adults (ages 18–22) found that Internalizing was associated with lower pons FA (Romer et al., 2018). Internalizing showed no association with mean diffusivity (across three studies) (Modabbernia et al., 2022; Cardenas-Iniguez et al., 2022; Neumann et al., 2020), or axial and radial diffusivity (across two studies) (Modabbernia et al., 2022; Neumann et al., 2020), spanning childhood (ages 6–10) and preadolescence (ages 9–10).

Externalizing. Externalizing was positively associated with global FA in one study of children (ages 6–10) (Neumann et al., 2020). In preadolescents (ages 9–10), global FA was not associated with two measures of externalizing, derived from a correlated-factor model and ICA (Modabbernia et al., 2022). ROI-based analyses in young adults (ages 18–22) found no association between externalizing and pons FA (Romer et al., 2018). Externalizing (bi-factor model) was negatively associated with global radial diffusivity in children (ages 6–10) (Neumann et al., 2020) but showed no association in preadolescents from the ABCD study when derived from a correlated-factor model and ICA (ages 9–10) (Modabbernia et al., 2022). There was no evidence of association between externalizing and mean or axial diffusivity across two studies of children (ages 6–10) and preadolescents (ages 9–10) (Modabbernia et al., 2022; Neumann et al., 2020).

3.5. Functional neuroimaging studies

3.5.1. Functional connectivity

General Psychopathology.

Four studies investigated the relationship between general psychopathology and functional connectivity in preadolescents (ages 9–10) from the ABCD cohort (at baseline) (Lees et al., 2021; Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). General psychopathology was measured using higher-order (Lees et al., 2021), bi-factor (Sripada et al., 2021), and one-factor models (Karcher et al., 2021; Hong et al., 2023). Higher general psychopathology was associated with lower functional connectivity within the default mode network (DMN) across three studies (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021) and showed no association in one study (using a higher-order model) (Lees et al., 2021). General psychopathology was also associated with lower functional connectivity within the dorsal attention network (DAN) across three studies (Lees et al., 2021; Hong et al., 2023; Sripada et al., 2021) but showed no association in one (using a one-factor model) (Karcher et al., 2021). General psychopathology was associated with higher functional connectivity within the visual network (VIS) (Hong et al., 2023) in one study (one-factor model), with lower functional connectivity in another (bi-factor model) (Sripada et al., 2021) and showed no association in the remaining two studies (Lees et al., 2021; Karcher et al., 2021). No association was found for functional connectivity within the cingulo-opercular (CON), cingulo-parietal (CPN), salience (SAL), ventral attention (VAN), auditory (AUD), and somatomotor hand (SMH) networks across all four studies (Lees et al., 2021; Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). There was also no evidence of association between general psychopathology and within-network connectivity in an 'unassigned' network across three studies (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021), or with within-network connectivity in the cerebellum across two studies (Lees et al., 2021; Sripada et al., 2021).

Two studies of ABCD participants found that general psychopathology was associated with higher connectivity between the DMN and DAN (Lees et al., 2021; Hong et al., 2023) and between the VAN and frontoparietal (FPN) networks (Lees et al., 2021; Sripada et al., 2021). One study found that general psychopathology significantly increased the proportion of variance explained in functional network connectivity between the DMN and VAN (relative to a baseline model with only covariates); however, this was not replicated in a hold-out sample of ABCD participants (Karcher et al., 2021). An additional study found that general psychopathology was associated with lower connectivity between the DMN and VAN networks (Sripada et al., 2021). Several other associations with between-network connectivity were identified in only a single study and showed no association in the remaining studies (Appendix B, Table S6). Lastly, in young adults from the DNS (ages 18–22), connectome-wide analyses found that general psychopathology was associated with functional connectivity in four regions located within the visual network, including the left lingual gyrus, right middle occipital gyrus, and two parcels within the left middle occipital gyrus (Elliott et al., 2018). Follow-up analyses revealed that general psychopathology was associated with higher connectivity between the visual association cortex and DMN and between the visual association cortex and FPN. In contrast, general psychopathology was associated with lower connectivity between the visual association cortex and somatomotor network.

Specific Transdiagnostic Symptom Dimensions.

Four studies investigated the relationship between specific transdiagnostic symptom dimensions and within- and between-network functional connectivity. However, no significant associations were reported across more than one study aside from a single finding. Specifically, the neurodevelopmental symptom dimension was associated with lower connectivity within the DMN in the ABCD cohort (ages 9–10) (Karcher et al., 2021) and participants from the PNC (ages 8–22) (Modabbernia et al., 2022).

3.6. Other analyses

There were several relationships between transdiagnostic symptom dimensions and biological variables that were only investigated in a single study and are not reported here (Tables S5-7). There were three functional neuroimaging studies that examined different brain regions and experimental tasks (i.e., n-back, emotional n-back, and an economic choice lottery task) (Lees et al., 2021; Shanmugan et al., 2016; Kim-Spoon et al., 2021). Other studies included analyses of regional cerebral blood flow, (Kaczkurkin et al., 2018) PGSs and brain structure, (Fernandez-Cabello et al., 2022) multimodal DTI measures, (Alnæs et al., 2018) and brain age derived from multiple structural neuroimaging measures (Caspi et al., 2020). Finally, one study examined the relationship between brain structure and a latent measure of behavioural disinhibition (van Rooij et al., 2021).

4. Discussion

This systematic review aimed to synthesize evidence from research investigating the biological correlates of latent transdiagnostic dimensions of psychopathology in the general population, across the lifespan. The following section summarises key findings by broad biological domain (i.e., genomic, neuroimaging) and phenotype (i.e., general psychopathology and specific transdiagnostic symptom dimensions). Implications for research investigating associations across the lifespan, as well as potential developmental and age-specific associations emerging from the included studies, are discussed. Interpretations of general psychopathology in the context of genomic and neurobiological evidence are discussed. Methodological issues are highlighted, including those which point to the need for caution in interpretation and those which may explain some of the heterogeneity in results observed across included studies. Finally, directions for future research are provided and limitations of the current review are addressed.

4.1. Genomic research studies

General psychopathology.

General psychopathology was non-specifically associated with genetic risk for a wide range of psychiatric disorders and maladaptive traits in the general population. Several disorder- and trait-specific PGSs were significantly positively associated with general psychopathology across multiple studies (i.e., ADHD, neuroticism, depression, schizophrenia, anxiety, and PTSD). Additional studies examined associations between general psychopathology and transdiagnostic PGSs that reflect genetic risk for multiple psychiatric disorders (i.e., 'polygenic p-factors). These genomic p-factors emerged across different samples (TEDS, UK Biobank, HRS) and developmental periods (childhood to adolescence and midlife to older adulthood) and were consistently found to predict phenotypic measures of general psychopathology (Allegrini et al., 2020; Grotzinger et al., 2019; Gard et al., 2021). The results of included studies align with twin and molecular genetic research demonstrating evidence of widespread pleiotropy and shared genetic associations across psychiatric disorders (Waszczuk et al., 2020; Martin et al., 2018; Wray et al., 2014). They also provide compelling evidence that estimates of general psychopathology reflect an underlying genetic liability towards diverse manifestations of mental illness, supporting the biological validity of general psychiatric phenotypes.

Specific transdiagnostic symptom dimensions.

Specific transdiagnostic symptom dimensions were also significantly associated with a wide range of PGSs in the general population. However, positive associations among these dimensions showed a greater level of specificity than those found for general psychopathology. That is, associations were predominately found for PGSs that capture genetic risk for disorders and traits which form part of their constituent symptom dimensions. For example, internalising was mostly positively associated with PGSs that reflect risk for internalising-related disorders and traits, such as depression (Riglin et al., 2020; Pat et al., 2022; Musci et al., 2016; Jermy et al., 2022) and neuroticism (Chen et al., 2022; Cuevas et al., 2021). Conversely, externalising was mostly associated with externalising-related PGSs (e.g., ADHD, disinhibition, number of sexual partners, adventurousness) (Waszczuk et al., 2021; Pat et al., 2022; Li, 2019). These findings are consistent with hierarchical models of psychopathology, which predict that genetic variants associated with specific symptoms/syndromes (e.g., depression) captured by a given dimension (e.g., internalising) will be more strongly associated with that dimension than with others (e.g., externalising) (Waszczuk et al., 2020). However, this was not entirely consistent across exposure-outcome pairings (e.g., anxiety-PGSs were not associated with internalising-related phenotypes across multiple studies) and further research is needed to confirm this pattern of association (Chen et al., 2022; Cuevas et al., 2021).

The included studies also found evidence of shared and unique genetic associations across specific symptom dimensions. For instance, PGSs that were significantly associated with a given specific symptom dimension were consistently also associated with general psychopathology across studies, indicating shared genetic influences. There was *some* evidence of shared genetic associations across specific symptom dimensions (e.g., depression-PGSs were positively associated with internalising, externalising and neurodevelopmental dimensions) (Pat et al., 2022) but these were only found *within* individual studies. In addition, dimension-specific associations were reported *within* several individual studies (Riglin et al., 2020; Waszczuk et al., 2021; Lahey et al., 2022; Chen et al., 2022) but there was limited evidence of unique and replicable associations between specific symptom dimensions and PGSs found across studies. Notable exceptions to this include consistent negative associations between internalising and ADHD-PGSs (Riglin et al., 2020; Waszczuk et al., 2021; Lahey et al., 2022; Chen et al., 2022) and positive associations between internalizing and PGSs for intelligence and educational attainment in early development (Waszczuk et al., 2021; Chen et al., 2022). Several quantitative genetic studies have demonstrated evidence of unique genetic influences on higher-order transdiagnostic symptom dimensions, (Lahey et al., 2011; Waldman et al., 2016) subdimensions, (Waszczuk et al., 2014; Kendler et al., 2003) and measures of specific psychiatric symptoms or syndromes (Kendler et al., 2013). Research using genomic structural equation modeling has also found evidence of genetic variants that are uniquely associated with transdiagnostic dimensions when defined by genetic correlations rather than symptom- or disorder-level correlations (Grotzinger et al., 2022). As such, the relative lack of dimension-specific associations found across studies included in the review may reflect certain methodological limitations rather than an absence of unique genetic associations across different levels of the structural hierarchy.

For instance, case-control GWASs based on categorically defined psychiatric phenotypes likely capture genetic variants that are highly pleiotropic. As such, PGSs constructed from these studies may capture non-specific variance in psychopathology and therefore lack the specificity needed to identify dimension-specific associations (Waszczuk et al., 2021). Future GWASs investigating phenotypes at different levels of the symptom hierarchy (e.g., internalising, externalising) may yield more precise PGSs that are better able to capture unique associations (Waszczuk et al., 2023). Some heterogeneity in the results may also be explained by different approaches to the construction of PGSs themselves (Appendix B, Table S5). For example, PGSs for same phenotype can be constructed using the summary statistics from different GWASs, which may identify different genetic variants associated with the target phenotype. Discovery GWASs can also differ substantially in sample size (across GWASs of the same phenotype and across GWASs of different phenotypes), with lower sample sizes limiting power to detect effects of different genetic variants and lowering the accuracy of a given PGS (Andlauer and Nöthen, 2020). Researchers may also adopt different p-value thresholds in deciding which genetic variants were significantly associated with a given phenotype in discovery GWASs (Andlauer and Nöthen, 2020). These and other factors impact the composition of PGSs and may explain why some significant associations failed to replicate across studies.

4.2. Neuroimaging research studies

4.2.1. Gray matter structure

General psychopathology.

General psychopathology was predominately associated with broad, non-specific reductions in gray matter structure across the included studies. For instance, the included studies found evidence that general psychopathology was significantly negatively associated with global measures of CT, (Romer et al., 2021a) SA, (Mewton et al., 2022a; Romer et al., 2023) and GMV (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021). Whole-brain analyses also tended to reveal evidence of widespread regional associations across each of these metrics (Mewton et al., 2022a; Romer et al., 2023, 2021a; Snyder et al., 2017; Durham et al., 2021). Importantly, regional associations tended to be largely or entirely non-significant after controlling for global effects, further suggesting that reductions in gray matter structure are widely distributed (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Durham et al., 2021).

These results provide compelling evidence that shared neurobiological vulnerabilities underpin diverse manifestations of psychopathology in the general population. In line with this, alterations in gray matter structure have been independently linked to various psychiatric disorders and cross-disorder research demonstrates that these associations are largely shared across diagnostic categories (Goodkind et al., 2015; Opel et al., 2020). The predominant pattern of global/widespread associations also aligns with theoretical predictions that the biological correlates of higher-order symptom dimensions will show broad, non-specific associations with different biological mechanisms and processes (Zald and Lahey, 2017). However, evidence of global alteration does not necessarily imply that all brain regions are equally affected. Meta-analytic research indicates that brain-wide patterns of covariance in gray matter structural networks that are altered across different disorders show non-random organization and may be driven by reductions within specific large-scale networks, including prefrontal and temporal regions (Hettwer et al., 2022). Consistent with these findings, two ROI-based analyses found that general psychopathology was associated with lower GMV in prefrontal and temporal regions (Parkes et al., 2021; Snyder et al., 2017) and functional imaging research pointed to a central role of disrupted connectivity in the DMN (which comprises both the prefrontal cortex and medial temporal lobe).

Specific Transdiagnostic Symptom Dimensions.

Specific symptom dimensions were similarly associated with broad, non-specific reductions in gray matter structure across various metrics. This included negative global and regional associations with CT, (Romer et al., 2021a) SA, (Mewton et al., 2022a; Romer et al., 2023, 2021a; Modabbernia et al., 2022) and GMV (Mewton et al., 2022a; Romer et al., 2023; Kaczkurkin et al., 2019; Parkes et al., 2021). However, some studies reported fewer regionally-specific associations with specific symptom dimensions compared to general psychopathology (Kaczkurkin et al., 2019; Parkes et al., 2021; Snyder et al., 2017). Moreover, regional associations with a given symptom dimension tended to overlap with those found for general psychopathology and/or other specific symptom dimensions. There was evidence of dimension-specific associations *within* several studies, specifically between: fear and CT; (Kaczkurkin et al., 2019) internalizing and CT; (Romer et al., 2023) externalizing and SA; (Romer et al., 2021a) internalizing and GMV; (Snyder et al., 2017) and anxious-misery and GMV (Kaczkurkin et al., 2019; Parkes et al., 2021). However, only one of these associations was reported across more than a single study.

It is difficult to draw conclusions regarding the lack of dimension-specific associations found across studies given limited research and substantial methodological differences (e.g., sample size, latent variable models, measurement of brain structure). More consistent evidence of association may emerge from studies attempting to directly replicate existing research. Alternatively, the lack of dimension-specific associations may indicate that brain structural alterations are shared across higher-order dimensions (e.g., general psychopathology, internalizing, externalizing), whilst other factors (e.g., environmental) contribute more to differential symptom expression. However, though more specific than general psychopathology, many of the higher-order symptom dimensions included in these studies capture a broad (i.e., heterogeneous) range of psychiatric symptoms. Unique biological correlates may be more likely to emerge at lower levels of the symptom hierarchy. For example, the relationship between internalizing and GMV showed mixed results across studies, including non-significant, (Romer et al., 2023; Durham et al., 2021) negative, (Mewton et al., 2022a) and positive associations (Snyder et al., 2017). However, two studies examined the internalizing subdimensions of anxious-misery and fear in the PNC and both found that fear was negatively associated with GMV whilst anxious-misery was positively associated (Kaczkurkin et al., 2019; Parkes et al., 2021). These divergent associations among lower-order subdimensions may explain the inconsistencies between studies investigating internalizing more broadly (i.e., contrasting patterns of association between lower-order subdimensions may effectively cancel each other out); however, this interpretation should be considered cautiously given that it is based on only two studies of the same sample.

4.2.2. White matter microstructure

General psychopathology.

Few studies investigated the relationship between white matter microstructure and transdiagnostic symptom dimensions. Studies of children and preadolescents (ages 6–10) found that general psychopathology was negatively associated with global FA (Neumann et al., 2020) and showed no evidence of regionally-specific associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). In contrast, research in young adults (18−22) found that general psychopathology was associated with reduced FA specifically within the bilateral pons, after controlling for global effects (Romer et al., 2018). This association was subsequently replicated in a sample of participants at midlife (age 45) (Romer et al., 2021b) but not in childhood (ages 6–10) (Neumann et al., 2020). These findings *may* indicate that regionally-specific associations with FA emerge later in development, perhaps due to neurodegeneration of certain white matter pathways as a consequence of prolonged exposure to psychopathology. However, further research is needed to replicate these findings before meaningful conclusions can be drawn.

Specific transdiagnostic symptom dimensions.

Associations with specific transdiagnostic symptom dimensions were more mixed. Internalizing was negatively associated with global but not regional FA in a single study (Neumann et al., 2020). However, other analyses found no evidence of global (Modabbernia et al., 2022) or regional associations (Cardenas-Iniguez et al., 2022; Neumann et al., 2020). Conversely, externalizing was positively associated with global and regional FA in a single study (Neumann et al., 2020) but showed no association with either global (Modabbernia et al., 2022) or regional FA in others (Cardenas-Iniguez et al., 2022). Regional associations were not statistically significant for both phenotypes in the one study that controlled for global effects, (Neumann et al., 2020) which may indicate a distributed effect. The positive association observed between externalizing and FA is intriguing, particularly as externalizing and related disorders have previously been linked to greater levels of FA (Cardenas et al., 2013; Teeuw et al., 2022). However, as above, further research is needed to replicate this finding.

4.2.3. Functional connectivity

General psychopathology.

General psychopathology was associated with widespread alterations in connectivity within- and between several large-scale networks across the included studies. However, the findings discussed below (i.e., those reported across multiple studies) were all from cross-sectional studies of ABCD participants and as such, the extent to which they generalize to different samples and developmental periods is unclear. In terms of within-network connectivity, the strongest evidence was found for *lower* connectivity within the DMN and DAN (Karcher et al., 2021; Hong et al., 2023; Sripada et al., 2021). The DMN represents a network of brain regions that exhibit correlated patterns of activity during rest (i.e., when an individual is not engaged in a particular task or otherwise exposed to some external stimulus) (Raichle, 2015). This network is responsible for various cognitive functions related to internal mental activity (e.g., spontaneous thought) and self-referential mental processes (e.g., self-monitoring, introspection) (Andrews-Hanna, 2012). In contrast, the DAN is involved with various attentional processes and is primarily characterized by its association with top-down control during tasks requiring focused attention (Corbetta and Shulman, 2002; Fox et al., 2005). As such, findings from the included studies may indicate that general psychopathology is broadly associated with alterations in functional networks dedicated to both internally- and externally-focused cognitive processes. Importantly, impaired cognitive function (e.g., attentional control) and dysregulated thought are core features of many psychiatric disorders. Interestingly, the DMN neurotypically exhibits ‘anti-correlations’ (i.e., opposing patterns of activity between networks) with other control networks, including the DAN (Fox et al., 2005). Reduced negative correlations between the two networks indicate further disruption to the balance of networks supporting internally- and externally-focused cognition and have also been implicated in several disorders (Patriat et al., 2016; Hu et al., 2017; Posner et al., 2016; Owens et al., 2020a). In line with this, two included studies found that general psychopathology was associated with *greater* connectivity between the DMN and DAN (Lees et al., 2021; Hong et al., 2023). Reduced negative correlations between these networks may serve as a transdiagnostic feature of broad mental illness; however, additional research is needed to replicate these findings (particularly across other samples and age groups).

4.3. Biological associations with transdiagnostic symptom dimensions across the lifespan

As noted, the majority of included studies were restricted to cross-sectional analyses of youth (i.e., childhood to young adulthood). This focus on younger samples and the relative lack of longitudinal analyses makes it difficult to draw conclusions about developmental associations. However, some findings may reflect age-specific differences and warrant further investigation in future research.

4.3.1. Genomic research studies

Longitudinal genomic studies were conducted only in childhood and adolescent samples (ages 7–16) (Allegrini et al., 2020; Riglin et al., 2020; Lahey et al., 2022; Chen et al., 2022). There was evidence of age-specific differences in genetic associations with different symptom dimensions *within* most of these studies (Riglin et al., 2020; Lahey et al., 2022; Chen et al., 2022). Two of these studies revealed PGSs that became significantly associated with a given symptom dimension in a genetically coherent manner in later developmental periods (Riglin et al., 2020; Chen et al., 2022). For example, depression-PGSs were not associated with internalising in childhood but were positively associated in adolescence (Riglin et al., 2020). These findings align with epidemiological research demonstrating increases in the prevalence of internalising-related disorders between childhood and adolescence, which suggest a developmental role in the activation of genetic influences on internalising during puberty (Moffitt et al., 2007). Of note, PGSs were primarily constructed using summary statistics from GWASs of adult samples, which may capture genetic risk that emerges in later developmental periods, potentially explaining why positive associations only emerged in later developmental periods across these studies

(Allegrini et al., 2022). Future research should examine these associations using PGSs from GWASs of similar age groups and explicitly test whether PGSs show greater genetic coherence with specific symptom dimensions in later development.

Some results *across* studies also point to potential developmental associations. For example, general psychopathology showed some evidence of developmental stability in its association with general PGSs (i.e., polygenic p-factors) (Allegrini et al., 2020; Grotzinger et al., 2019; Gard et al., 2021) and neuroticism-PGSs (Gard et al., 2021; Waszczuk et al., 2021; Chen et al., 2022; Jones et al., 2018). Both of these PGSs were consistently positively associated with general psychopathology across different development periods, including midlife to older adulthood. In contrast, ADHD-PGSs may show developmental differences in association with general psychopathology. ADHD-PGSs were positively associated with general psychopathology across six studies (spanning childhood to adolescence) (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022) but showed no association in a sample of midlife to older adult participants (Gard et al., 2021). Meta-analytic evidence indicates that ADHD declines significantly in adulthood (Faraone et al., 2006) and age-specific differences in the prevalence of ADHD have been observed between younger elderly adults and older elderly adults (Michielsen et al., 2012). As such, this lack of association may indicate age-specific declines in the contribution of genetic risk for ADHD to the general expression of psychopathology in later life. However, the lack of association between ADHD-PGSs and general psychopathology in older adults was only found in a single study. It should also be noted that the ADHD-PGSs for this study were constructed using summary statistics from a GWAS that predominately used childhood samples (Demontis et al., 2019) and thus, these PGSs may simply show less association in older samples.

4.3.2. Structural neuroimaging studies

Only one study examined the relationship between brain structure and transdiagnostic symptom dimensions longitudinally, (Romer et al., 2023) finding that lower global CT in preadolescence was uniquely associated with steeper reductions in (but not the mean levels of) internalizing across time (ages 9–12). Across studies, general psychopathology was consistently negatively associated with cortical SA but not CT (Mewton et al., 2022a; Romer et al., 2023) in ABCD participants (ages 9–12). However, the inverse was found in a single study of participants at midlife from the Dunedin Study (age 45), such that general psychopathology was negatively associated with CT but not SA (Romer et al., 2021a). This pattern of association was largely consistent with that found for specific symptom dimensions (Mewton et al., 2022a; Romer et al., 2023; Modabbernia et al., 2022).

These two metrics (CT, SA) are genetically distinct components of GMV, which follow different developmental trajectories and undergo significant structural changes throughout childhood and early adulthood. CT tends to peak in childhood before decreasing linearly throughout childhood and adolescence, whilst surface area reaches its peak in preadolescence, plateaus, and then decreases subtly across adolescence and early adulthood (Tamnes et al., 2017; Wierenga et al., 2014). In contrast, midlife represents a period of relative stability in terms of cortical structure, where neurodegenerative and ageing processes become the predominate drivers of change (Peters, 2006; Oschwald et al., 2019). The negative association between SA and general psychopathology in preadolescence may therefore reflect disruptions to normative neurodevelopmental processes (which may precede or follow from the onset of psychopathology). Conversely, the negative association between CT and general psychopathology may reflect accelerated ageing or neurodegenerative processes that follow from prolonged exposure to mental illness. This is supported by another included study, which found that general psychopathology was associated with greater brain age (calculated from various indices of brain structure) at age 45 (Caspi et al., 2020). Further research is needed to replicate this association at midlife and longitudinal research should specifically examine whether the relationship between brain structure (i.e., SA and CT) and general psychopathology changes across development.

4.4. Interpretations of general psychopathology in the context of genomic and neurobiological research

The interpretation of general and specific transdiagnostic symptom dimensions is the subject of ongoing debate in the literature. Prominent substantive interpretations suggest that general psychopathology reflects trait negative emotionality (e.g., neuroticism), impaired emotion regulation, cognitive deficits, and/or disordered thought processes (Smith et al., 2020; Caspi and Moffitt, 2018b). Each of these constructs can be broadly captured under the domains of impaired emotional functioning (e.g., negative emotionality, impaired regulation of emotion) and impaired cognitive functioning (e.g., cognitive deficits, disordered thought processes), which aligns with a more parsimonious and all-encompassing interpretation offered for general psychopathology i.e., that it reflects general *impairment (*Smith et al., 2020*)*. In line with this interpretation, we propose that a vast array of genetic variants act pleiotropically to predispose individuals to general impairments in the structural and functional neural mechanisms supporting cognitive and emotional functioning, which in turn contribute to the expression of general psychopathology. Individual differences in the type (e.g., specific SNPs) and number of contributing genetic variants (as well as in environmental factors) allow for variation in the nature and severity of alterations to brain structure and function, which may account for the observed variation in levels of general psychopathology between individuals.

Several findings from the included studies support the interpretation that general psychopathology reflects impairment in cognitive and emotional functioning. For example, general psychopathology was consistently inversely associated with PGSs for educational attainment and intelligence (Waszczuk et al., 2021; Chen et al., 2022). In terms of trait- and disorder-specific associations, the strongest evidence was found for neuroticism- and ADHD-PGSs. PGSs for neuroticism capture genetic risk for trait negative emotionality and were consistently positively associated with general psychopathology across four studies (Gard et al., 2021; Waszczuk et al., 2021; Chen et al., 2022; Jones et al., 2018). ADHD-PGSs were positively associated with general psychopathology across six of the included studies (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022; Lahey et al., 2022; Brikell et al., 2020; Chen et al., 2022). ADHD is characterised by marked deficits in cognitive (e.g., attentional control, working memory, response-inhibition) and emotional functioning (e.g., emotion regulation, emotion recognition, negative emotionality). In general population samples, ADHD-PGSs have been found to be associated with impaired cognitive function (independently of their association with ADHD symptoms) (Stergiakouli et al., 2016; Martin et al., 2015) and trait negative emotionality (Du Rietz et al., 2018). As such, ADHD-GWASs may be capturing the pleiotropic effects of genetic variants associated with broader domains of cognitive and emotional impairment, in addition to more specific variance at the level of lower-order dimensions (e.g., externalizing, neurodevelopmental) or specific disorders (e.g., ADHD-specific variance).

These and other genetic variants associated with the expression of mental illness likely exert their influence indirectly via their impact on early brain development and subsequent impact on cognitive and emotional functioning. It is well-established that cognitive and emotional processes emerge from complex and co-ordinated interactions among large-scale structural and functional brain networks, which are themselves under genetic influence (Rasch et al., 2010; P.O.F. T. Guimarães et al., 2022; Elliott et al., 2019a). It is also important to note that cognitive and emotional functioning are not distinct from one another but are inextricably connected and supported by shared structural and functional brain correlates (Pessoa, 2008; Okon-Singer et al., 2015). Indeed, many aspects of impaired emotional functioning (e.g., excessive rumination, maladaptive information processing/recall, poor emotional regulation) are connected to important facets of cognitive function (e.g., attentional control, response inhibition).

Interestingly, associations between greater cognitive function and brain structure (i.e., CT and SA) essentially reflect the inverse of associations found between greater general psychopathology and brain structure in the included studies. For example, greater cognitive function is associated with larger SA but not CT in preadolescents and with greater CT in midlife (Schnack et al., 2015). Genetic influences on cognitive function (e.g., PGSs for educational attainment) have likewise been found to be positively associated with global brain volume in population-based samples (Elliott et al., 2019b) and specifically with global volume and SA but not CT in young adults (Mitchell et al., 2020). Similarly, trait negative emotionality has been linked to smaller global brain volume and widespread reductions in white matter microstructure (Bjørnebekk et al., 2013) and GWASs have demonstrated negative genetic correlations between neuroticism and global SA (Grasby et al., 2020). Finally, functional brain networks that were consistently associated with general psychopathology in the included studies (e.g., the DMN and DAN) are also linked to cognitive and emotional functioning. For example, anti-correlations between the DMN and DAN have consistently been linked to cognitive performance, (Wang et al., 2019; Owens et al., 2020b; Hampson et al., 2010) which aligns with evidence that general psychopathology is associated with greater connectivity between these two networks. High negative emotionality has likewise been linked to alterations in whole-brain functional connectivity (Servaas et al., 2015) and specifically to lower connectivity within the DMN (Li et al., 2022) and DAN, (Simon et al., 2020) which is further consistent with associations found for general psychopathology in the included studies.

4.5. *Methodological considerations*

4.5.1. *Latent variable models*

The findings of this review must be interpreted in light of considerable heterogeneity in methodological approaches taken across studies. Most importantly, included studies varied substantially in terms of observable indicators of psychopathology (e.g., assessment scales) and in the statistical models used to extract latent symptom dimensions from those indicators. The most commonly used approach was a bi-factor model, which is consistent with a previous systematic literature review examining risk and protective factors of empirical models of psychopathology in youths aged 10–24 (Lynch et al., 2021). The bi-factor model is distinct from other commonly used factor analytic approaches, such as correlated-factor and higher-order models (Markon, 2019; van Bork et al., 2017). In a correlated-factor model, a given number of latent variables (e.g., internalizing, externalizing) are specified to account for the shared variance among a set of psychiatric indicators (e.g., symptoms). In higher-order models, the set of indicators load onto lower-order factors (as in a correlated factor model) and a higher-order general factor (e.g., general psychopathology) is derived from the variance shared among those lower-order factors. As such, the general factor *explains* the shared variance of a given number of lower-order factors and is only indirectly related to indicators included in the model (Markon, 2019; van Bork et al., 2017). In contrast, bi-factor models include both general and specific (e.g., internalizing, externalizing) factors but the general factor loads directly onto the indicators and all factors within the model are specified to be orthogonal to one another. That is, general and specific factors in a bi-factor model are statistically independent (uncorrelated) and thus, the specific factors explain the shared variance across subsets of indicators (e.g., psychiatric symptoms) that remains *after the effects of the general factor have been removed (*Markon, 2019; van Bork et al., 2017). Bi-factor models are commonly used in studies examining the latent structure of psychopathology because they tend to demonstrate superior goodness of fit (Watts et al., 2019) and ease of interpretation. However, goodness of fit is increasingly recognized to be an insufficient indicator of structural validity and many authors now recommend comparisons across different modelling approaches (Lynch et al., 2021; Forbes et al., 2021).

Although each model is closely related, the interpretation of general and specific factors and the nature of their associations with external (e.g., biological) variables differs substantially depending on which statistical approach is adopted. For example, ADHD-PGSs were positively associated with both externalizing and neurodevelopmental dimensions across multiple studies. However, ADHD-PGSs were only positively associated with externalizing when using a higher-order model (Pat et al., 2022) or when modelling externalizing in isolation within a LGC model (Li, 2019) and there was no evidence of association when using a bi-factor model (Riglin et al., 2020) or otherwise controlling for the effects of general psychopathology (Waszczuk et al., 2021). In contrast, ADHD-PGSs were consistently positively associated with the neurodevelopmental dimension across multiple structural models, including the bi-factor model (Riglin et al., 2020; Waszczuk et al., 2021; Pat et al., 2022). Of note, one study found that the positive association between ADHD-PGSs and the neurodevelopmental dimension was the only significant association to emerge across 22 different PGSs after controlling for general psychopathology (Waszczuk et al., 2021). Consideration of these different modelling approaches suggests that ADHD-PGSs may be more strongly associated with the neurodevelopmental dimension than externalizing. This is also supported by quantitative genetic research, which similarly found that ADHD was significantly correlated with the neurodevelopmental dimension (and no others) after controlling for general psychopathology and that this association was largely driven by genetic effects (Du Rietz et al., 2021).

4.5.2. *Genomic methods*

Effect sizes were small across the included genomic studies (i.e., >0.15; Supplementary Table S5), which is common in research investigating associations between PGSs and psychiatric phenotypes (Bogdan et al., 2018; Choi et al., 2020a). Studies also varied considerably in sample size (i.e., from $N = 488$ to $N = 332{,}050$ participants) and in the size of discovery GWAS used to construct PGSs, both of which impact the ability to detect significant associations (Bogdan et al., 2018). Indeed, both PTSD- and MDD-PGSs showed significant associations with general psychopathology in preadolescents when constructed from well-powered GWASs and no association when constructed from GWASs with considerably smaller sample sizes. Greater consistency in the associations observed across studies will likely emerge from the use of larger sample sizes and PGSs constructed from more powered GWASs.

The included studies also varied considerably in terms of approaches to the measurement and analysis of biological variables, which may partially explain some of the heterogeneity in results across the included studies. In the genomics literature, associations with a given PGS were found to vary between studies that did and did not control for the effects of other PGSs. For example, ADHD-PGSs were negatively associated with internalising in two studies of ABCD participants that controlled for general and specific symptom dimensions but not other PGSs (Waszczuk et al., 2021; Lahey et al., 2022). However, another study of the same sample found no evidence of association when controlling for other PGSs (Pat et al., 2022). In addition, some PGSs were not associated with a given symptom dimension when examined in isolation but showed significant positive associations when controlling for other PGSs. The clearest example of this was found for the relationship between depression-PGSs and internalizing, externalizing, somatic and detachment dimensions in ABCD participants (Waszczuk et al., 2021; Pat et al., 2022). These results highlight the importance of carefully considering the inclusion of other PGSs (even if not directly important to a given analysis) when examining polygenetic associations with transdiagnostic symptom dimensions. Not controlling for other PGSs can introduce confounding effects associated with genetic influences not accounted for in the analysis, which may explain differences in the results observed across studies. However, SNPs can also overlap substantially between different PGSs, meaning that the inclusion of multiple PGSs in a single model can introduce multicollinearity among predictors (Choi et al., 2020b). Multicollinearity among predictors can produce unstable coefficient estimates, difficulties interpreting the individual contributions of a given predictor, and may also result in different observations regarding the significance and magnitude of associations across studies (P. Vatcheva and Lee, 2016).

4.5.3. Neuroimaging methods

In the neuroimaging literature, controlling for global effects (e.g., total GMV) resulted in substantially different findings. As mentioned, regionally-specific associations between symptom dimensions and numerous measures of brain structure (including both gray matter structure and white matter microstructure) tended to be largely or entirely non-significant after controlling for global effects. This coupled with consistent evidence that transdiagnostic symptom dimensions are associated with global measures of brain structure suggests that the neural architecture underlying broad expressions of psychopathology is widely distributed throughout the brain. This pattern of results calls into question the findings of several included studies, which reported regionally-specific associations found via whole-brain or ROI-based analyses not controlling for global effects. More broadly, it has important implications for research investigating the neurobiological underpinnings of psychopathology, which has historically focused on identifying disorder-specific correlates within relatively discrete brain regions. This is not to say that regionally-specific associations cannot be found (or that global associations are not driven by alterations within specific brain regions); (Hettwer et al., 2022) however, it does point to the importance of including global effects as a covariate in future analyses. Indeed, identifying regional associations with general and specific symptom dimensions that consistently survive controlling for global effects (e.g., lower pontine FA, cerebellar GMV) may serve as particularly important biological markers.

Another important consideration is the directionality of associations between biology and psychopathology. Measures of brain structure and function are often investigated for the potential as predictive markers of psychopathology; however, research indicates that psychopathology can also precede neurobiological abnormalities (Blok et al., 2023). Disentangling the temporal ordering of associations between biology and psychopathology is therefore critical to accurately modelling the structure and biological underpinnings of mental illness and to developing effective predictive models. Few of the included studies examined longitudinal associations between brain structure or function and transdiagnostic symptom dimensions. One study found that baseline measures of brain structure (i.e., SA and GMV) in the ABCD cohort predicted general and specific symptom dimensions across the first three waves of data collection (Romer et al., 2023). Conversely, another found that general psychopathology (derived from psychiatric assessment data across the lifespan) was associated with greater brain age at midlife (age 45) (Caspi et al., 2020). These findings likely indicate bi-directional effects between brain structure and psychopathology; however, further longitudinal research is urgently needed to better characterise these relationships.

4.6. Directions for future research

The review identified several directions for future research. Firstly, future research should directly investigate whether different biological correlates emerge for a given symptom dimension depending on the latent variable approach used in the analysis. Studies attempting to identify dimension-specific associations should control for the effects of other symptom dimensions (including general and specific transdiagnostic phenotypes). Bi-factor models may be particularly useful as they allow for identifying correlates that are associated with variance in psychopathology that is not shared across general and specific symptom dimensions; however, caution is needed when interpreting associations with phenotypes derived from this approach and efforts should be made to replicate associations with a given phenotype using different structural models. In terms of biological approaches, studies aiming to identify associations between symptom dimensions and PGSs should simultaneously model multiple PGSs where possible and ensure that correlations among PGSs are appropriately controlled for. Future research may also benefit from GWASs that specifically target transdiagnostic phenotypes (e.g., internalizing, externalizing) rather than disorder-specific phenotypes. Likewise, studies aiming to identify regional associations between symptom dimensions and brain structural correlates should control for global effects. Neuroimaging studies should also explore the contribution of specific brain regions (e.g., frontal and temporal regions) or networks (e.g., the DMN and DAN) to observed global associations. The review also identified several understudied symptom dimensions (e.g., thought disorder, somatic, detachment dimensions) and biological measures (e.g., task-based neural activation, white matter structure) that may yield further insights into the biological correlates of higher-order dimensions of psychopathology. Finally, longitudinal research across different (narrowly defined) developmental periods and age groups (particularly older adulthood) is urgently needed to inform our understanding of relationships between biological factors and transdiagnostic dimensions of psychopathology across the lifespan.

4.7. Limitations

There are several limitations to the review that are important to discuss. Firstly, there were notable methodological differences between the included studies (e.g., latent variable models, size of discovery and test samples, PGS construction and other measurement of biological variables, covariates included in analyses), which likely accounts for much of the heterogeneity observed in the results. Secondly, several associations were investigated in only one or few studies, preventing the ability to draw meaningful conclusions for these exposure/outcome relationships. Thirdly, only studies of general population samples were eligible for inclusion. Whilst this increases the generalisability of results, it is possible that biological variables will show different patterns of association at greater levels of symptom severity (e.g., in clinical samples). Fourth, although the review was intended to synthesise evidence from research investigating the biological correlates of transdiagnostic symptom dimensions *across the lifespan*, the vast majority of included studies (particularly within the neuroimaging literature) were limited to cross-sectional samples of youth and young adults. As such, we were unable to draw strong conclusions about age- and developmentally-specific biological associations across different symptom dimensions. Fifth, several limitations may influence the generalisability of findings from the review. For instance, a substantial number of the included studies were conducted using ABCD data and findings may not replicate across different samples of the same age group. More broadly, the majority of reviewed studies are based on Western samples, further adding to the issue of generalisability. This was particularly problematic in the genomics literature, where analyses were often explicitly restricted to samples of European ancestry. This is due to the fact that PGSs are primarily constructed from GWASs of European samples and tend to perform poorly when applied to samples of other ancestries, (Martin et al., 2019) suggesting that polygenetic associations with general and specific symptom dimensions may not replicate across different racial and ethnic groups. Sixth, the review only included studies examining higher-order symptom dimensions and subdimensions. The inclusion of studies investigating specific individual symptoms, signs, or maladaptive traits that are shared across diagnostic categories was beyond the scope of the current study; however, there will likely be important biological associations at these lower-levels of the symptom hierarchy. Finally, the findings of this review are presented via narrative synthesis rather than meta-analysis. This was due to vast methodological differences across studies and the limited number of associations between a given symptom dimension and biological variable that were examined across multiple studies.

4.8. Conclusions

To our knowledge, this is the first systematic review to synthesize evidence from studies investigating the latent structure and underlying biology of psychopathology in the general population and to characterize these relationships across the lifespan. The findings of this review suggest that general psychopathology reflects broad genetic and neurobiological vulnerabilities that are shared across different manifestations of mental illness. The review found limited evidence of biological correlates that are uniquely associated with specific/lower-order transdiagnostic dimensions (e.g., internalizing, externalizing); however, this is likely due to substantial methodological differences and limitations between the existing studies. Several factors must be carefully considered when interpreting the results of studies investigating biological associations with general and specific transdiagnostic dimensions. This includes the choice of latent variable model (e.g., bifactor v. higher-order models), as well as the inclusion of biological controls (e.g., different PGSs, global measures of brain structure) and phenotypic covariates (e.g., controlling for general and specific symptom dimensions) in analyses. Several promising avenues for future research and important gaps in the current evidence base were identified. In particular, there is a need for more longitudinal research across different age groups and developmental periods in order to determine when and how biological differences impact the trajectories of general and specific/lower-order symptom dimensions.

Declarations of Interest

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Open AI in order to edit/refine text included in the main manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105431.

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Appendix B

Investigating the molecular genetic, genomic, brain structural, and brain functional correlates of latent transdiagnostic dimensions of psychopathology across the lifespan: Protocol for a systematic review and meta-analysis of cross-sectional and longitudinal studies in the general population

Preface

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Investigating the molecular genetic, genomic, brain structural, and brain functional correlates of latent transdiagnostic dimensions of psychopathology across the lifespan: Protocol for a systematic review and meta-analysis of cross-sectional and longitudinal studies in the general population

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Background: Research using latent variable modelling has identified a superordinate general dimension of psychopathology, as well as several specific/lower-order transdiagnostic dimensions (e.g., internalising and externalising) within the meta-structure of psychiatric symptoms. These models can facilitate discovery in genetic and neuroscientific research by providing empirically derived psychiatric phenotypes, offering greater validity and reliability than traditional diagnostic categories. The prospective review outlined in this protocol aims to integrate and assess evidence from research investigating the biological correlates of general psychopathology and specific/lower-order transdiagnostic symptom dimensions. Cross-sectional and longitudinal studies investigating general population samples of any age group or developmental period will be included to capture evidence from across the lifespan.

Methods and analysis: MEDLINE, Embase, and PsycINFO databases will be systematically searched for relevant literature. The review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligibility criteria were designed to capture psychiatric genetic (i.e., molecular genetic and genomic) and neuroimaging (i.e., brain structural and brain functional) studies investigating latent transdiagnostic dimension(s) or structural model(s) of psychopathology across any age group. Studies which include or exclude participants based on clinical symptoms, disorders, or relevant risk factors (e.g., history of abuse, neglect, and trauma) will be excluded. Biometric genetic research (e.g., twin and family studies), candidate gene studies, neurophysiology studies, and other non-imaging based neuroscientific studies (e.g., post-mortem studies) will be excluded. Study quality and risk of bias will be assessed using the Joanna Briggs Checklist for Analytical Cross-Sectional Studies, the Joanna Briggs Checklist for Cohort Studies, and the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. Meta-analysis will be conducted if sufficient data is available.

Discussion: This protocol outlines the first systematic review to examine evidence from studies investigating the latent structure and underlying biology of psychopathology and to characterise these relationships developmentally across the lifespan. The prospective review will cover a broad range of statistical techniques and models used to investigate latent transdiagnostic dimensions of psychopathology, as well as a numerous genetic and neuroscientific methods.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/], identifier[CRD42021262717].

KEYWORDS

psychopathology, p-factor, internalising, externalising, genomic, brain structure, brain function, lifespan

Introduction

Psychiatric genetic and neuroscientific research informs our understanding of the aetiology, course, and consequences of mental illness, improves diagnostic accuracy, and guides the development of effective and biologically informed preventative interventions, and treatment strategies. Over the past three decades, significant advances in genetic sequencing and neuroimaging brought the promise of ushering in an unprecedented era of discovery in biological psychiatry (1–3). However, despite these methodological developments, researchers have made little progress in identifying clinically useful biomarkers for different psychiatric disorders or in reducing the burden of mental illness in the general population (3, 4). A growing consensus among researchers is that this lack of progress has been driven by reliance on the categorical model of psychopathology in psychiatric research, which is increasingly recognised to provide suboptimal phenotypes through which to investigate the biological underpinnings of mental illness (5–9).

Latent variable models of psychopathology

As an alternative to the categorical approach, latent variable models of dimensional psychopathology have been proposed. Seminal factor-analytic studies demonstrated that two latent transdiagnostic dimensions of psychopathology (i.e., internalising and externalising) could be extracted from patterns of covariation across a range of common psychiatric disorders (10, 11). The internalising dimension typically captures more emotionally focused symptoms, maladaptive traits and/or disorders (e.g., depression, anxiety, and specific phobia), whereas the externalising dimension captures those that are more behaviourally focused (e.g., substance use, inattention, and aggression) (6, 12). Thus, closely related indicators of supposedly distinct expressions of psychopathology (e.g., of depression and anxiety) are assigned to a given higher-order symptom dimension (e.g., internalising), which reflects the patterns of comorbidity between them. Subsequent research, which included broader measurement of psychopathology, identified an additional thought disorder dimension capturing more psychotic like symptoms (e.g., delusions, hallucinations, and disorganised thought) (13, 14). Several other latent transdiagnostic dimensions of psychopathology have since been identified and some (e.g., internalising and externalising) have also been found to bifurcate into additional subfactors (15).

Importantly, significant positive correlations among these latent dimensions led to the identification of a superordinate general dimension of psychopathology (often referred to as the p-factor) (16). This general dimension of psychopathology suggests that the meta-structure of mental illness can be understood hierarchically, including both a *single* general symptom dimension, as well as several specific/lower-order transdiagnostic symptom dimensions (e.g., internalising, externalising, and thought disorder) that sit at lower levels of the hierarchy. General psychopathology is argued to reflect an underlying liability to develop any and all manifestations of psychopathology (17, 18); however, the validity and substantive meaning of this dimension is the subject of ongoing debate (19, 20). Researchers have advanced several theories as to the substantive meaning of general psychopathology, including that it reflects negative emotionality (21), impaired emotional regulation (22), disordered thought processes (17), and functional impairment (23).

Advantages of latent transdiagnostic dimensional models in genetic and neuroscientific research

Latent transdiagnostic dimensional models can advance our understanding of the genetic and neural correlates of psychopathology. For one, dimensional phenotypes offer greater precision and statistical power than traditional diagnostic categories, facilitating discovery in genetic and neuroscientific research (7, 8). For example, traditional case-control studies impose arbitrary symptom thresholds in selecting cases and thereby suffer from considerable loss of information with respect to variations in symptom severity (e.g., subthreshold cases) (7). By contrast, dimensional phenotypes capture the full range of symptom severity, allowing for more precise estimates of a given association between biology and symptom expression.

Another advantage of the latent variable approach is that it allows for directly modelling the observed correlational structure and dimensionality of psychiatric symptoms, providing more valid and reliable phenotypes than traditional disorder categories (15). Indeed, accumulating evidence indicates that the biological correlates of psychopathology are largely consistent with the latent hierarchical structure identified through phenotypic research (7, 8, 24). For instance, genome-wide association studies (GWAS) have consistently demonstrated evidence of widespread pleiotropy across different diagnostic categories (25, 26). That is, genes influencing the expression of psychopathology are largely shared across different psychiatric disorders, consistent with the observed correlational structure of psychiatric symptoms. Similarly, recent meta-analytic research has demonstrated evidence of shared abnormalities in both brain structure and function across a range of common psychiatric disorders (27, 28). There is also evidence that the genetic and neural mechanisms underlying different manifestations of psychopathology are associated with trait-like, subclinical manifestations of psychopathology in the general population, supporting the dimensionality of psychiatric symptoms (29, 30). Examining evidence from studies that *directly* investigate the underlying biology of transdiagnostic, hierarchically defined symptom dimensions should, therefore, enhance our understanding of the relationship between genetics, neurobiology, and mental illness.

Lastly, latent dimensional models allow for investigating the biological correlates of psychopathology at various levels of specificity and across the full range of phenotype severity (7, 8, 24). Researchers can target genetic and neural mechanisms that are associated with broad, non-specific manifestations of psychopathology, as well as those associated with specific/lower-order dimensions and subdimensions. Importantly, identifying biological correlates that are distinctly and consistently associated with general psychopathology and specific/lower-order symptom dimensions is critical to supporting the validity of the hierarchical model, as well as its utility in genetic and neuroscientific research (24). As such, the upcoming review will integrate and assess evidence from studies investigating the genetic (i.e., molecular genetic and genomic) and neural (i.e., brain structural and brain functional) correlates of latent transdiagnostic phenotypes at multiple levels of specificity (i.e., general psychopathology and specific/lower-order transdiagnostic symptom dimensions) and evaluate whether there is evidence of distinct and replicable biological correlates at different levels of the symptom hierarchy.

Investigating the latent structure and biological correlates of psychopathology across the lifespan

The latent hierarchical structure of psychopathology has been replicated across different age groups and developmental periods, from early childhood through to older adulthood (21). However, research to date has primarily been conducted using cross-sectional samples of adults (15). Consequently, important gaps exist in our understanding of the onset and developmental course of different symptom dimensions and of the biological factors driving differences in the trajectories of these dimensions across the lifespan (15, 21). At the level of categorical diagnoses, research has long demonstrated evidence of age- and developmentally specific patterns in the onset and course of psychiatric disorders, as well as periods associated with both increased and decreased risk of mental illness (31). These trajectories are driven by genetic, neurobiological, and environmental factors that precede the onset of psychopathology, as well as both normative and non-normative changes in gene expression, neurobiology and environmental risk that occur across the lifespan (9, 31–33). Disentangling the temporal ordering of associations between genetics, neurobiology, and symptom expression across different age groups and developmental periods is therefore critical to accurately modelling the structure and biological underpinnings of psychopathology. From a clinical perspective, this research is of paramount importance because it guides the development of biologically informed preventative and early intervention efforts (e.g., by identifying biomarkers that predict the onset of psychopathology), as well as the development of effective treatment strategies (e.g., by identifying biomarkers associated with active psychopathology, or prolonged exposure to psychopathology, which provide targets for clinical and pharmacological intervention) (34).

As such, the upcoming review will integrate existing evidence from studies investigating transdiagnostic symptom dimensions and their underlying biology in any age group in order to assess evidence from across the lifespan. Cross-sectional studies will be included to integrate and assess evidence of the molecular genetic, genomic, brain structural, and brain functional mechanisms and processes which correlate with different latent dimensional phenotypes age-specifically and across age groups. Longitudinal research will be included to integrate and assess evidence regarding the temporal ordering of associations between genetics, neurobiology, and the onset and course of latent dimensional phenotypes across different timeframes and developmental periods. In addition, the review will highlight priority (i.e., understudied and promising) areas for future genetic and neuroimaging research investigating latent dimensional phenotypes across different age groups and developmental periods.

While there are several published reviews examining evidence from studies investigating the latent structure and underlying biology of psychopathology (6–9, 15, 35), none of these reviews were conducted systematically and those which focused specifically on genetic and neuroimaging research (7–9) included only a select number of studies directly investigating the biological correlates of different latent dimensional phenotypes. One systematic review has examined evidence of risk and protective factors (including biological factors) associated with general and specific latent symptom dimensions (36). However, this review was restricted to samples of youth aged 10–24 years old, characterising only a narrow (albeit highly important) developmental period. The upcoming review will extend these findings by systematically reviewing evidence from across the lifespan, providing a more comprehensive examination of evidence from studies investigating the biological correlates of general and specific/lower-order dimensions of psychopathology.

The prospective review

The current paper outlines the protocol for an upcoming systematic review aiming to:

1. Integrate and assess evidence from cross-sectional and longitudinal studies investigating the molecular genetic, genomic, brain structural, and brain functional correlates of general psychopathology and specific/lower-order symptom dimensions across the lifespan in the general population.
2. Determine whether there is evidence of distinct genetic and/or neural correlates that are associated with general psychopathology and specific/lower order transdiagnostic symptom dimensions.
3. Determine whether there is evidence of age-related differences in the genetic and neural correlates of general psychopathology and specific/lower-order transdiagnostic symptom dimensions.

A systematic literature review will be conducted to identify cross-sectional and longitudinal studies investigating the genetic (i.e., molecular genetic and genomic) and neural (i.e., brain structural and brain functional) correlates of latent transdiagnostic dimensions of psychopathology in the general population [e.g., (37, 38)]. Studies investigating any age group or developmental period will be included to integrate evidence from across the lifespan. Studies investigating any latent transdiagnostic dimension(s) (e.g., general psychopathology, internalising, externalising, and thought disorder) or latent structural model(s) (e.g., bifactor models and hierarchical models) will be included to capture evidence of shared and distinct biological correlates associated with transdiagnostic symptom dimensions across multiple levels of specificity. This will be the first systematic literature review to specifically investigate the molecular genetic, genomic, brain structural, and brain functional correlates of

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latent transdiagnostic dimensions of psychopathology and the first to characterise these relationships systematically across the lifespan.

Methods

Study design

This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement (see **Supplementary Table 1**) (39). The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42021262717). Any amendments made to the protocol will be documented through PROSPERO.

Search strategy

A comprehensive search strategy will be used to identify relevant literature from three different electronic databases (i.e., Embase, MEDLINE, and PsycINFO). The search strategy is provided in the **Supplementary material** (see **Supplementary Tables 2–4**). Relevant literature will be searched across each database, with no additional restrictions imposed on the date, language, or type of publication. The reference lists of all included articles and relevant reviews will be manually searched for additional citations. Each search strategy includes a broad combination of relevant database-specific subject headings and additional keywords, developed by identifying terms used to index highly relevant papers across the three databases and by adapting the search terms of previous systematic literature reviews that examined latent dimensional models of psychopathology (21, 36). Search strings will be adapted for each database, given that they each index papers according to different subject-headings (40). The search strategy captures three major domains: latent variable models of psychopathology; molecular genetic and genomic research; and neuroimaging research. The overall search strategy, combining each different domain, functions as follows: (latent variable model terms AND psychopathology terms) AND (molecular genetic OR genomic research terms), OR (brain structural OR brain functional neuroimaging research terms).

Eligibility criteria

The research questions and eligibility criteria for the review were developed using the Population Exposure Comparator Outcome Study (PECOS) framework (41).

Inclusion criteria

Population

1. Only studies investigating general population samples will be eligible for inclusion.
2. Studies investigating any age group will be eligible.
3. Only studies investigating human participants will be eligible.

Exposure

1. Studies using any latent variable modelling technique (e.g., factor analysis, principal component analysis, and structural equation modelling) to investigate latent transdiagnostic psychiatric phenotypes as the exposure will be eligible for inclusion.
   a. Studies investigating any latent transdiagnostic dimension(s) of psychopathology (e.g., general psychopathology, internalising, externalising, and thought disorder) will be eligible.
   b. Studies investigating any latent structural model(s) of psychopathology (e.g., bifactor models, hierarchical models, and correlated factor models) will be eligible.
2. Studies using any technique to investigate molecular genetic or genomic variables as the exposure (with the exception of candidate gene studies) will be eligible for inclusion.
3. Studies using any neuroimaging technique to investigate any brain structural or brain functional variable as the exposure will be eligible for inclusion.
4. Both whole-brain and region of interest neuroimaging studies will be eligible.

Comparator (not applicable)

Outcomes

1. For studies that treat psychiatric phenotypes as the exposure, the outcome measure must include at least one biological variable (i.e., molecular genetic, genomic, brain structural, and/or brain functional).
2. For studies that treat biological variables as the exposure, at least one latent transdiagnostic dimension of psychopathology (e.g., general psychopathology, internalising, and externalising) must be measured as the outcome.
3. Only studies reporting empirical data will be included.

Study characteristics

1. Only peer-reviewed studies will be included.
2. Both cross-sectional and longitudinal studies will be eligible.

3. Studies including any sample size will be eligible.
4. Studies written in any language will be eligible.

Exclusion criteria

Population

1. Studies in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or maltreatment) will be excluded.
2. Studies of non-human animals will be excluded.

Exposures/outcomes

1. Studies investigating specific symptom (i.e., first order) dimensions or any other latent variable that does not capture transdiagnostic psychopathology (i.e., that does not include indicators from across different psychiatric disorder categories) as either the exposure or outcome will be excluded.
2. Studies in which transdiagnostic dimensional measures of psychopathology are treated as the exposure or outcome but are not measured using latent variable techniques (e.g., total scores on instruments with broad measurement of psychopathology) will be excluded.
3. Studies that include biometric genetic measures (e.g., twin, family, and adoption studies) will be excluded.
4. Candidate gene studies will be excluded.
5. Neurophysiological studies (e.g., studies using electroencephalography to measure neural activity) will be excluded.
6. Neuroscientific studies using techniques other than neuroimaging (e.g., post-mortem studies) will be excluded.

Study characteristics

1. Publications that do not report peer-reviewed research (e.g., grey literature and conference abstracts) or original empirical findings (e.g., reviews, opinion pieces, letters, books, or book chapters) will be excluded.

Population

As the review aims to capture evidence from across the lifespan, studies investigating human participants of all age groups will be eligible for inclusion. The review will only include studies using general population samples. Any study in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or trauma) will not be eligible. Although studies using clinical samples provide important evidence (e.g., identifying biological correlates that are distinctly associated with greater symptom severity), including studies of both general population and clinical samples is beyond the scope of the upcoming review. Studies investigating general population samples were chosen over studies of clinical samples for the following reasons: (1) general population samples capture the full distribution of psychopathology (compared to clinical samples, which capture only the more severe end of this distribution); (2) the results are more generalisable than the results of studies investigating clinical samples; and (3) general population samples are more commonly studied in the relevant literature than clinical samples. Of note, studies in which participants were selected on the basis of characteristics not related to psychopathology or relevant risk factors (e.g., studies of university students, particular age groups, or particular genetic ancestries) will be eligible for inclusion.

Exposures/outcomes

Given the bidirectional nature of many relationships between psychiatric symptoms, genetics, and neurobiology (31), the review will include studies that treat either psychopathology (i.e., latent transdiagnostic dimensional phenotypes) or the biological correlates of psychopathology (i.e., molecular genetic, genomic, brain structural, or brain functional) as the exposure (see **Figure 1**). For studies treating psychiatric phenotypes as the exposure, at least one biological variable (i.e., molecular genetic, genomic, brain structural, or brain functional) must be measured as the outcome. For studies treating biological variables as the exposure, at least one latent transdiagnostic dimension of psychopathology (e.g., general psychopathology, internalising, externalising, and thought disorder) must be measured as the outcome. Whether latent dimensional phenotypes were treated as the exposure or outcome will be discussed, as will the implications that this has for the findings of each study (e.g., the effect of psychopathology on brain structure or the effect of brain structure on psychopathology). All outcomes will also be assessed with reference to the latent variable models used to extract different dimensional phenotypes and the implications that this has for the interpretation of the results. (42). The review will provide detailed summaries of significant findings, evaluate the quality of the analysis methods and outcome measures used, as well as the timing of outcome measurement.

The review will include studies investigating a wide range of latent dimensional phenotypes as either exposure or outcome. Studies using any indicators/measures (e.g., self-report, informant-report, and clinician-rated measures) of psychopathology, any latent variable techniques (e.g., factor analysis, principal component analysis, and structural

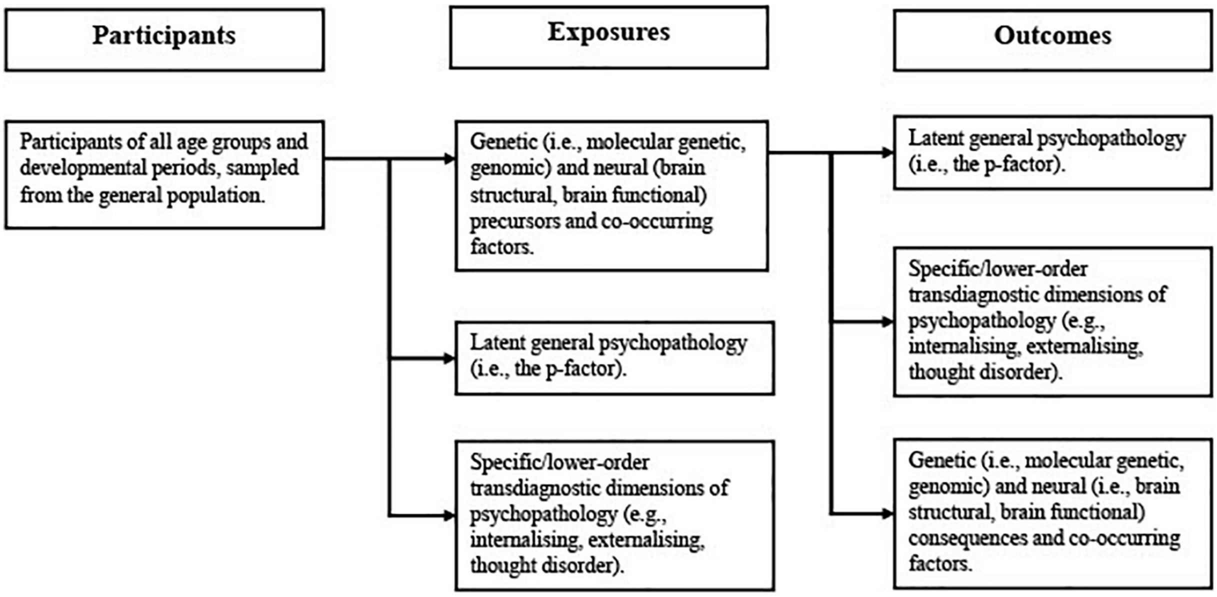

FIGURE 1
Exposure/outcome relationships that will be examined in the upcoming review.

equation modelling), and any model (e.g., bifactor, hierarchical, correlated factor, and single factor) to extract transdiagnostic dimensional phenotypes will be eligible. Studies using latent class analysis or hybrid models that measure psychopathology as a transdiagnostic, dimensional construct will also be eligible. Studies investigating general psychopathology (i.e., the p-factor); individual specific/lower-order dimensions (e.g., internalising and externalising) and sub-dimensions (e.g., disinhibited externalising, antagonistic externalising, fear, and distress); as well as studies investigating multiple dimensions simultaneously (e.g., hierarchical models and correlated factor models) will all be eligible for inclusion. Studies investigating first-order symptom dimensions will be excluded. Studies that use non-latent measures of transdiagnostic dimensional phenotypes (e.g., total scores on instruments with broad measurement of psychopathology) will also be excluded.

The review will also include a wide range of biological variables, treated as either exposure or outcome. Molecular genetic and genomic research studies will be eligible for inclusion, encompassing a wide range of variables and methods used in genetic research (e.g., polygenic risk scores and genomic structural equation modelling). Studies using biometric genetic methods (i.e., family, twin, and adoption studies) are beyond the scope of the review and will not be included. Candidate gene studies, which are widely considered obsolete and unlikely to produce replicable findings in psychiatric genetics (43, 44), will also be excluded from the review. All structural and functional neuroimaging studies will be eligible for inclusion, encompassing a similarly wide range of variables (e.g., white matter integrity and grey matter volume) and methods (e.g., structural and functional magnetic resonance imaging and diffusion tensor imaging) used in neuroscientific research. The review will also include both whole-brain and region of interest neuroimaging studies. Neurophysiological studies (e.g., studies measuring neural activity *via* electroencephalography) and other neuroscientific studies that do not use imaging-based techniques (e.g., post-mortem studies) are beyond the scope of the review and will not be included.

Comparators

As studies investigating latent variable models of psychopathology preclude the need for a control group, no criteria are necessary for this component of the PECOS framework.

Study characteristics

Only peer-reviewed research will be eligible for inclusion in the review. Both cross-sectional and longitudinal study designs will be eligible. No minimum sample size restrictions will be imposed; however, sample size will be considered when assessing the methodological quality of included studies. Studies written in a language other than English will be included where possible. Studies of non-human animals will be excluded. Grey literature and conference abstracts will also be excluded, as will reviews, opinion pieces, letters, books, and any other publications that do not report peer-reviewed research or original empirical findings.

Selection procedure

Two reviewers (i.e., NH and SL) will be involved in screening and study selection procedures for the review. Following de-duplication, reviewer one (NH) will screen all titles and abstracts from across the three databases to identify eligible studies. Reviewer two (SL) will independently screen a random selection of 25% of the titles and abstracts to ensure accuracy of study selection. Cohen's kappa will be calculated to measure inter-rater agreement between the two reviewers, with a high level of agreement defined as a Cohen's kappa of 0.80 or above (45). Following title and abstract screening, the full-texts of all included articles will be screened by both reviewers to further assess study eligibility. Cohen's kappa will also be calculated to determine inter-rater agreement following full-text screening. Disagreements at any stage of the screening process (i.e., title and abstract or full-text) will be resolved through consultation among the two reviewers. If disagreements cannot be resolved, a third member of the research team (i.e., LM, SR, or MW) will be consulted to reach consensus. A PRISMA flowchart will be used to display results from each stage of the screening process.

Data extraction

All citations will be imported to Covidence (46) for title, abstract and full-text screening. Study data will be extracted independently by NH using a data extraction spreadsheet developed by the research team. NH will pilot the spreadsheet using a random selection of included studies. Study authors will be contacted in the event that any necessary data has not been reported. Specific details about the types of data to be extracted from included studies is provided in **Table 1**.

Data synthesis

The results of all included genetic (i.e., molecular genetic and genomic) and neuroscientific (i.e., brain structural and brain functional) studies will be reported separately. Tables will report information about: study characteristics (i.e., study design, age, and gender); psychopathology exposure or outcome variables (e.g., general psychopathology and specific/lower-order transdiagnostic symptom dimensions); statistical methods (i.e., factor analysis, principal components analysis, and structural equation modelling) and models (i.e., bi-factor, correlated factor, and hierarchical models) used to measure latent symptom dimensions; biological exposure or outcome variables (i.e., molecular genetic, genomic, brain structural, and brain functional); methods used to measure biological variables; outcome statistics (e.g., measures of effect and effect sizes); and a summary of the main findings.

If sufficient data is available, meta-analyses will be conducted to examine the genetic (i.e., molecular genetic and genomic) and/or neural (i.e., brain structural and brain functional) correlates of latent psychiatric phenotypes (e.g., general psychopathology, internalising, and externalising). Subgroup analyses will investigate whether results vary by age and sex. Sensitivity analyses will assess the impact of study

TABLE 1 Data to be extracted from all included studies.

Type of data	Details
Study information	Name of author(s); year of publication; country in which data was collected.
Study characteristics	Name of study/dataset; study design (i.e., cross-sectional or longitudinal); follow-up details for longitudinal studies (i.e., number of follow-ups and time between follow-ups); setting (i.e., population-based and community-based); research domain (i.e., molecular genetics, genomics, brain structural, and brain functional); sample size.
Participant characteristics	Age (i.e., range and mean); age at each wave (for longitudinal studies); sex (i.e., proportion male and female); nationality, race, and ethnicity.
Psychopathology data	Assessment of psychopathology (e.g., measurement instruments and diagnostic criteria); type of indicators used (e.g., symptom-level, trait-level, joint symptom and trait level, and disorder-level); mode(s) of assessment (e.g., self-report, informant-report, and clinician-rated); dimensions of psychopathology (e.g., general psychopathology, internalising, externalising, and thought disorder); statistical methods for modelling psychopathology (e.g., confirmatory factor analysis and principal components analysis); type of model(s) (e.g., bi-factor, correlated-factors, and hierarchical).
Genetic data	Type of molecular genetic or genomic variables (e.g., single nucleotide polymorphisms); genetic methods and analysis techniques (e.g., polygenic risk scores, genomic SEM).
Neuroimaging data	Neuroimaging focus (e.g., region of interest and whole-brain); neuroimaging techniques (e.g., structural MRI, resting-state fMRI and task-based fMRI, and diffusion tensor imaging); type of task for task-based fMRI; neuroimaging variables (e.g., grey matter volume and white matter integrity).
Outcome data	Analysis methods; test statistics; p-values; measures of association (e.g., R^2); reported effect sizes; covariates included in analysis; reported interactions; summary of main findings.

SEM, structural equation modelling; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging.

quality. The meta-analysis will be conducted in accordance with evidence-based recommendations for quantitative synthesis of observational studies and separate analyses will be performed for cross-sectional and longitudinal studies (47, 48). A random-effects model will be used to account for the expected heterogeneity in participant characteristics and methodologies between studies (47). For neuroimaging analyses, a cluster-level familywise-error-corrected threshold of $p < 0.05$ will be used to control for false positives, in accordance with best-practice recommendations (49). If sufficient data is not available for meta-analysis, a narrative synthesis of the results from included studies will be completed. Findings will be broadly organised by biological domain (i.e., molecular genetic, genomic, brain structural, and brain functional). For each biological domain, findings will be further organised according to the psychiatric phenotype (i.e., general and/or specific/lower-order latent dimensions) investigated in each analysis and according to the age group or developmental period being investigated. For longitudinal studies, evidence of biological factors that predict general psychopathology and specific/lower-order symptom dimensions will be separated from those that follow from general and specific/lower-order dimensions. A detailed summary of all significant findings will be provided.

Quality assessment and risk of bias

Following data extraction, the quality of each included study will be assessed independently by NH using checklists from the Joanna Briggs Institute (50). Cross-sectional studies will be evaluated using the Checklist for Analytical Cross-Sectional Studies and longitudinal studies will be evaluated using the Checklist for Cohort Studies (50). The review will also include assessment of the overall quality of evidence at the outcome level, scored by NH using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (51). The GRADE system provides a transparent framework for estimating the certainty with which review authors can assert that a given estimate of an effect is representative of the true effect (52). Level of certainty is assessed with reference to study design and within-study risk of bias, heterogeneity, indirectness of evidence, imprecision, and publication bias (51).

Discussion

This paper outlines the protocol for a systematic review of studies investigating the biological correlates of latent transdiagnostic dimensions of psychopathology in general population samples across all age groups and developmental periods. Specifically, the review aims to integrate and assess evidence from studies investigating the molecular genetic, genomic, brain structural, and brain functional correlates of general psychopathology and specific/lower-order transdiagnostic symptom dimensions across the lifespan. This will be the first review to systematically examine the biological correlates of latent general psychopathology and specific/lower-order symptom dimensions and the first to characterise these relationships developmentally across the lifespan. The review is broadly intended to: integrate and assess the existing body of evidence; provide researchers with targets for investigating biological mechanisms and processes that are associated with latent transdiagnostic dimensional phenotypes at multiple levels of specificity; to identify targets for research investigating age- and developmentally specific relationships between biology and latent transdiagnostic dimensions of psychopathology; and to assess evidence regarding the temporal ordering of these relationships.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

NH conceptualised the study, developed the methods and protocol, is the guarantor of the review, is responsible for data extraction, as well as quality and risk of bias assessments, and wrote the first draft of the manuscript. SL, MW, SR, and LM assisted with development of the methods and protocol. NH and SL were responsible for title and abstract screening and full-text screening. All authors revised and gave approval on the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1036794/full#supplementary-material

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Appendix C

Supplementary material for the Chapter 2 protocol

Preface

This is the supplementary material provided for the Chapter 2 protocol paper. It includes the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (Supplement Table 1) and the search strategies to be used for Embase, PsycINFO, and MEDLINE databases (Supplementary Tables 2-4).

SUPPLEMENTARY MATERIAL

Supplement Table 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol[1]

Section and topic	Item No	Checklist item	Items Reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	☒
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☒
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒
Support:			
Sources	5a	Indicate sources of financial or other support for the review	☒
Sponsor	5b	Provide name for the review funder and/or sponsor	☐
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	☒
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☒

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	☒
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☒
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☒
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☒
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	☒
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☒
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☐
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☒

Supplement Table 2

Embase search strategy

Database	Domain	Search terms
Embase	Latent dimensional models of psychopathology	**1. SH: exp factor analysis/ or principal component analysis/** **OR** **2.** general factor* or p-factor* or factor analys?s or "latent class analys?s" or "item response theory" or "factor mixture model*" or (transdiagnostic* adj4 (model* or structur* or dimension* or spectr*)) or (dimension* adj4 (model* or structur* or spectr*)) or (latent* adj4 (model* or structur* or dimension* or spectr*)) or (hierarch* adj4 (model* or structur* or dimension* or spectr*)) or CFA or PCA **AND** **3. SH: exp mental disease/ or exp psychiatry/** **OR** **4.** psychopatholog* or psychiatr* or internali?ing or externali?ing or thought disorder*
	Brain structural and brain functional neuroimaging studies	**5. SH: neuroimaging/ or nuclear magnetic resonance imaging/ or functional magnetic resonance imaging/ diffusion tensor imaging/ or functional connectivity/** **OR** **6.** (structur* connect* or function* connect* or (brain adj structur*) or (brain adj function*) or (neural adj (correlate* or structur* or substrate*)) or neuroimaging).mp
	Molecular genetic and genomic studies	**7. SH: Genetic analysis/ or behavior genetics/ or exp human genetics/ or genetic association/ or genetic variability/ or genetic correlation/ or genetic predisposition/ or pleiotropy/ or genetic risk score/ or genome analysis/ or genome-wide association study/ or single nucleotide polymorphism/** **OR** **8.** polygen* or pleiot* or "polygenic risk score*" or SNP* or GWA* or PGRS or PGS

Note 1. [Latent dimensional models of psychopathology] AND [brain structural OR brain functional] OR [molecular genetic OR Genomic]; SH, Subject Heading; CFA, Confirmatory Factor Analysis; PCA, Principal Component Analysis; SNP, Single Nucleotide Polymorphism; GWA, Genome-Wide Analysis; PGRS, Polygenic Risk Scores; PGS, Polygenic Scores.
Note 2. No limits were imposed on the date, language, or publication type for any of the three search strategies.
Note 3. The search strategy was executed across all three databases on 13 July 2021.
Note 4. This search returned 3581 articles (prior to de-duplication).

Supplement Table 3

PsycINFO search strategy

Database	Domain	Search terms
PsycINFO	Latent dimensional models of psychopathology	**1. SH: latent variables/ or exp factor analysis/ or latent class analysis/ or latent profile analysis/ or item response theory/ or principal component analysis/** **OR** **2.** (general factor* or p-factor* or factor analys?s or "latent class analys?s" or "item response theory" or "factor mixture model*" or (transdiagnostic* adj4 (model* or structur* or dimension* or spectr*)) or (dimension* adj4 (model* or structur* or spectr*)) or (latent* adj4 (model* or model* or structur* or dimension* or spectr*)) or (hierarch* adj4 (structur* or model* or dimension* or spectr*)) or CFA or PCA).mp **AND** **3. SH: exp psychopathology/ or exp psychiatry/ or exp mental disorders/** **OR** **4.** (psychopatholog* or psychiatr* or internali?ing or externali?ing or thought disorder*).mp
	Brain structural and brain functional neuroimaging studies	**5. SH: neuroimaging/ or exp magnetic resonance imaging/ or brain connectivity/** **OR** **6.** (structur* connect* or function* connect* or (brain adj structur*) or (brain adj function*) or (neural adj (correlate* or structur* or substrate*)) or neuroimaging).mp
	Molecular genetic and genomic studies	**7. SH: Genetics/ or Genes/ or Behavioral Genetics/ or Population Genetics/ or exp Genomics/ or Polymorphism/** **OR** **8.** (Polygen* or pleiot* or "single nucleotide polymorphism*" or SNP* or genetic association* or genome-wide association* or GWA* or "genetic risk score*" or "polygenic risk score*" or PGRS or PGS).mp

Note 1. [Latent dimensional models of psychopathology] AND [brain structural OR brain functional] OR [molecular genetic OR Genomic]; SH, Subject Heading; CFA, Confirmatory Factor Analysis; PCA, Principal Component Analysis; SNP, Single Nucleotide Polymorphism; GWA, Genome-Wide Analysis; PGRS, Polygenic Risk Scores; PGS, Polygenic Scores.
Note 2. No limits were imposed on the date, language, or publication type for any of the three search strategies.
Note 3. The search strategy was executed across all three databases on 13 July 2021.
Note 4. This search returned 985 articles (prior to de-duplication).

Supplement Table 4

MEDLINE search strategy

Database	Domain	Search terms
MEDLINE	Latent dimensional models of psychopathology	**1. SH: Latent class analysis/ or principal component analysis/ or factor analysis, statistical/** **OR** 2. (general factor* or p-factor* or factor analys?s or latent class analys?s or item response theory or factor mixture model* or (transdiagnostic* adj4 (model* or structur* or dimension* or spectr*)) or (dimension* adj4 (model* or structur* or spectr*)) or (latent* adj4 (model* or structur* or dimension* or spectr*)) or (hierarch* adj4 (structur* or model* or dimension* or spectr*)) or CFA or PCA).mp **AND** **3. SH: Psychopathology/ or exp Psychiatry/ or exp Mental Disorders/** **OR** 4. (Psychopathol* or psychiatr* or internali?ing or externali?ing or thought disorder*).mp
	Brain structural and brain functional neuroimaging studies	**5. SH: exp Neuroimaging/ or Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging** **OR** 6. (structur* connect* or function* connect* or (brain adj structur*) or (brain adj function*) or (neural adj (correlate* or structur* or substrate*)) or neuroimaging).mp
	Molecular genetic and genomic studies	**7. SH: Genetics/ or Human Genetics/ or Genetics, Behavioral/ or Genetics, Population/ or Genetic Predisposition to Disease/ or exp Genetic Association Studies/ or Polymorphism, Single Nucleotide/ or Genetic Variation/ or Genomics/ or Polymorphism, Genetic/ or Genetic Pleiotropy/** **OR** 8. (Polygen* or pleiot* or SNP* or GWA* or genetic risk score* or polygenic risk score* or PGRS or PGS).mp

Note 1. [Latent dimensional models of psychopathology] AND [brain structural OR brain functional] OR [molecular genetic OR Genomic]; SH, Subject Heading; CFA, Confirmatory Factor Analysis; PCA, Principal Component Analysis; SNP, Single Nucleotide Polymorphism; GWA, Genome-Wide Analysis; PGRS, Polygenic Risk Scores; PGS, Polygenic Scores.
Note 2. No limits were imposed on the date, language, or publication type for any of the three search strategies.
Note 3. The search strategy was executed across all three databases on 13 July 2021.
Note 4. This search returned 1650 articles (prior to de-duplication).

Appendix D

A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood

Preface

This study was published as **Hoy, N**., Waszczuk, M., Sunderland, M., Lynch, S.J., Sachdev, P.S., Brodaty, H., Reppermund, S., Mewton, L. (2025). A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood. *Psychological Medicine*, *55*, e5. https://doi.org/10.1017/S0033291724003490.

NH conceptualized the study with support from LM, SR, MW, and MS. NH conducted all analyses and drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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A longitudinal investigation of the relationship between dimensional psychopathology, gray matter structure, and dementia status in older adulthood

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Abstract

Background. The structure of psychopathology can be organized hierarchically into a set of transdiagnostic dimensional phenotypes. No studies have examined whether these phenotypes are associated with brain structure or dementia in older adults.
Methods. Data were drawn from a longitudinal study of older adults aged 70–90 years at baseline ($N = 1072$; 44.8% male). Confirmatory factor models were fit to baseline psychiatric symptoms, with model fit assessed via traditional fit indices, model-based reliability estimates, and evaluation of model parameters. Bayesian plausible values were generated from the best-fitting model for use in subsequent analyses. Linear mixed models examined intraindividual change in global and regional gray matter volume (GMV) and cortical thickness over 6 years. Logistic regression examined whether symptom dimensions predicted incident dementia over 12 years.
Results. A higher-order model showed a good fit to the data (BIC = 28,691.85; ssaBIC = 28,396.47; CFI = 0.926; TLI = 0.92; RMSEA = 0.047), including a general factor and lower-order dimensions of internalizing, disinhibited externalizing, and substance use. Baseline symptom dimensions did not predict change over time in total cortical and subcortical GMV or average cortical thickness; regional GMV or cortical thickness in the frontal, parietal, temporal, or occipital lobes; or regional GMV in the hippocampus and cerebellum (all p-values >0.5). Finally, baseline symptom dimensions did not predict incident dementia across follow-ups (all p-values >0.5).
Conclusions. We found no evidence that transdiagnostic dimensions are associated with gray matter structure or dementia in older adults. Future research should examine these relationships using psychiatric indicators capturing past history of chronic mental illness rather than current symptoms.

Introduction

As the number and proportion of older adults continue to expand globally (World Health Organization, 2022), it is increasingly important to understand the mechanisms and processes that impact healthy aging in this population. In particular, novel approaches are needed to identify potential targets for the prevention of neurodegeneration and dementia in later life. An extensive body of research indicates that psychiatric disorders are associated with alterations in brain structure and function across the lifespan, including accelerated brain aging (Cole et al., 2019; Wrigglesworth et al., 2021). Several psychiatric disorders are also associated with a greater likelihood of dementia diagnoses in later life (Richmond-Rakerd et al., 2022) and genomic research indicates shared biological mechanisms between psychiatric and neurodegenerative diseases (including dementia; Wingo et al., 2022). These associations appear to cut across traditional diagnostic categories, with a range of putatively distinct psychiatric disorders being nonspecifically associated with both neurodegeneration and dementia risk. This raises the possibility that transdiagnostic models may hold more utility than traditional diagnostic categories in research aiming to disentangle the relationships between psychopathology, neurodegeneration, and dementia in later life.

Transdiagnostic dimensional models of psychopathology

Transdiagnostic dimensional models of psychopathology have recently gained popularity as an alternative approach to the classification of mental illness (Kotov et al., 2017, 2020; Kotov et al., 2021; Krueger et al., 2021; Watson et al., 2022). In these models, psychiatric symptoms and traits are placed at the lowest level of a structural hierarchy and grouped together into higher-order dimensions (e.g., internalizing, externalizing) based on their patterns of covariance (Kotov et al., 2017, 2021). For example, the internalizing dimension captures covariation among emotional indicators of psychopathology (e.g., anxiety, depression), while externalizing captures more behaviorally focused indicators (e.g., disinhibition, aggression, substance use; Krueger et al., 2021; Watson et al., 2022). These phenotypes also tend to exhibit positive correlations with one another, suggesting the presence of a single superordinate dimension of psychopathology (i.e., general psychopathology; Kotov et al., 2021) This general dimension is argued to reflect a general underlying liability toward the full spectrum of mental illness (Caspi et al., 2014; Caspi & Moffitt, 2018a).

Transdiagnostic dimensional models of psychopathology in neuroscientific research

The underlying neurobiology of mental illness is closely aligned with the structure of psychopathology identified through phenotypic research. For example, the neural correlates of specific psychiatric disorders are associated with subclinical symptom expression in general population samples, supporting the dimensionality of mental illness (Besteher et al., 2020). Meta-analytic evidence further indicates that abnormalities in both brain structure and function are largely shared across putatively distinct diagnostic categories (Goodkind et al., 2015; McTeague et al., 2017; Sha et al., 2019), consistent with the correlational structure of psychopathology identified through latent variable modeling. These findings indicate that the neural architecture underlying mental illness is poorly aligned with the discrete categorical boundaries of traditional classification systems. In contrast, transdiagnostic models directly estimate the observed dimensionality and correlational structure of psychopathology (e.g., comorbidity). The phenotypes derived from these models show greater validity and reliability than discrete (e.g., categorical) phenotypes, with the resulting increase in power substantially decreasing the need for larger sample sizes (Markon et al., 2011). The hierarchical structure of these models also allows researchers to investigate the neural correlates of psychopathology at different levels of specificity (i.e., the correlates of general and specific/lower-order symptom dimensions; Latzman & DeYoung, 2020; Zald & Lahey, 2017). An important advantage of this approach is that it allows for disentangling shared from unique associations, which would be otherwise obscured in case–control studies of individual psychiatric disorders. Given these advantages, the use of transdiagnostic dimensional models may facilitate discoveries with respect to the relationship between psychopathology and brain health in older adulthood.

However, a recent systematic review found that not a single study has investigated associations between brain structure and transdiagnostic symptom dimensions specifically in older adults (i.e., 60 years or older; Hoy et al., 2023). In younger samples, transdiagnostic symptom dimensions were consistently associated with pervasive alterations in gray matter structure across several studies (Hoy et al., 2023). For example, general and specific/lower-order dimensions (e.g., internalizing, externalizing) were associated with lower global measures of gray matter volume (GMV) and surface area in multiple studies spanning childhood to young adulthood (Kaczkurkin et al., 2018; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). These findings highlight the utility of dimensional models in psychiatric neuroscience, which has historically aimed to identify disorder-specific correlates within relatively discrete brain regions. Further research is needed to examine whether these phenotypes are also associated with reduced gray matter structure in older adulthood and to determine whether there is evidence of age-specific differences in the nature of these associations. In particular, establishing that these phenotypes can be used to predict change in gray matter structure over time in older adults would provide novel targets for the promotion of brain health in this population.

Dimensional models of psychopathology as a novel framework for investigating the relationship between mental illness and dementia

An extensive body of evidence indicates that psychiatric illness is associated with cognitive decline and dementia risk in older adulthood. Several systematic reviews and meta-analyses have demonstrated a link between individual psychiatric disorders and dementia risk (Becker et al., 2018; Cai & Huang, 2018; Velosa et al., 2020). A recent population-based study of 1.7 million people also found that those with *any mental disorder* were significantly more likely to develop a dementia diagnosis in older adulthood (Richmond-Rakerd et al., 2022). This research suggests that psychopathology is nonspecifically associated with dementia risk; however, no studies have directly examined whether transdiagnostic dimensional phenotypes can be used to predict diagnoses of dementia in older adults. Determining whether these phenotypes can be used to predict diagnoses of dementia will provide important insights into the relationship between mental illness and one of the leading causes of burden of disease in older adulthood. Moreover, establishing the predictive utility of these phenotypes would facilitate the development of novel preventative strategies that target dimensional psychopathology while simultaneously reducing the risk of dementia in older adulthood.

The current study

The current study aimed to determine whether transdiagnostic symptom dimensions can be used to predict intraindividual change in gray matter structure over 6 years of follow-up and incident dementia over 12 years of follow-up in older adults. The aims, research questions, and analytic plan were preregistered on Open Science Framework (OSF; https://rb.gy/1nz92g). For the primary analyses, it was hypothesized that higher severity of general and/or specific symptom dimensions at baseline would predict a greater decline in global cortical GMV, subcortical GMV, and cortical thickness across time. For secondary analyses, it was hypothesized that higher severity of general and/or specific symptom dimensions at baseline would predict a greater decline in regional GMV and cortical thickness across time. Finally, it was hypothesized that greater general and/or specific symptom dimensions would predict a greater likelihood of a dementia diagnosis at any wave.

Methods

Sample and study design

Data were drawn from the Sydney Memory and Ageing Study (MAS; Sachdev et al., 2010), a longitudinal study of community-dwelling older adults in Sydney, Australia. Participants were 1037 older adults aged between 70–90 years old ($M = 78.84$; $SD = 4.82$;

Table 1. Baseline sample characteristics for the full sample and the MRI subsample

	Full sample (N = 1037)		MRI subsample (n = 532)[a]	
Categorical covariates	N	%	N	%
Sex (male)	465	44.8	242	45.5%
Continuous covariates	Mean	SD	Mean	SD
Age (years/continuous)	78.84	4.82	78.41	4.68
Education (years/continuous)	11.60	3.47	11.80	3.60
Total GMV (mm^3)	-	-	552,914.1	52,540.02
Average cortical thickness (mm)	-	-	2.43	0.11
Other characteristics	N	%	N	%
Race/ethnicity				
Caucasian	1016	98.4	517	97.2
Asian	10	1.0	9	1.7
Mixed	3	0.3	2	0.4
Other	4	0.4	2	0.4
Dementia Status	N	%	N	%
Dementia diagnosis[b]	269	25.9	-	-

Note. This table outlines the baseline characteristics for the full sample of participants from the Sydney Memory and Ageing Study (MAS) and the subsample of participants who completed MRI scanning at baseline.
[a]Follow-up MRI data were collected at Wave 2 (n = 417) and Wave 4 (n = 262).
[b]Dementia diagnosis data indicate the number of participants who received a diagnosis of dementia at *any follow-up wave.* Participants who received a diagnosis at one wave but not at subsequent waves were removed from the analysis (n = 7).

44.8% male) at baseline (Table 1). Participants were followed across seven waves of data collection, with assessments occurring every 2 years (alongside brief phone interviews in intervening years). Informants were recruited for the majority of participants (93.9%), provided that they had contact with the participant for at least 1 hour per week and could answer questions regarding their cognitive ability and daily functioning. Recruitment and study enrollment took place between September 2005 and November 2007. Inclusion criteria included the following: (1) aged between 70–90 years old; (2) living in the community; (3) able to speak/write in English; and (4) ability to consent. Exclusion criteria included the following: (1) previous dementia diagnosis or diagnosis of dementia after comprehensive in-study assessment at baseline; (2) psychotic symptoms, schizophrenia diagnoses, or bipolar diagnoses; (3) diagnosis of multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy; (4) medical or psychological conditions that prevent participation; or (5) a Mini-Mental State Examination (Folstein et al., 1975) score of <24 (adjusted for age, education, and non-English speaking background). The MAS sample and study design are described in detail elsewhere (Sachdev et al., 2010) and outlined in the Supplementary Material (Appendix A).

Indicators of psychopathology

Indicators of psychopathology were derived from multiple self- and informant-report measures administered at baseline. The 15-item Geriatric Depression Scale (GDS) was designed to measure depressive symptoms over the past week in older adults (Yesavage et al., 1982). The Goldberg Anxiety Scale (GAS) is a 9-item measure of anxiety symptoms over the past month (Goldberg et al., 1988). The Kessler 10 (K10) is a 10-item measure of psychological distress over the past 30 days (Kessler, 1994). The Neuropsychiatric Inventory (NPI) assesses a range of psychiatric symptoms in people with dementia (Cummings et al., 1994), administered to informants of nondemented participants at baseline. The current study only included NPI items relating to agitation/aggression, irritability/lability, and disinhibition. Finally, substance use was measured via a combination of self-report items relating to alcohol and nicotine use. Items from these measures were included in subsequent latent variable models as indicators of latent internalizing (i.e., GDS, GAS, and K10 items), disinhibited externalizing (i.e., NPI screening items for agitation/aggression, disinhibition, and irritability/lability), and substance use (i.e., alcohol and nicotine use items). Further details of symptom-level indicators are included in all latent variable models and are provided in Appendix B and Supplementary Table S1. Tetrachoric correlations among those indicators are provided in Supplementary Table S2.

Brain structural outcome measures

Details of the neuroimaging protocol are described in detail elsewhere (Sachdev et al., 2010) and outlined in the Supplementary Material (Appendix C). Briefly, all participants were invited to complete brain magnetic resonance imaging (MRI), and consenting participants were further screened for contraindications (i.e., pacemaker, metallic implant or foreign bodies, cochlear implants, ferromagnetic homeostatic clips, claustrophobia). Approximately half of the sample (50.75%) agreed to complete MRI scanning at baseline (n = 544). Following quality control procedures (Jiang et al., 2014) and exclusions due to medical issues that emerged after consenting to MRI scans (e.g., back problems), the final analytic sample size at baseline was n = 532. Follow-up MRI scans were also completed at Wave 2 (n = 417) and Wave 4 (n = 262). We conducted paired samples t-tests and chi-square tests to examine differences in covariates (i.e., age, sex, education, total GMV, average cortical thickness) between those with complete and incomplete MRI follow-up data (Table S3). Those with complete MRI data were significantly younger at baseline and had larger total GMV at baseline, compared to those with incomplete MRI data. The present study used preprocessed structural neuroimaging data (i.e., cortical and subcortical volume, cortical thickness). GMV and cortical thickness within 68 cortical regions and GMV within 19 subcortical regions (including the brain stem) were used to construct brain structural variables for primary and secondary outcomes. Primary outcomes included global measures of brain structure, that is, total cortical GMV, total subcortical GMV, and average cortical thickness. Secondary outcomes included 10 region-of-interest (ROI) measures, that is, total GMV and average cortical thickness in the frontal, parietal, temporal, and occipital lobes, as well as total GMV in the bilateral hippocampus and cerebellum. All brain structural variables were winsorized to be within ±3 standard deviations (SD) of the mean (M).

Dementia status outcome

All participants were free of dementia at baseline. Dementia status was determined via consensus diagnosis from a multidisciplinary panel of experts at each wave of data collection, on the basis of available clinical, neuropsychological, laboratory, and neuroimaging data. Further details of the diagnostic procedures are described in detail elsewhere (Sachdev et al., 2010) and outlined in the Supplementary Material (Appendix D). For the current study, a single binary variable was used to indicate whether participants were diagnosed with dementia at *any follow-up wave* (across 12 years of follow-up). Participants coded as having dementia at one wave and no dementia at subsequent waves (n = 7) were removed from the analysis.

Model estimation and assessment of model fit

The latent structure of psychopathology was examined using confirmatory factor analysis (CFA) of symptom-level categorical indicators of mental illness in the full sample at baseline. Four CFA models that are most commonly used to measure the latent structure of psychopathology were fit to the data (i.e., a one-factor model, a correlated-factors model, a bi-factor model, and a higher-order factor model). The use of confirmatory factor analytic models and allocation of indicators to specific/lower-order factors was based on extensive research detailing the latent structure of psychopathology (Caspi et al., 2014; Caspi & Moffitt, 2018b; Kotov et al., 2017, 2021; Krueger et al., 2021; Watson et al., 2022). The best-fitting factor model was selected for inclusion in subsequent analyses based on traditional fit indices, model-based estimates of reliability, and evaluation of model parameters (e.g., the significance, direction, and standard errors of the factor loadings). Details of model estimation and assessment of model fit are presented in the Supplementary Material (Appendices E–G) and examples of the Mplus code for each latent variable model are provided on OSF (https://osf.io/uhds9/).

Bayesian plausible values

Bayesian plausible values (BPVs) were generated for each participant and each latent symptom dimension. BPVs are a *set* of factor scores derived from multiple imputations that provide more reliable estimates and address biases in measurement (Muthen & Asparouhov & Muthen, 2010). Calculating BPVs involves taking multiple random draws (i.e., imputations) from the posterior distribution of factor score estimates for each participant, providing a range of plausible values for a given factor score. For each participant, 100 plausible values were estimated for each latent factor (i.e., 100 imputed factor scores from the posterior distribution were estimated for general and specific/lower-order factors). BPV estimation was conducted in Mplus Version 8.10 (Muthén & Muthén, 2017). The 100 data sets were then analyzed simultaneously in R version 4.3.2 using (generalized) linear regression and (generalized) linear mixed models within a multiple imputation framework (mitml R package; Bates et al., 2015). Factor scores derived from CFA models provide a single-point estimate of psychopathology for a given symptom dimension. The distributions of these scores are highly skewed when relying on categorical indicators, as in the current study. These scores are also likely to contain substantial random error (i.e., factor indeterminacy; Wu, 2005); however, we were unable to directly calculate factor determinacy in the current study due to the inclusion of multiple dichotomous indicators (Beauducel & Hilger, 2017; Ferrando & Lorenzo-Seva, 2018; Forbes et al., 2021). In contrast, BPVs offer a less biased estimation of the population mean and variance of psychopathology by accounting for the uncertainty around factor scores through multiple imputations. An alternative approach would be to estimate associations simultaneously within a structural equation modeling framework; however, this was unable to be done in the current study due to model complexity.

Analysis plan

Our primary analyses examined whether baseline general and specific/lower-order symptom dimensions predict intraindividual change in total cortical GMV, total subcortical GMV, and average cortical thickness across follow-up waves. Baseline BPVs for general and specific/lower-order symptom dimensions were entered as predictors in a series of linear mixed models with brain structural measures included as the outcome variable. All linear mixed models examined associations between one set of BPVs (e.g., for general psychopathology) and one brain structural variable (e.g., total GMV). Nesting of longitudinal measurements in participants was handled via the use of random intercepts and wave was represented as a categorical variable. All linear mixed models included sex, age, education, and MRI scanner as covariates. The primary estimate of interest was the wave by dimension interaction (e.g., wave by general psychopathology), which indicates whether there was an association between baseline symptom dimensions and change in outcomes over time. The following equation provides an example of the linear mixed models used to estimate wave x dimension interactions:

$$\begin{aligned}\text{Total GMV} = {} & \text{general psychopathology} + \text{wave} + \text{sex} + \text{age} \\ & + \text{education} + \text{scanner} + \text{wave} * \text{general} \\ & \text{psychopathology} + (1|\text{ID}).\end{aligned}$$

Secondary analyses examined whether baseline general and specific/lower-order symptom dimensions predict intraindividual change in regional measures of GMV and cortical thickness across follow-up waves. Specific outcome measures included: total GMV and average cortical thickness in the frontal, parietal, temporal, and occipital lobes, as well as total GMV in the bilateral hippocampus and cerebellum. These analyses followed the same methodology as for primary outcomes. All linear mixed models included sex, age, education, MRI scanner, and either total GMV or average cortical thickness as covariates. Additional secondary analyses examined whether baseline general and specific/lower-order symptom dimensions predict dementia status across 12 years of follow-up. Baseline BPVs were entered separately as predictors in a series of logistic regression models, with dementia status at any wave included as a binary outcome variable. All analyses were run over 100 imputations and the results were pooled into a final set of estimates within a multiple imputation framework. Missing data were handled via Full Information Maximum Likelihood (FIML) in Mplus. Benjamini–Hochberg false discovery rate (FDR) correction was used to correct for multiple testing, with an FDR threshold of 5% ($\alpha = 0.05$; Appendix H). Examples of the R code used to conduct these analyses are provided on OSF (https://osf.io/uhds9/). There were two minor deviations from the preregistered analysis, which are outlined in Appendix I.

Post-hoc analyses

Most research investigating the neural correlates of transdiagnostic symptom dimensions has been conducted cross-sectionally in samples of youth. As such, post-hoc analyses examined whether general and specific/lower-order dimensions predict baseline measures of gray matter structure in older adulthood. Baseline BPVs for general and specific/lower-order symptom dimensions were entered separately as predictors in a series of linear regression models, with baseline measures of GMV and cortical thickness included as the outcome variables. These analyses examined associations with the same brain structural measures (i.e., global and regional) included in primary and secondary analyses. All analyses included sex, age, education, and MRI scanner as covariates. Analyses of regional brain structure included additional controls for either total GMV or average cortical thickness. All analyses (i.e., primary, secondary, and post-hoc) of regional gray matter structure were also re-run without controlling for total GMV or average cortical thickness in order to examine both absolute and relative effects. Finally, we ran a series of unconditional linear mixed models (i.e., without predictors included) to examine the trajectories of each brain structural outcome measure over time (Appendix J). For all post-hoc analyses, Benjamini–Hochberg FDR correction was used to correct for multiple comparisons, with an FDR threshold of 5% ($\alpha = 0.05$).

Results

Structural validity of latent variable models

Traditional model fit statistics for the four CFA models are provided in Table S4 and model-based estimates of reliability are provided in Table S5. The best-fitting model based on traditional fit statistics (i.e., BIC, ssaBIC, CFI, TLI, and RMSEA values) was the bi-factor model. However, bi-factor models have a tendency to provide a better fit than competing models when relying solely on traditional fit statistics and there is growing interest in the use of alternative approaches to model selection (Forbes et al., 2021; Watts et al., 2019). The higher-order model was superior in terms of model-based estimates of reliability (i.e., ECV, PUC, Omega H/HS values) and evaluation of model parameters. The higher-order model (Figure 1) was selected for inclusion in subsequent analyses, based on: (1) evaluation of standardized factor loadings (i.e., all positive in direction and significant for the higher-order model); (2) lower standard errors of the factor loadings (i.e., more precise estimates of these parameters); (3) evidence of multidimensionality yet poor reliability of general and specific factors of the bi-factor model based on model-based reliability coefficients (i.e., ECV, PUC, Omega H/HS values); and (4) evidence of greater construct reliability and replicability of specific factors (i.e., greater H values). For the higher-order model estimated using WLSMV, the disinhibited-externalizing factor loaded most strongly on the general factor (0.574), followed by internalizing (0.368), and substance use (0.322). These factor loadings are consistent with those of the higher-order model estimated using MLR (disinhibited externalizing = 0.55; internalizing = 0.375; substance use = 0.356). Model selection procedures are detailed extensively in the Supplementary Material (Appendices E–G). Standardized factor loadings and standard errors for all latent variable models (run using MLR and WLSMV estimation) are presented in Supplementary Tables S6–S13. Given inconsistent conclusions depending on approaches to model selection (e.g., model fit statistics v. model-based estimates of reliability), additional sensitivity analyses were conducted by re-running all models (from primary, secondary, and post-hoc analyses) using the bi-factor model to generate BPVs.

Primary outcomes

Table 2 presents the results of analyses examining whether latent dimensions of baseline psychopathology derived from a higher-order factor model predict variations in global measures of brain structure across time. There was little evidence that general and lower-order dimensions of psychopathology at baseline were associated with a change in total cortical GMV, total subcortical GMV, or average cortical thickness across subsequent waves. Standardized results for analyses of global brain structure are presented in Supplementary Table S14.

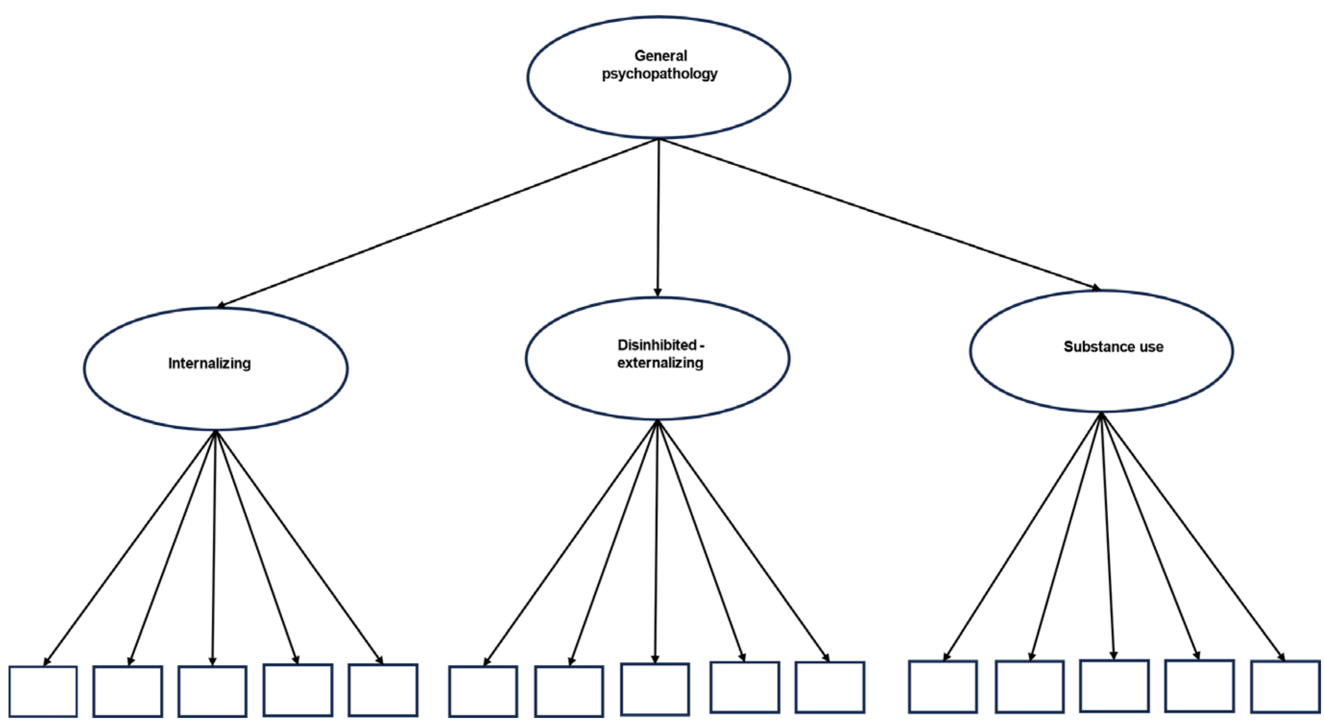

Figure 1. Figure representing the hierarchical structure of psychopathology in the Sydney MAS sample.
Note. Sydney MAS, Memory and Ageing Study. This figure outlines the higher-order confirmatory factor model that was derived from symptom-level indicators of psychopathology at baseline and subsequently included in all primary, secondary, and post-hoc analyses. In this model, observable indicators are specified to load onto one of three specific factors (labeled internalizing, disinhibited externalizing, and substance use), and these factors are specified to load onto a single higher-order general dimension of psychopathology. Latent symptom dimensions are depicted using circles and observable indicators of psychopathology are depicted using squares.

Secondary outcomes

The results for all secondary outcome measures are presented in Tables S15–S18. Pooled estimates of the BPVs for general and lower-order dimensions were not associated with a change in GMV across time in any cortical or subcortical ROI (Tables S15 and S17). Substance use was associated with increased cortical thickness over time within the parietal lobe at Wave 2 (β = 0.006; SE = 0.003; p = 0.049); however, this association did not survive FDR correction (Table S16). No other symptom dimensions were associated with regional cortical thickness over time. BPVs for general and lower-order factors were also not significantly associated with dementia status across waves (Table S18).

Post-hoc analyses

Post-hoc analyses revealed no evidence of association between general psychopathology and total cortical GMV, total subcortical GMV, or average cortical thickness at baseline (Table 2). Internalizing was negatively associated with total cortical GMV (β = −3319; SE = 1469.747; p = 0.024) but not total subcortical GMV or average cortical thickness at baseline; however, this association did not survive FDR correction. Disinhibited externalizing and substance use factors were not associated with any global measure of gray matter structure at baseline. When controlling for global effects (i.e., total GMV, average cortical thickness), general and lower-order factors were not associated with baseline GMV or cortical thickness in any ROI (Tables S15–S17). Internalizing was significantly

Table 2. Results from analyses examining whether transdiagnostic symptom dimensions derived from a higher-order factor model predict global measures of gray matter structure

	Total cortical volume				Total subcortical volume				Average cortical thickness			
	β	SE	95% CI	p	β	SE	95% CI	p	β	SE	95% CI	p
GP												
BL model	−1578	1823.333	−5157.59, 2002.51	0.387	−2196	787.472	−1767.02, 1327.79	0.780	−0.002	0.006	−0.01, 0.01	0.798
LMM												
GP*Wave2	9187	1265.720	−2393.52, 2577.27	0.942	1093	538.220	−948.01, 1166.54	0.839	−0.001	0.004	−9082.25, 0.007	0.850
GP*Wave4	3804	1646.124	−2855.91, 3616.66	0.817	1223	658.623	−1172.12, 1416.72	0.853	−0.003	0.005	−126.51, 0.007	0.606
INT												
BL model	−3319	1469.747	−6200.30, −438.25	0.024	2278	601.183	−1155.71, 1201.27	0.970	−0.005	0.005	−0.01, 0.004	0.318
LMM												
INT*Wave2	−1721	985.085	−2103.10, 1758.84	0.861	−1696	412.369	−978.03, 638.75	0.681	0.001	0.003	−5333.31, 0.007	0.784
INT*Wave4	1866	1245.753	−576.79, 4308.87	0.134	9701	498.514	−880.33, 1074.35	0.846	−0.002	0.004	−9746.73, 0.005	0.587
DEXT												
BL model	−5992	1378.737	−3305.43, 2107.04	0.664	−1569	604.027	−1343.60, 1029.88	0.795	−0.000	0.005	−0.009, 0.009	0.990
LMM												
DEXT*Wave2	5446	978.383	−1866.16, 1975.08	0.956	1988	415.050	−616.28, 1013.84	0.632	−0.000	0.003	−0.006, 0.006	0.980
DEXT*Wave4	1512	1240.205	−2285.78, 2588.09	0.903	1632	497.070	−813.25, 1139.57	0.743	−0.001	0.004	−0.008, 0.006	0.705
SUB												
BL model	−1974	1570.047	−5051.80, 1103.81	0.209	−4528	655.149	−1737.33, 831.79	0.490	−0.001	0.005	−0.01, 0.009	0.863
LMM												
SUB*Wave2	6314	1057.530	−1441.56, 2704.38	0.550	−9505	434.037	−945.84, 755.74	0.827	−0.004	0.003	−103.33, 0.003	0.287
SUB*Wave4	4447	1264.064	−2922.62, 2033.21	0.725	−5759	526.833	−1033.39, 1032.23	0.999	−0.005	0.004	−130.81, 0.003	0.223

Note. BL, baseline; LMM, linear mixed models; GP, general psychopathology; INT, internalizing; DEXT, disinhibited externalizing; SUB, substance use. BL Model refers to linear regression models predicting baseline GMV. LMM refers to linear mixed models predicting intraindividual change in GMV across waves. In all models, pooled estimates of multiply imputed general and specific factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to false discovery rate (FDR) correction, with bold text indicating significant associations. No results were significant after FDR correction.

negatively associated with baseline GMV in the bilateral frontal lobe ($\beta = -1332$; SE = 585.206; $p = 0.023$) and bilateral temporal lobe ($\beta = -8305$; SE = 375.023; $p = 0.027$) when not controlling for total GMV; however, neither association survived FDR correction (Table S15). Disinhibited externalizing and substance use factors were not associated with baseline GMV or cortical thickness in any ROI when controlling or not controlling for global effects (Tables S15–S17). To examine the extent to which education might be driving our results, all analyses for the higher-order model were re-run without including education as a covariate. Before FDR correction, we found a significant negative effect of BPVs for the substance use factor on GMV within the occipital lobe ($\beta = -408.499$; SE = 206.464; $p = 0.048$) when not controlling for total GMV. All other outcomes were consistent with our initial analyses, suggesting that education did not confound the relationship between dimensions of psychopathology and gray matter structure in the current study. Results from post-hoc analyses using BPVs generated from a bi-factor model were consistent with those found for the higher-order model and are outlined in the Supplementary Material (Appendix K, Tables S19–S22). It should be noted that the results from analyses using BPVs generated for the bi-factor model are unlikely to be informative, given the problems evident in the factor loadings (e.g., the substantial number of factor loadings that were nonsignificant, negative in direction, and/or small in magnitude; Appendix G).

Discussion

This study examined associations between latent transdiagnostic dimensions of psychopathology, gray matter structure, and dementia status in older adults. Consistent with previous research (Kotov et al., 2017, 2021), our confirmatory factor models demonstrated that psychopathology in older adulthood can be organized hierarchically into a set of general and specific/lower-order transdiagnostic symptom dimensions. However, no associations between these dimensions and changes in brain structure remained after FDR correction. Specifically, we found no evidence that baseline estimates of general and lower-order symptom dimensions predicted intraindividual change in global or regional gray matter structure across time. Our post-hoc analyses found no evidence of an association between transdiagnostic symptom dimensions and baseline measures of global and regional gray matter. There was also no evidence that general and lower-order dimensions predicted incident dementia, across 12 years of follow-up.

Strengths and limitations

There are several strengths and limitations to the current study that are important to consider. Firstly, our study included a large sample size and repeated measurements of both brain structure (over 6 years of follow-up) and consensus diagnoses of dementia (across 12 years of follow-up). That said, future research would benefit from examining potential relationships with other neuroimaging measures (e.g., of white matter microstructure, functional connectivity) and more nuanced examination of dementia (e.g., specific subtypes rather than a general binary outcome measure). In addition, our study used a rigorous and theory-driven approach to modeling the latent structure of psychopathology. However, our measurement was somewhat limited by the lack of detailed psychiatric assessment in our data set. We were restricted to modeling internalizing and two subdimensions of externalizing because we did not have enough indicators to specify more commonly studied dimensions (e.g., broad externalizing, thought disorder). In addition, while there were a large number of indicators for internalizing there were substantially fewer indicators for the other lower-order factors. Our disinhibited-externalizing factor was defined by only three indicators (all informant-report items from the NPI) and our substance use factor was defined entirely by indicators of alcohol and nicotine use (as illicit substance use is uncommon in older adults). These limitations impact the extent to which we can compare our results to those found in younger samples. Future research would benefit from investigating these relationships using dimensional models derived from a more extensive set of psychiatric indicators.

It is also important to consider the selection criteria of the Sydney MAS when interpreting our results. While participants with mild cognitive impairment were eligible for inclusion and represented 36.7% of the sample at baseline (Tsang et al., 2013), those diagnosed with dementia or who scored below 24 on the Mini-Mental State Examination were excluded. This has the advantage of reducing potentially confounding effects of dementia and significant cognitive impairment, allowing for clearer examination of the extent to which psychopathology contributes to these outcomes in an otherwise healthy sample of older adults. However, these selection criteria also limit the representativeness of the Sydney MAS sample (Sachdev et al., 2010; Tsang et al., 2013). It is possible that these criteria selected for participants with a lower range of structural brain changes over time and a lower incidence of later onset dementia compared to the general population of those aged 70 years or older. The MAS sample is also relatively well educated (average education = 11.6 years) and not racially diverse (98.4% Caucasian), further limiting the generalizability of our results. Future research may therefore benefit from investigating these relationships in a more representative sample of older adults. However, few available large-scale longitudinal studies in community-dwelling older adults include detailed psychiatric assessment, as well as neuroimaging and dementia status data.

The neural correlates of transdiagnostic symptom dimensions in older adulthood

The lack of significant associations between symptom dimensions and gray matter structure in the current study is inconsistent with findings in younger samples. Several cross-sectional studies have reported that general psychopathology, internalizing, and externalizing are associated with lower global and regional measures of gray matter structure from childhood to young adulthood (Kaczkurkin et al., 2019; Mewton et al., 2022; Parkes et al., 2021; Romer et al., 2023). These studies capture a critical period in which the brain undergoes substantial structural changes, with cortical thickness peaking in childhood and decreasing from childhood to adolescence and surface area peaking in preadolescence and decreasing slowly from adolescence to early adulthood (Tamnes et al., 2017; Wierenga et al., 2014). The majority of psychiatric disorders also tend to emerge between childhood and young adulthood (Solmi et al., 2022), perhaps driven by disruptions to normative maturational processes in the brain during this highly sensitive period of neurodevelopment. In contrast, the clinical picture of psychopathology in older adulthood may reflect: (1) symptoms that emerge early in development and persist or re-occur across the lifespan; (2) symptoms that first emerge in older adulthood; or (3) symptoms that specifically precede or follow from the onset of cognitive decline and dementia. Psychiatric symptoms that emerge in later life may be driven more strongly by environmental factors and physical comorbidities than genetic influences, which may exert less of an impact on brain structure. In the present study, our measurement models predominately included indicators of current symptom expression and may therefore be capturing late onset psychopathology. Future research should examine whether the relationship between transdiagnostic symptom dimensions and brain health in older adulthood differs as a function of age at symptom onset. Alternatively, potential associations between psychopathology and brain structure may be obscured by the impacts of age-related pathologies and neurodegeneration that emerge specifically in older adulthood. In either case, the inconsistency in results between our study and studies of younger samples underscores the importance of investigating these relationships across different age groups and highlights the complexities of doing so specifically in older populations. It is also important to consider sample size limitations when interpreting the lack of significant associations found for our longitudinal analyses of gray matter structure. MRI data were only available in a subsample of participants at baseline (n = 532), with substantial attrition across waves (n = 417 at Wave 2 and n = 262 at Wave 4). As such, it is possible that our analyses were not adequately powered to detect the effects of dimensional psychopathology on within-person changes in brain structure over time. This limitation was unavoidable given that our study relied upon secondary analysis of existing data and that there are few other large-scale studies of older adults that include the data necessary to address our research questions (i.e., broad measurement of psychopathology, repeated MRI measures). Furthermore, there were significant differences between those with complete versus incomplete follow-up MRI data. Specifically, those with complete MRI data were younger and had larger total GMV at baseline. As noted, age was included as a covariate in all analyses to control for age-related variation in GMV and missing data on the outcome was handled using maximum likelihood within a mixed model framework, which is more valid than complete case analysis (Dong & Peng, 2013). However, the overrepresentation of participants with greater baseline GMV in the follow-up sample may have reduced variability in GMV change, further limiting statistical power to detect associations with psychopathology dimensions. Additionally, since participants with higher baseline GMV may experience a different rate of decline than those with lower baseline GMV, our findings might not fully capture the broader relationship between psychopathology and intraindividual change in GMV over time in older adulthood.

Transdiagnostic symptom dimensions as predictors of incident dementia in older adulthood

We found no evidence that general and specific/lower-order transdiagnostic symptom dimensions predict incident dementia. These findings are somewhat surprising given extensive evidence that dementia is associated with a range of psychiatric disorders (Becker et al., 2018; Cai & Huang, 2018; Mo et al., 2023; Richmond-Rakerd et al., 2022; Velosa et al., 2020). In the MAS sample specifically, previous studies have shown that baseline symptoms of depression, anxiety, apathy, and agitation are associated with mild cognitive impairment (Brodaty et al., 2012; Shahnawaz et al., 2013). However, the only indicators of psychopathology that have been found to predict incident dementia at follow-up in this sample are depressive symptoms (Brodaty et al., 2012). It may be that the relationship between current psychopathology and dementia risk is driven by specific symptoms (e.g., depressive symptoms) rather than transdiagnostic dimensions, perhaps indirectly through their association with certain physiological mechanisms and processes (e.g., increased cortisol levels, vascular risk factors, neuroinflammation) that are also implicated in dementia (Bennett & Thomas, 2014). Indeed, depressive symptoms are highly correlated with many other forms of psychopathology, which might account for the observed associations between dementia and a range of psychiatric disorders (Mo et al., 2023; Richmond-Rakerd et al., 2022). That said, further research is needed to thoroughly examine whether transdiagnostic symptom dimensions can be used to predict incident dementia in older adults. As noted, psychopathology in older adulthood may reflect symptoms that emerged earlier in development or had their onset in later life. These presentations likely follow distinct etiological pathways and may confer different risks with respect to the onset of dementia in older adulthood. For example, transdiagnostic dimensions derived from symptoms that were present earlier in development may be more likely to predict incident dementia due to their longer-term impacts on brain health and other related risk factors that unfold across the lifespan. Transdiagnostic symptom dimensions may also show greater predictive utility for specific subtypes of dementia (e.g., those characterized by psychiatric and behavioral disturbances, such as frontotemporal dementia) than for general measures of dementia status. There may also be a threshold effect in which dementia is transdiagnostically associated with clinically significant psychopathology but not with subthreshold symptom dimensions derived from general population samples, as in the current study. Finally, future research should also investigate the predictive utility of other symptom dimensions that are commonly investigated in younger samples (e.g., broad externalizing), which may show stronger associations with dementia.

Conclusions

This is the first study to investigate the relationships between transdiagnostic symptom dimensions, brain structure, and dementia status in older adulthood. We found no evidence that transdiagnostic symptom dimensions are associated with gray matter structure or dementia status in this population. However, given that our current understanding of the neural correlates of transdiagnostic symptom dimensions comes almost exclusively from studies of youth, this study represents an important first step in determining the nature of these associations in an important and understudied age group. Future research would benefit from investigating these relationships in older adults using dimensional models derived from a more detailed set of psychiatric indicators. In addition, future studies should investigate whether age of symptom onset, normative brain aging, and age-related pathologies, impact the relationship between transdiagnostic symptom dimensions, brain structure, and dementia risk in later life.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291724003490.

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Competing interest. None to declare.

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Appendix E

Supplementary materials for Chapter 2

Appendix E.1

Deviations from protocol

There were some minor changes to the original protocol. Firstly, the protocol stated that studies in which participants were included or excluded based on clinical symptoms, psychiatric disorders, or relevant risk factors (e.g., history of abuse, neglect, or maltreatment) will be excluded. This was amended because many of the large-scale datasets (e.g., the ABCD study) used in the included studies have some exclusion criteria surrounding severe forms of psychopathology. Specifically, studies using datasets that excluded participants on the basis of severe psychopathology (e.g., psychosis, substance use in preadolescents) were eligible for inclusion in the review. Secondly, the protocol stated that the overall quality of evidence at the outcome level would be assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Brożek et al., 2009; Granholm et al., 2019). However, the GRADE system applies primarily to meta-analyses (not performed for the current study; Meader et al., 2014) and imposes penalties on observational study designs that may lead to unnecessary decreases in the reported quality of evidence (Yousefifard & Shafiee, 2023). Therefore, the GRADE system was not used in the present review.

Table S1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section and Topic	Item #	Checklist item	Location where item is reported [1]
TITLE			
Title	1	Identify the report as a systematic review.	Pg. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pgs. 4, 7, 8
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pgs. 7-8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pgs. 9-12, 14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg. 9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg. 12
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pgs. 9-12, Protocol

Section and Topic	Item #	Checklist item	Location where item is reported [1]
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplementary Material, Protocol
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg. 12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Supplementary Material
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg. 12
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Supplementary Material
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they	N/A

Section and Topic	Item #	Checklist item	Location where item is reported [1]
		were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Pgs. 14-31, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary Material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplementary Material, Tables 1-3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pgs. 32-48
	23b	Discuss any limitations of the evidence included in the review.	Pgs. 44-48
	23c	Discuss any limitations of the review processes used.	Pgs. 50-51, Supplementary Material
	23d	Discuss implications of the results for practice, policy, and future research.	Pgs. 44-50

Section and Topic	Item #	Checklist item	Location where item is reported [1]
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pgs. 8-9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary Material
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg. 52
Competing interests	26	Declare any competing interests of review authors.	Pg. 52
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary Material

Note. From Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71.

[1] Page numbers refer to the published journal article (see Appendix A).

Supplementary Tables S2-S7

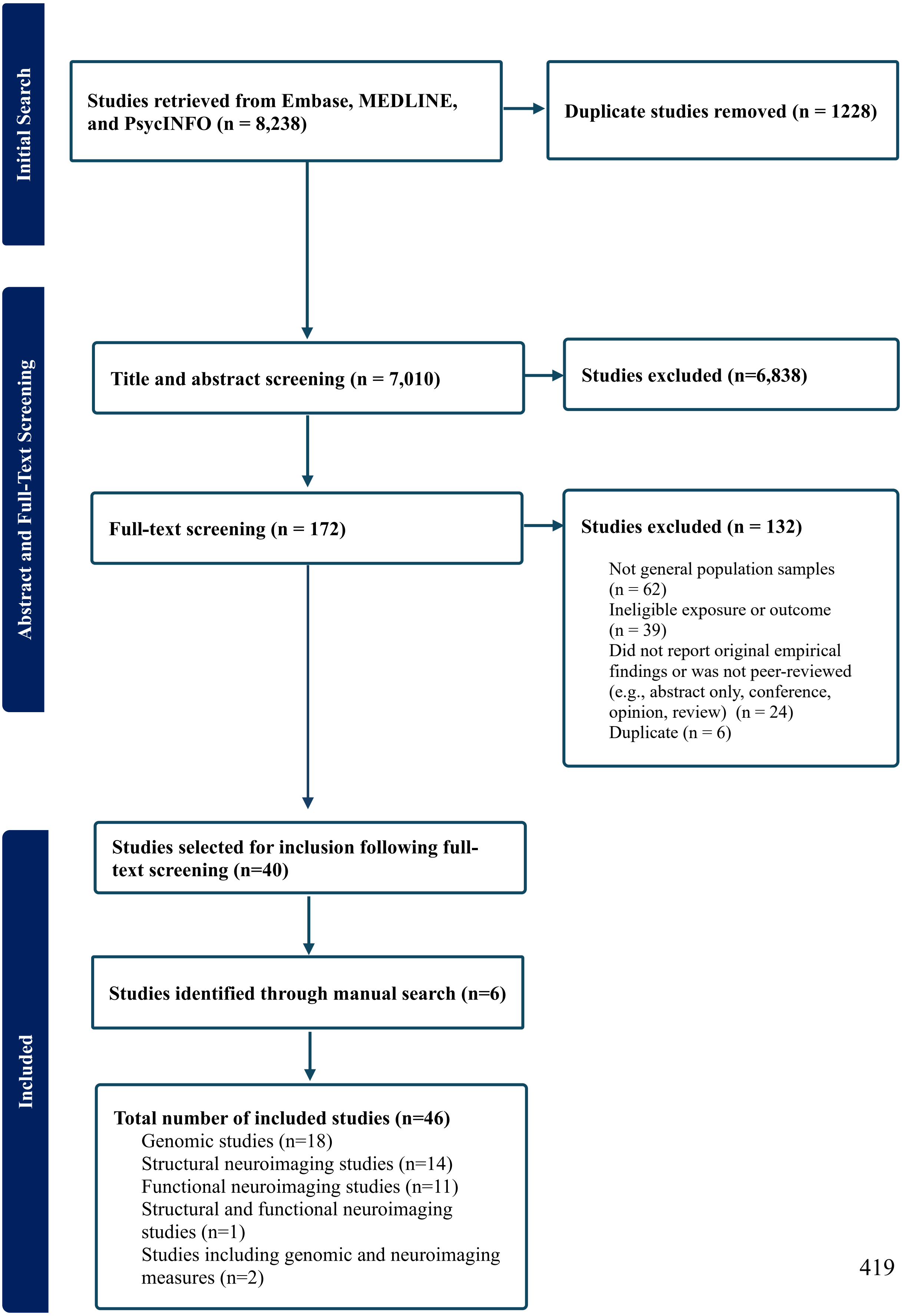
The remaining supplementary tables for **Chapter 2** are best presented as a spreadsheet due to the size of some tables. This spreadsheet can be accessed via the online publication. A direct link to the download and description of all supplementary materials contained in the file are additionally provided below.

Tables S2-S7 from **Chapter 2**: Download spreadsheet (73KB)

Supplementary materials include: Search strategy (Table S2); Quality assessment (Table S3); Overview of datasets used in included studies (Table S4); detailed description of genomic studies included in the review (Table S5); detailed description of structural neuroimaging studies included in the review (Table S6); detailed description of functional neuroimaging studies included in the review (Table S7).

Figure S1

PRISMA flowchart detailing the identification, screening, and inclusion of studies in the review



Supplementary References

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Appendix F

Supplementary materials for Chapter 3

Appendix F.1

Indicators of cognitive function

Indicators of cognitive function were drawn from the online follow-up assessments completed between 2014 and 2015 (Category IDs: 118, 120-122). Cognitive indicators were drawn specifically from the following tests: Trail Making Task A (TMTA), Trail Making Task B (TMTB), Fluid Intelligence, Numeric Memory, and the Symbol Digit Substitution Test (SDST). In the Trail Making Task, participants were presented with a series of labelled circles that were positioned randomly across the screen. For TMTA, all circles were labelled with numbers and participants were required to select all of the numbers in order (i.e., 1, 2, 3) in as short a timeframe as possible. For TMTB, the circles were labelled with either numbers or letters and participants were required to alternate between the two types whilst selecting them in numeric and alphabetical order (e.g., 1, A, 2, B, 3, C) in as short a timeframe as possible. For the current study, time to complete the numeric path (TMTA) and time to complete the alphanumeric path (TMTB) were used as cognitive indicators. Both of these variables were not normally distributed and as such, were transformed using the natural log transformation (ln(x)) prior to inclusion in latent variable models. The Fluid Intelligence test primarily measured abstract verbal and numerical reasoning. The test included 14 items assessing different aspects of verbal and numerical reasoning (e.g., addition, word interpolation, positional arithmetic, synonyms and antonyms, alphanumeric substitutions). Total scores were included as indicators of cognitive function in subsequent latent variable models, reverse coded such that higher scores indicated poorer performance. In the Numeric Memory test, participants were presented with a series of numbers that increased by one digit with each subsequent trial (e.g. a two-digit number was presented in the first trial, a three-digit number was presented in the second trial, and so on). For each trial, the number would be presented briefly on the screen and participants were instructed to enter the number they had just seen immediately after it had disappeared.

The number of digits across trials ranged from two to 12. The current study selected total number of digits remembered correctly as the indicator of cognitive function, reverse coded such that higher scores indicated worse performance. In the Symbol Digit Substitution test, participants are presented with a series of grids in which symbols are required to be matched with a corresponding number that is shown via a key presented on the screen. For the current study, number of symbol digit matches made correctly was selected as the cognitive indicator. Outliers were handled by removing scores < 3 or > 36, consistent with previous research (Kendall et al., 2017). This variable was also reverse coded such that higher scores were equal to worse cognitive performance. Data cleaning and transformations were performed in IBM SPSS Statistics (Version 28).

Appendix F.2

Model-specification for confirmatory factor models estimated in the full sample

The latent structure of psychopathology was examined using four commonly studied confirmatory factor analysis models: a one-factor model, a correlated-factors model, a bi-factor model, and a higher-order factor model (Figures S1-S2). For the one-factor model, all indicators were specified to load onto a single latent factor (labelled general psychopathology). For the correlated-factor model, all indicators are specified to load onto one of four correlated latent factors (labelled internalizing, addictions and substance use, thought disorder, and cognitive dysfunction). For the bi-factor model, all indicators loaded onto a general latent factor and one of four specific latent factors (i.e., internalizing, addiction and substance use, thought disorder, and cognitive dysfunction). In this model, the general and specific factors were specified to be orthogonal to one another (i.e., statistically independent). For the higher-order model, all indicators were specified to load onto one of four correlated lower-order factors (i.e., internalizing, addiction and substance use, thought disorder, and cognitive dysfunction) and each of these latent factors were specified to load onto a single higher-order factor (i.e., the general factor). The specific/lower-order factors specified in relevant models (i.e., the correlated factors, bi-factor, and higher-order models) were defined as internalizing, addictions and substance use, thought disorder, and cognitive dysfunction. The internalizing factor was defined by indicators of depression, anxiety, post-traumatic stress, and suicidality/self-harm. The addictions and substance use factor was defined by indicators of alcohol use, cannabis use, behavioral addictions (e.g., gambling), addictions to prescription or over-the-counter medications, and addictions to illicit or recreational substances. The thought disorder factor was defined by indicators of psychoticism including delusions and hallucinations (e.g., believing an unreal conspiracy against self, believing in unreal communications or signs, hearing unreal voices, and seeing unreal visions) and mania (e.g., periods of extreme irritability, periods of mania/excitability). Finally, the cognitive dysfunction factor was defined by total scores/times on each of the aforementioned cognitive tests, with higher scores indicating worse cognitive performance. All indicators of psychopathology were categorical (i.e., binary and ordinal) and all indicators of cognitive function were continuous (Table S1). For all models, the first factor loading was fixed to 1 for model identification. All models were estimated using weighted least squares mean variance (WLSMV) and DELTA parametrization in Mplus version 8.10 (Muthén & Muthén, 2017).

Appendix F.3

Model-based estimates of reliability examined in the full sample

Additional model-based indices of reliability were calculated for the bi-factor model (using standardized factor loadings; Dueber, 2017), including the explained common variance (ECV), omega hierarchical (ωH) and omega hierarchical subscale (ωHS), and the percent uncontaminated correlations (PUC). Details regarding the definitions and recommended thresholds for these values was previously described in **Chapter 1** (Section 1.2.2) but are reiterated here to provide a self-contained overview of the model-based reliability estimates used in this chapter. ECV quantifies the proportion of shared variance among indicators attributable to the general factor relative to specific factors (Reise et al., 2013). Values greater than 0.70 indicate a robust general factor and values over 0.85 suggest unidimensionality (Rodriguez et al., 2016b). PUC indicates the proportion of correlations among indicators that solely reflect variance from the general factor (i.e., without influence from specific factors; Reise et al., 2013), with values above 0.70 supporting unidimensionality (Reise et al., 2013; Rodriguez et al., 2016a). Omega hierarchical (ωH) and omega hierarchical subscale (ωHS) estimate the proportion of variance in total and subscale scores attributable to the general and specific factors, respectively, after controlling for the influence of other factors (Reise et al., 2013). Values greater than 0.80 are generally considered to indicate acceptable reliability for the general factor and values greater than 0.75 indicate acceptable reliability for the specific factors (Reise et al., 2013; Rodriguez et al., 2016a). The H coefficient (H) captures the extent to which variance in a given factor is well-defined by its indicators and further reflects the replicability of that factor across independent samples (Hancock & Mueller, 2001; Rodriguez et al., 2016a). H can be calculated for general and specific factors in a bi-factor model and for the lower-order factors in a higher-order model, with values ranging from 0-1 and higher values reflecting greater reliability and replicability. Values > 0.7 are generally considered acceptable (Hancock & Mueller, 2001).

Appendix F.4

Sensitivity Analyses

A series of sensitivity analyses were conducted to evaluate the influence of method variance and demographic covariates on the latent structure of the best-fitting model and the strength of associations between lower-order factors and the general factor. Firstly, psychiatric and cognitive indicators were assessed differently (i.e., psychopathology was assessed via categorical self-report measures and cognition was assessed via continuous performance-based measures) and at different time points (i.e., psychopathology was assessed between 2016 and 2017, cognition was assessed between 2014 and 2015). This method variance may have impacted the best-fitting model, potentially explaining the relatively low loading of cognitive dysfunction on the general factor. Secondly, the best-fitting model from the primary analysis did not control for any covariates that could influence the underlying latent structure. In particular, the inclusion of raw cognitive test scores without controlling for the influence of age and education might have introduced bias in the measurement models given that these demographic factors are known to influence cognition in older adults (Piccininni et al., 2023). All models were estimated using DELTA parameterization and the WLSMV estimator in Mplus version 8.10 (Muthén & Muthén, 2017). Due to missing data on years of education (n = 1003), the sample size for Supplementary Models 2-3 was reduced to N = 111,709. Mplus code for each of the three models is provided on OSF (https://osf.io/hdxqp/files/osfstorage) and in Appendix I.

Supplementary model 1: method factors

To account for the potential influence of method variance, the best-fitting model was re-estimated in the full sample with the inclusion of two method factors. The higher-order model was specified as in the main analysis; however, the first factor loading was freely estimated and the means and variances of the latent factors were fixed to 0 and 1, respectively. Two method factors were included in this model, one which captured all self-report indicators of psychopathology and one which captured all continuous performance-based measures of cognition (Figure S3). The method factors were specified to be orthogonal to all substantive factors in the model (i.e., general psychopathology, internalizing, addictions and substance use, cognitive dysfunction) but were allowed to correlate with each other. Factor loadings for indicators of the psychopathology method factor were constrained to be equal to one another and factor loadings for indicators of the cognition method factor were also constrained to be equal. The underlying assumption of this specification is that the method variance impacts all indicators to the same degree rather than varying from item to item (Lance & Fan, 2016). This model fit the data well (CFI = 0.942; TLI = 0.938; RMSEA = 0.040) and standardized loadings of the observed indicators on the lower-order factors remained significant, positive in direction, and substantial in magnitude (i.e., $\lambda > 0.3$). Internalizing demonstrated the strongest loading on the general factor ($\lambda = 0.962$) and thought disorder demonstrated the second highest loading ($\lambda = 0.431$). The loading of the cognitive dysfunction dimension on the general factor increased substantially ($\lambda = 0.138$), whilst the loading of addictions and substance use decreased ($\lambda = 0.067$) when method factors were included in the model.

Supplementary model 2: demographic covariates

The second sensitivity analysis aimed to examine the influence of certain demographic covariates on the overall model structure of the best-fitting model. Specifically, the best-fitting model was re-estimated in the full sample whilst controlling for baseline age (years/continuous) and education (years/continuous). The first factor loading was freely estimated and the factor means and variances were fixed to 0 and 1, respectively. Years of education was estimated from a question addressing qualifications (data-field: 6138) included in baseline assessments for the UK Biobank. Participants were able to select one or more educational qualifications from a predefined list. The highest level of education attained was mapped to the International Standard for Classification of Education to produce an estimate of years of education (Table S3), following the methods of several previous studies using data from the UK Biobank (Wang et al., 2024; Xie et al., 2023; Zhao et al., 2024). Demographic covariates were regressed on the lower-order factors, which enabled controlling for their influence on both the psychopathology dimensions and the cognitive dysfunction dimension defined by raw cognitive test scores. The covariate model demonstrated good fit to the data (CFI = 0.934; TLI = 0.931; RMSEA = 0.041) and standardized factor loadings of observed indicators on each of the lower-order factors remained significant, positive in direction, and substantial in magnitude (i.e., > 0.3). The thought disorder factor demonstrated the strongest loading on the general factor ($\lambda = 0.758$), followed by internalizing ($\lambda = 0.717$), addictions and substance use ($\lambda = 0.390$), and cognitive dysfunction ($\lambda = 0.135$). Notably, the loading of cognitive dysfunction on the general factor again showed substantially stronger loadings on the general factor relative to the model in the primary analysis without covariates (i.e., $\lambda = 0.135$ compared to $\lambda = 0.078$).

Supplementary model 3: method factors and demographic covariates

Given that both of the supplementary models revealed stronger associations between cognitive dysfunction and the general factor, a final sensitivity analysis was conducted in which both the method factors from Supplementary Model 1 and the demographic covariates from Supplementary Model 2 were included simultaneously. This model also demonstrated good fit to the data (CFI = 0.938; TLI = 0.934; TLI = 0.040) and the standardized loadings of observed indicators on the lower-order factors remained significant, positive in direction, and substantial in magnitude (i.e., $\lambda > 0.3$). The internalizing dimension had the strongest loading on the general factor ($\lambda = 0.721$), followed by thought disorder ($\lambda = 0.602$), cognitive dysfunction ($\lambda = 0.184$) and addictions and substance use ($\lambda = 0.154$). Overall, the strength of association between cognitive dysfunction and the general factor increased relative to the primary model when controlling for method variance and demographic covariates (i.e., age and education). The weaker association between addictions and substance use and the general factor in Supplementary Model 1 (i.e., the method factor model) suggests that part of this association in the primary analysis was driven by method-related noise. This attenuation was partially mitigated by adjusting for age and education in Supplementary Model 3, suggesting that the method factor model was underestimating the true strength of the relationship due to unaccounted-for demographic influences (i.e., substantive variance). Notably, when both method variance and demographic covariates were accounted for (i.e., Supplementary Model 3), the loadings of cognitive dysfunction on the general factor were comparable to those of addictions and substance use, with a slightly stronger loading for the cognitive dysfunction dimension.

Appendix F.5

Model-specification for multigroup measurement invariance testing

Measurement invariance was conducted in a step-wise fashion, beginning with configural invariance, lower-order metric/scalar invariance, and higher-order metric/scalar invariance. Note that for models including binary indicators and WLSMV estimation, metric invariance is not identifiable and it is recommended to test for metric and scalar invariance in a single step (Muthén & Muthén, 2018). In the context of higher-order models, it is necessary to examine scalar invariance of the first-order factors first and then to examine scalar invariance of the second-order factors in a subsequent step (Chen et al., 2005; Rudnev et al., 2018). All measurement invariance models were estimated using DELTA parameterization and the WLSMV estimator in Mplus version 8.10 (Muthén & Muthén, 2017).

The baseline model tested for configural invariance, in which the factor loadings, item thresholds (for categorical indicators) and item intercepts (for continuous indicators), were freely estimated across age groups (Chen et al., 2005; Rudnev et al., 2018). The means (intercepts) of the lower-order factors were freely estimated across groups and the means of the higher-order factor were fixed to 0 across groups (Rudnev et al., 2018). For the psychopathology factors (defined by categorical indicators), the first threshold of one indicator for a given factor was fixed to 0 (Rudnev et al., 2018). For the cognitive dysfunction factor (defined by continuous indicators), the intercept of one indicator was fixed to 0 (Rudnev et al., 2018). The factor loading of the first indicator for each factor (i.e., lower- and higher-order) was fixed to 1 for model identification. Scale factors for binary and ordinal indicators were fixed to 1 across groups (Muthén & Muthén, 2018).

The next model tested for metric/scalar invariance of the lower-order factor structure, with factor loadings of the lower- and higher-order indicators, item thresholds (for categorical indicators), and item intercepts (for continuous indicators), all held equal across groups (Chen et al., 2005; Rudnev et al., 2018). The means (intercepts) of the lower-order factors were freely estimated across groups and the means of the higher-order factors were fixed to 0 across groups. The factor loading of the first indicator for each factor (i.e., lower- and higher-order) was fixed to 1 for model identification. Scale factors for categorical indicators were fixed to 1 in the reference group (i.e., those aged 55-59 years old) and freely estimated across the remaining age groups (Muthén & Muthén, 2018). The first threshold of one indicator for a given psychopathology factor (defined by categorical indicators) was fixed to 0 and the intercept of one indicator for the cognitive dysfunction factor (defined by continuous indicators) was fixed to 0.

The final model tested for metric/scalar invariance of the higher-order factor, in which the higher- and lower-order factor loadings, item thresholds and item intercepts, as well as the lower-order factor means, were all held equal across groups (Chen et al., 2005; Rudnev et al., 2018). The mean of one lower-order factor (i.e., internalizing) was fixed to 0 across groups for identification and the mean of the higher-order factor was freely estimated across groups. The factor loading of the first indicator for each factor (i.e., lower- and higher-order) was fixed to 1 for model identification. The first threshold of one indicator for a given psychopathology factor (defined by categorical indicators) was fixed to 0 and the intercept of one indicator for the cognitive dysfunction factor (defined by continuous indicators) was fixed to 0. Scale factors for categorical indicators were fixed to 1 in the reference group (i.e., those aged 55-59 years old) and freely estimated across the remaining age groups (Muthén & Muthén, 2018).

Appendix F.6

Model-selection in the full sample

The bi-factor model demonstrated the best fit to the data based on traditional indices of absolute and incremental model-fit (CFI = 0.962; TLI = 0.958; RMSEA = 0.033). The higher-order and correlated-factor models also demonstrated acceptable model fit based on these indices (CFIs = 0.936; TLIs = 0.933; RMSEAs = 0.042), whilst the one-factor model showed poor fit to the data (CFI = 0.836; TLI = 0.828; RMSEA = 0.067). However, examination of model parameters revealed several significant limitations to the bi-factor model (e.g., several standardized factor loadings that were negative in direction, non-significant, and small in magnitude; Table 3.3). In contrast, standardized factor loadings for all observed indicators across all latent factors for the higher-order model were significant, positive in direction, and had factor loadings > 0.3 (Table 3.3). The superiority of the higher-order model was further supported by examination of model-based reliability estimates (Table 3.2). For the bi-factor model, the ECV value indicated a weak general factor (i.e., < 0.7), accounting for 53.9% of the common variance among indicators included in the model. The Omega H index further indicated that the general factor accounted for 81.1% of the variance in total scores after partialling out the variance of the specific latent factors. Whilst there was evidence of multidimensionality amongst the included indicators (i.e., ECV for the general factor was < 0.85 and the PUC value was < 0.7), this was not reliably captured by the specific factors included in the model. ECV values for the specific factors ranged from 0.066 to 0.213 and Omega Hs values were below the recommended cut-offs for all internalizing and thought disorder (Omega Hs = 0.004 to 0.649, respectively). For the bi-factor model, H coefficient values were within the recommended threshold (i.e., > 0.70) for the general factor and for addictions and substance use, thought disorder, and cognitive dysfunction (H coefficients = 0.834 to 0.975); however, the internalizing factor demonstrated poor reliability and replicability (H = 0.676). In contrast, all lower-order factors from the higher-order model demonstrated acceptable reliability (H coefficients = 0.841 to 0.974). Moreover, all H coefficient values for the lower-order factors were greater in magnitude than those for the specific factors of the bi-factor model.

Table S1

Descriptions of psychiatric and cognitive indicators included in confirmatory factor analytic models

Observed indicators	Data-fields	Response options	Transformations
Internalizing			
Depression			
Over the last 2 weeks, how often have you been bothered by any of the following problems?			
Feeling down, depressed, or hopeless	20510	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Little interest or pleasure in doing things	20514	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	20518	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing

Observed indicators	Data-fields	Response options	Transformations
Feeling bad about yourself or that you are a failure or have let yourself or your family down	20507	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Feeling tired or having little energy	20519	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Poor appetite or overeating	20511	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Trouble concentrating on things, such as reading the newspaper or watching television	20508	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Trouble falling or staying asleep, or sleeping too much	20517	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Anxiety			
People differ a lot in how much they worry about things. Did you ever have a time when you worried a lot more than most people would in your situation?	20425	Prefer not to answer; Do not know; No; Yes	‘Prefer not to answer’ and ‘Do not know’ recoded as missing

Observed indicators	Data-fields	Response options	Transformations
Over the last 2 weeks, how often have you been bothered by any of the following problems?			
Feeling nervous, anxious or on edge	20506	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Becoming easily annoyed or irritable	20505	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Feeling afraid as if something awful might happen	20512	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Not being able to stop or control worrying	20509	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing
Being so restless that it is hard to sit still	20516	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	'Prefer not to answer' recoded as missing

Observed indicators	Data-fields	Response options	Transformations
Trouble relaxing	20515	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Worrying too much about different things	20520	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Suicidality/Self-harm			
Over the last 2 weeks, how often have you been bothered by… Thoughts that you would be better off dead or of hurting yourself in some way?	20513	Prefer not to answer; Not at all; Several days; More than half the days; Nearly every day	‘Prefer not to answer’ recoded as missing
Have you deliberately harmed yourself, whether or not you meant to end your life?[1]	*20480*	*Prefer not to answer; No; Yes*	*N/A*
Have you harmed yourself in the last 12 months, whether or not you meant to end your life?	20480	Prefer not to answer; No; Yes	‘Prefer not to answer’ recoded as missing. Those who responded ‘No’ to the screening question (20480) were coded as ‘No’ to this question.
Post-traumatic stress			

Observed indicators	Data-fields	Response options	Transformations
Next is a list of problems and complaints that people sometimes have in response to such extremely stressful experiences. Please indicate how much you have been bothered by that problem in the past month.			
Repeated, disturbing memories, thoughts, or images of a stressful experience?	20497	Prefer not to answer; Not at all; A little bit; Moderately; Quite a bit; Extremely	'Prefer not to answer' recoded as missing
Feeling very upset when something reminded you of a stressful experience?	20498	Prefer not to answer; Not at all; A little bit; Moderately; Quite a bit; Extremely	'Prefer not to answer' recoded as missing
Avoiding activities or situations because they reminded you of a stressful experience?	20495	Prefer not to answer; Not at all; A little bit; Moderately; Quite a bit; Extremely	'Prefer not to answer' recoded as missing
Substance Use and Addiction[2]			
Have you been addicted to or dependent on one or more things, including substances (not cigarettes/coffee) or behaviors (such as gambling)?	*20401*	*Prefer not to answer; Do not know; No; Yes*	*N/A*
Have you been addicted to alcohol?	20406	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' recoded as missing. Participants who responded 'No' to the screening question (20401) were coded as 'No' to this question.

Observed indicators	Data-fields	Response options	Transformations
Have you been addicted to illicit or recreational drugs?	20456	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' recoded as missing. Participants who responded 'No' to the screening question (20401) were coded as 'No' to this question.
Have you been addicted to or dependent on prescription or over-the-counter medication?	20503	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' recoded as missing. Participants who responded 'No' to the screening question (20401) were coded as 'No' to this question.
Have you been addicted to a behavior (such as gambling) or to anything else we have not mentioned?	20431	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' recoded as missing. Participants who responded 'No' to the screening question (20401) were coded as 'No' to this question.
***Alcohol Use*[3]**			
How often do you have a drink containing alcohol?	*20414*	*Prefer not to answer; Never; Monthly or less; 2 to 4 times a month; 2 to 3 times a week; 4 or more times a week*	*N/A*
How many drinks containing alcohol do you have on a typical day when you are drinking?	*20403*	*Prefer not to answer; 1 or 2; 3 or 4; 5 or 6; 7, 8 or 9; 10 or more*	*N/A*

Observed indicators	Data-fields	Response options	Transformations
How often do you have six or more drinks on one occasion?	*20416*	*Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily*	*NA*
How often during the last year have you found that you were not able to stop drinking once you had started?	20413	Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily	'Prefer not to answer' recoded as missing. Those who responded 'Never' to item 20414 or who responded '1 or 2' to item 20403 and 'Never' to item 20416 were coded as 'Never'
How often during the last year have you failed to do what was normally expected from you because of drinking?	20407	Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily	'Prefer not to answer' recoded as missing. Those who responded 'Never' to item 20414 or who responded '1 or 2' to item 20403 and 'Never' to item 20416 were coded as 'Never'
How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	20412	Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily	'Prefer not to answer' recoded as missing. Those who responded 'Never' to item 20414 or who responded '1 or 2' to item 20403 and 'Never' to item 20416 were coded as 'Never'

Observed indicators	Data-fields	Response options	Transformations
How often during the last year have you had a feeling of guilt or remorse after drinking?	20409	Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily	'Prefer not to answer' recoded as missing. Those who responded 'Never' to item 20414 or who responded '1 or 2' to item 20403 and 'Never' to item 20416 were coded as 'Never'
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	20408	Prefer not to answer; Never; Less than monthly; Monthly; Weekly; Daily or almost daily	'Prefer not to answer' recoded as missing. Those who responded 'Never' to item 20414 or who responded '1 or 2' to item 20403 and 'Never' to item 20416 were coded as 'Never'
Have you or someone else been injured as a result of your drinking?	20411	Prefer not to answer; No; Yes, but not in the last year; Yes, during the last year	'Prefer not to answer' recoded as missing and the latter two response options were collapsed into a single category (i.e., Yes)
Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?	20405	Prefer not to answer; No; Yes, but not in the last year; Yes, during the last year	'Prefer not to answer' recoded as missing and the latter two response options were collapsed into a single category (i.e., Yes)
Cannabis Use			

Observed indicators	Data-fields	Response options	Transformations
Have you taken cannabis (marijuana, grass, hash, ganja, blow, draw, skunk, weed, spliff, dope), even if it was a long time ago?[4]	*20453*	*Prefer not to answer; No; Yes, 1-2 times; Yes, 3-10 times; Yes, 11-100 times; Yes, more than 100 times*	*N/A*
Considering when you were taking cannabis most regularly, how often did you take it?[3]	20454	Prefer not to answer; Do not know; Less than once a month; Once a month or more, but not every week; Once a week or more, but not every day; Every day	'Prefer not to answer' and 'Do not know' recoded as missing. An additional category (i.e., 'Never consumed cannabis') was created for those who responded 'No' to the initial screening question (20453).
Thought Disorder			
Unusual of Psychotic Experiences			
Did you ever believe that there was an unjust plot going on to harm you or to have people follow you, and which your family and friends did not believe existed?	20468	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' and 'Do not know' recoded as missing
Did you ever believe that a strange force was trying to communicate directly with you by sending special signs or signals that you could understand but that no one else could understand (for example through the radio or television)?	20474	Prefer not to answer; Do not know; No; Yes	'Prefer not to answer' and 'Do not know' recoded as missing

Observed indicators	Data-fields	Response options	Transformations
Did you ever hear things that other people said did not exist, like strange voices coming from inside your head talking to you or about you, or voices coming out of the air when there was no one around?	20463	Prefer not to answer; Do not know; No; Yes	‘Prefer not to answer’ and ‘Do not know’ recoded as missing
Did you ever see something that wasn't really there that other people could not see?	20471	Prefer not to answer; Do not know; No; Yes	‘Prefer not to answer’ and ‘Do not know’ recoded as missing
Mania			
Have you ever had a period of time when you were so irritable that you found yourself shouting at people or starting fights or arguments?	20502	Prefer not to answer; Do not know; No; Yes	‘Prefer not to answer’ and ‘Do not know’ recoded as missing
Have you ever had a period of time when you were feeling so good, "high", "excited", or "hyper" that other people thought you were not your normal self or you were so "hyper" that you got into trouble?	20501	Prefer not to answer; Do not know; No; Yes	‘Prefer not to answer’ and ‘Do not know’ recoded as missing
Cognitive dysfunction	**Data-Field**	**Outcome Variable**	**Transformation**
Trail Making Task A	20156	Duration to complete	Natural log transformation (ln(x))
Trail Making Task B	20157	Duration to complete	Natural log transformation (ln(x))
Numeric Memory	20240	Maximum number of digits remembered correctly	Reverse coded (i.e., higher scores equal worse performance)

Observed indicators	Data-fields	Response options	Transformations
Fluid Intelligence	20191	Total number of correct responses (0-14)	Reverse coded (i.e., higher scores equal worse performance)
Symbol Digit Substitution	20159	Total number of symbol digit matches made correctly	Scores < 3 or > 36 were recoded as missing (Kendall et al., 2017). Reverse coded (i.e., higher scores equal worse performance).

Note. This table provides details regarding all of the psychiatric and cognitive indicators that were included in confirmatory factor analysis models for the current study. The Data-Fields column provides the field codes used for each indicator, as specified in the UK Biobank Data Dictionary (https://tinyurl.com/bddbsbm9). Psychiatric and cognitive indicators were drawn from UK Biobank's online follow-up assessment (Category ID: 100089; https://tinyurl.com/7c4fr7kp). Response options for self-reported psychiatric symptoms and specific outcome variables used from each of the included cognitive tests are outlined, as are any transformations that were performed prior to including these indicators in each of the models.

[1] Participants who responded 'Yes' to this screening question (20480) were asked a follow-up question about self-harm in the past year (20480) and those who responded 'No' were skipped. In the current study, those who responded 'No' to this screening question were coded as 'No' to the follow-up question about self-harm in the past year.

[2] Participants who responded 'Yes' to the first screening question (20401) were asked follow-up questions about specific addictions and those who responded 'No' were skipped.. In the current study, those who responded 'No' to the first screening question were coded as 'No' to follow-up questions about lifetime addictions (20406, 20456, 20503, 20431).

[3] Participants were asked an initial screening question assessing frequency of alcohol use (20414). Those who *did not* respond 'Never' to this question were then asked two follow-up questions: 1) How many drinks containing alcohol do you have on a typical day when you are drinking? (20403); and 2) How often do you have six or more drinks on one occasion (20416)? Additional follow-up questions (i.e., 20407-20409, 20412-20413) were not asked of participants who responded: 'Prefer not to answer' to 20403 or

20416 and either '1 or 2' to amount consumed on a typical day (20403) *or* 'Never' to frequency of consuming six or more drinks (20416); or '1 or 2' to amount consumed on a typical day (20403) and 'Never' to frequency of consuming 6 or more (20416). For the current study, participants who responded 'Never' to the screening item (20414) or who responded as '1 or 2' to item 20403 and 'Never' to item 20416 were recoded as 'Never' for each of the additional follow-up items.

[4] Those who responded 'Yes' to this screening question (20453) were asked the follow-up question regarding frequency of cannabis use (20454). Those who responded 'No' to the screening question were coded as 'Never consumed cannabis' for the follow-up question about frequency of use.

Table S2

Recoding of qualification variable to estimate years of education in UK Biobank participants

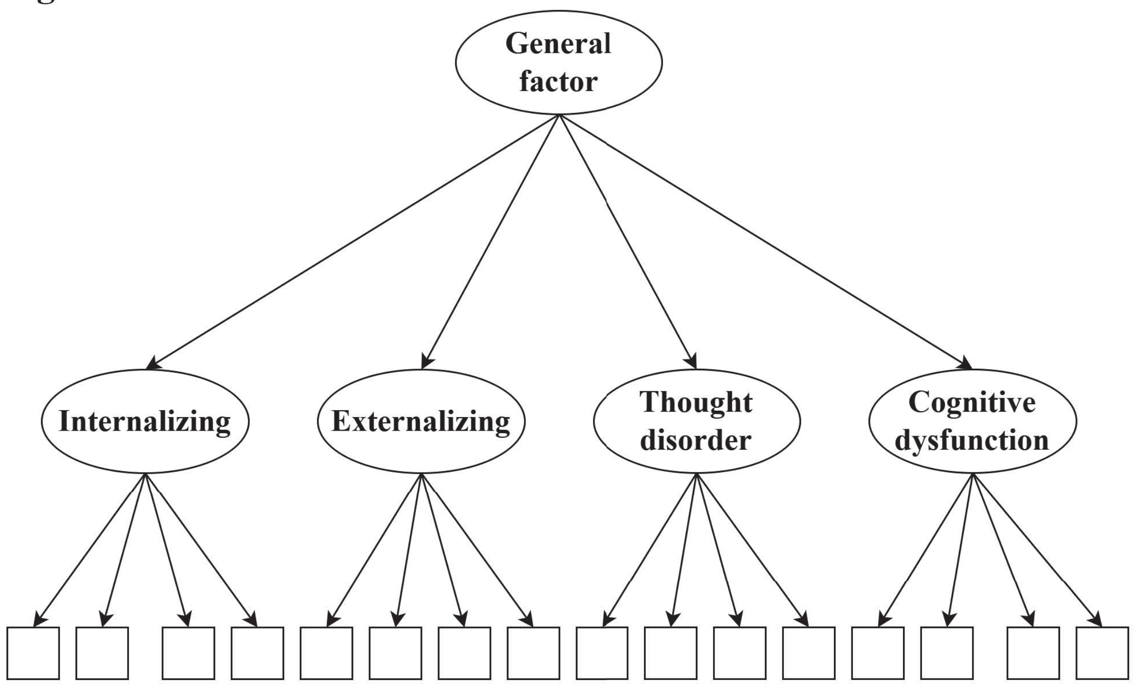
Response options for qualification variable in the UK Biobank study	ISCED coding	Estimated years of education
College or University degree	5	20
NVQ or HND or HNC or equivalent	5	19
Other professional qualifications (e.g., nursing, teaching)	4	15
A levels/AS levels or equivalent	3	13
O levels/GCSEs or equivalent	2	10
CSEs or equivalent	2	10
None of above	1	7
Prefer not to answer		Missing

Note. A levels, Advance levels; AS levels, Advanced Subsidiary levels; CSE, Certificate of Secondary Education; GCSEs, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; ISCED, International Standard Classification of Education; NVQ, National Vocational Qualification; O levels, Ordinary levels. This table outlines the categorical response options for qualification levels in the UK Biobank study and their corresponding estimated years of education, mapped according to the International Standard Classification of Education.

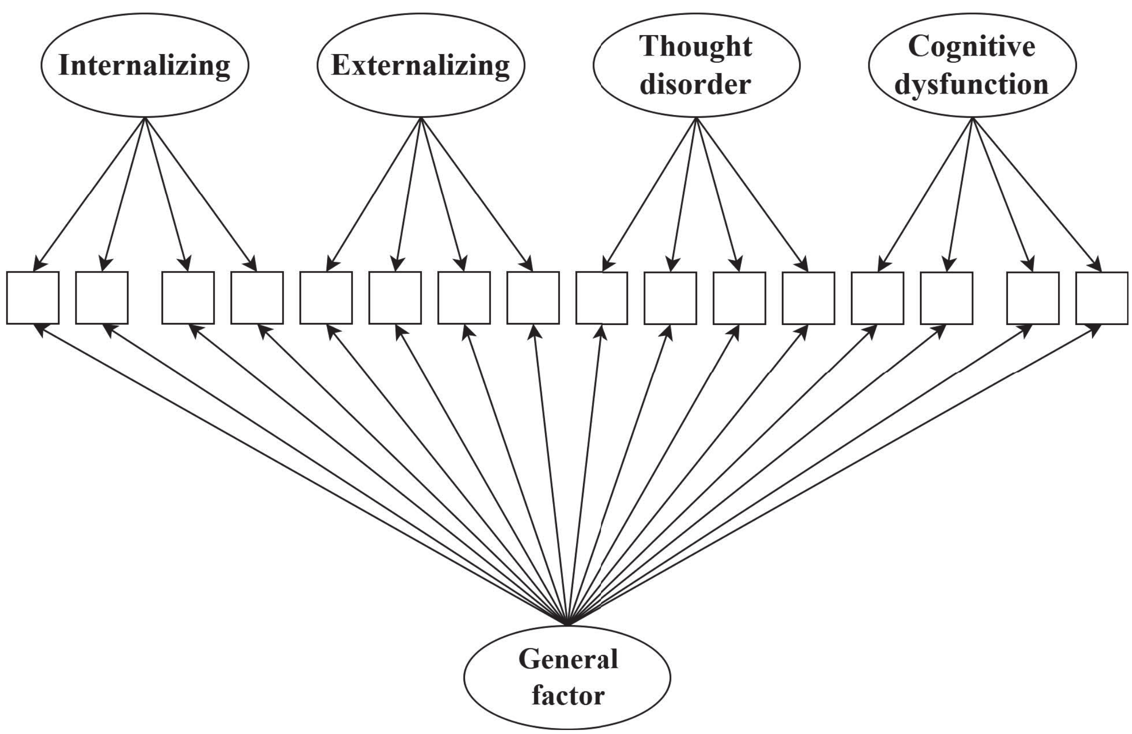
Figure S1

Higher-order and bi-factor confirmatory factor models estimated in the current study

Higher-order model



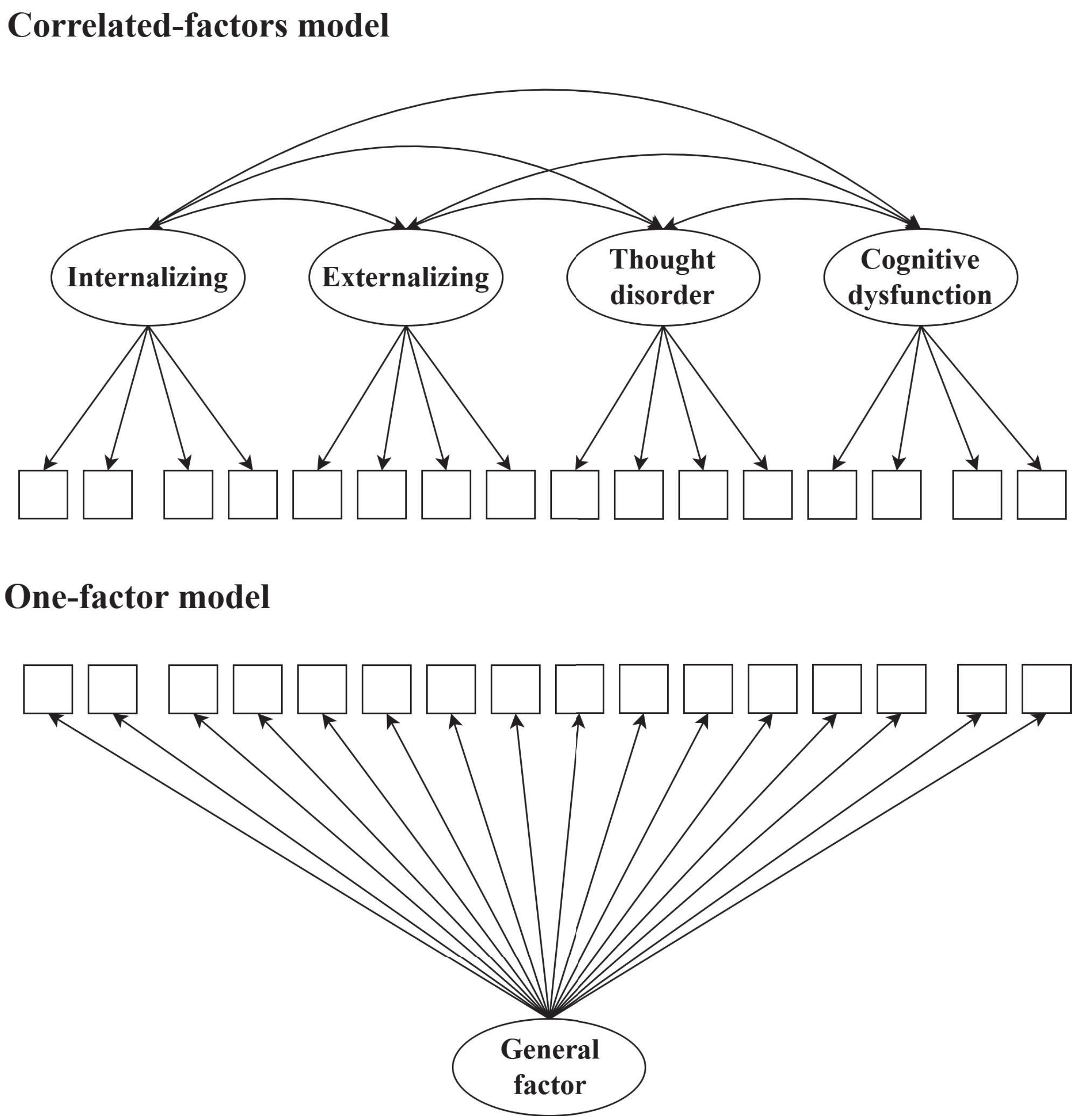
Bi-factor model



Note. This figure illustrates the higher-order and bi-factor models that were estimated in the primary analysis. Observed indicators are represented by squares and latent factors are represented by ellipses. Single-headed arrows represent the loadings of observed indicators on the corresponding latent factors. For the higher-order model, each observed indicator was specified to load onto one of the four lower-order correlated factors, which in turn loaded onto a higher-order general factor. For the bi-factor model, each observed indicator was specified to load onto one of four specific factors as well as onto a single general factor. Models were estimated using DELTA parameterization and the WLSMV estimator in Mplus version 8.10 (Muthén & Muthén, 2017).

Figure S2

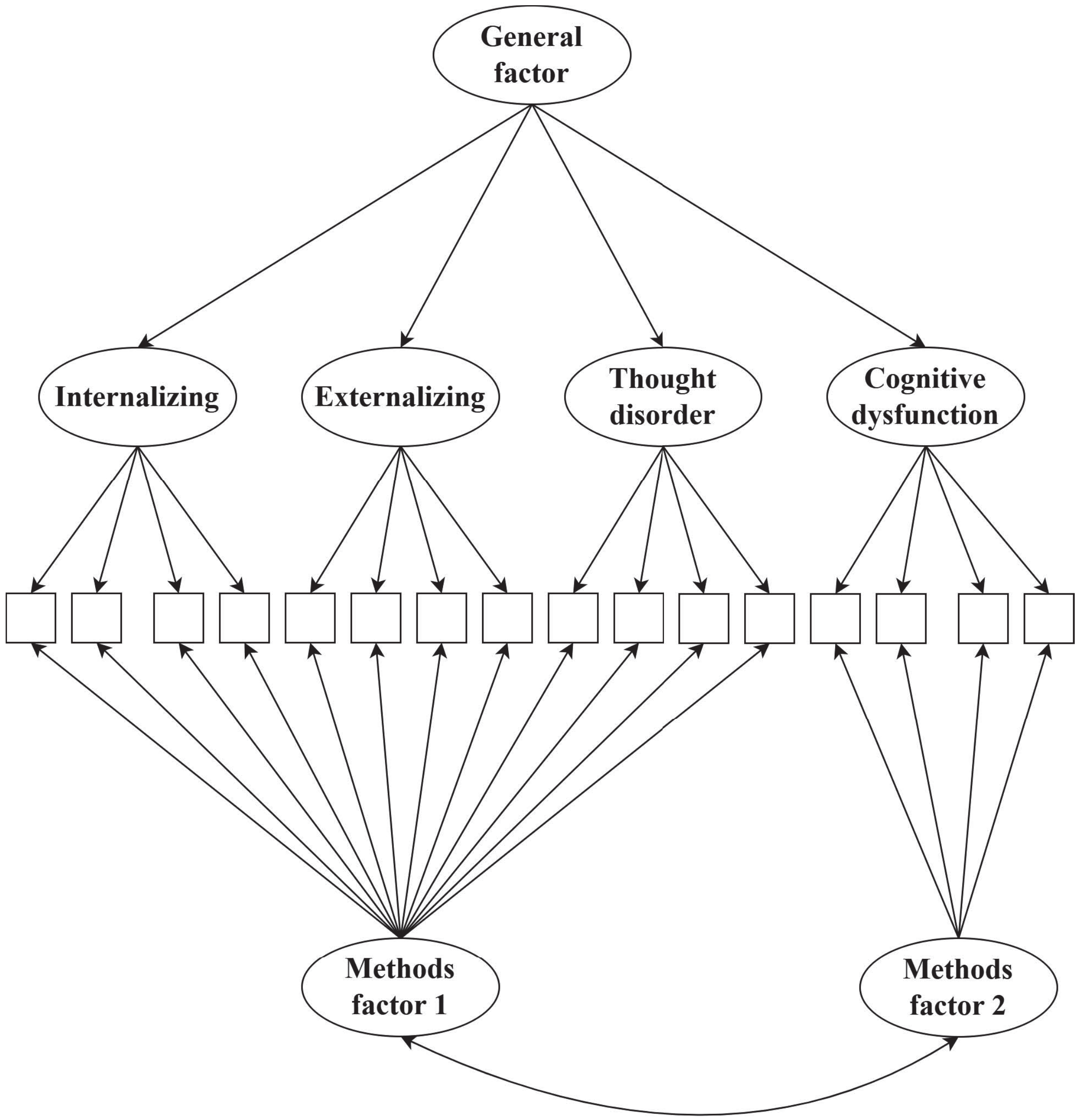
Correlated-factors and one-factor models estimated in the current study



Note. This figure illustrates the correlated-factors and one-factor models that were estimated in the primary analysis. Observed indicators are represented by squares and latent factors are represented by ellipses. Single-headed arrows represent the loadings of observed indicators on the corresponding latent factors. For the correlated-factors model, all observed indicators were specified to load onto one of four latent factors that were allowed to correlate with one another (indicated by the curved lines with double-headed arrows). For the one-factor model, all observed indicators were specified to load onto a single latent factor. Models were estimated using DELTA parameterization and the WLSMV estimator in Mplus version 8.10 (Muthén & Muthén, 2017).

Figure S3

Best-fitting higher-order model with method factors included



Note. This figure illustrates the best-fitting higher-order model with the inclusion of two method factors. Observed indicators are represented by squares and latent factors are represented by ellipses. Single-headed arrows represent the loadings of observed indicators on the corresponding latent factors. Each observed indicator was specified to load onto one of the four lower-order substantive factors, which in turn loaded onto a higher-order general factor. All psychopathology indicators were also specified to load onto a psychopathology methods factor and all cognitive indicators were specified to load onto a cognitive methods factor. The two method factors were specified to be orthogonal to all substantive factors but were allowed to correlate with one another (indicated by the curved line with double-headed arrows). Methods factor 1 refers to the psychopathology methods factor and Methods factor 2 refers to the cognitive methods factor. This model was estimated using DELTA parameterization and the WLSMV estimator in Mplus version 8.10 (Muthén & Muthén, 2017).

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Appendix G

Supplementary materials for Chapter 4

Appendix G.1

Participants and study design

Data were drawn from the Sydney Memory and Ageing Study (MAS; Sachdev et al., 2010), a longitudinal study of community-dwelling older adults. Participants were recruited from the electoral role of two federal government areas in Sydney, New South Wales, Australia (i.e., Kingsford-Smith and Wentworth). It is compulsory to register on the electoral role in Australia and registration data are publicly available. Prospective participants were first contacted via post and invited to participate if they were aged between 70-90 years old. Those who expressed an interest in the study were contacted via telephone and further assessed for eligibility. Informants were also recruited for the majority of participants (93.9%), provided that they had contact with the participant for at least one hour per week and were able to answer questions regarding their cognitive ability and daily functioning. Recruitment and study enrollment took place between September 2005 and November 2007. The final sample included 1037 older adults aged between 70-90 years old (M = 78.84; SD = 4.82; 44.8% male) at baseline. Study participants were followed across seven waves of data collection, with assessments taking place every two years (alongside brief phone interviews in intervening years). Inclusion criteria were: 1) aged between 70-90 years old; 2) living in the community; 3) able to speak and write in English; and 4) able to consent to participation. Exclusion criteria were: 1) previous diagnosis of dementia or received a diagnosis of dementia after comprehensive in-study assessment at baseline; 2) symptoms of psychosis, diagnosis of schizophrenia, or diagnosis of bipolar disorder; 3) a diagnosis of multiple sclerosis, motor neuron disease, developmental disability, or progressive malignancy; 4) medical or psychological conditions that prevent study participation; or 5) a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score of < 24 (adjusted for age, education, and non-English speaking background).

Appendix G.2

Indicators of psychopathology included in confirmatory factor models

Indicators of psychopathology were derived from multiple self- and informant-report measures administered at baseline. The 15-item Geriatric Depression Scale (GDS) was designed to measure depressive symptoms over the past week in older adults (Yesavage et al., 1982). The Goldberg Anxiety Scale (GAS) is a 9-item measure of anxiety symptoms over the past month (Goldberg et al., 1988). Items 5-9 of the GAS were only asked of participants who endorsed at least two of the first four GAS items and were therefore not included in subsequent latent variable models. The Kessler 10 (K10) is a 10-item measure of psychological distress over the past 30 days (R. ; M. D. Kessler, 1994). The Neuropsychiatric Inventory (NPI) assesses a range of psychiatric symptoms in people with dementia (Cummings et al., 1994), administered to informants of non-demented participants at baseline. The current study only included NPI items relating to agitation/aggression, irritability/lability, and disinhibition. Finally, substance use was measured via a combination of self-report items relating to alcohol and nicotine use. Alcohol items included past-year measures of frequency (i.e., how often have you had a drink containing alcohol?), heavy consumption (i.e., how often do you have six or more standard drinks on one occasion?), memory problems (i.e., how often have you been unable to remember what happened to you the night before because of drinking?) and concerns from others (i.e., has a relative, friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?). Nicotine items included frequency of use per day (i.e., average number of cigarettes per day while smoking) and age of initiation (i.e., how old were you when you started smoking?). Items from each of these scales were included in subsequent latent variable models as indicators of latent internalizing (i.e., GDS, GAS, and K10 items), disinhibited externalizing (i.e., NPI screening items for agitation/aggression, disinhibition, and irritability/lability), and substance use (i.e., alcohol and nicotine use items). After estimating the initial latent variable models, certain items from the GDS and K10 were found to have zero cells in bivariate correlation tables with substance use and NPI items. As the items used to capture internalizing exceeded those of the other latent factors, items from the GDS and K10 were dropped in order to preserve the number of indicators for disinhibited-externalizing and substance use factors. Further details of symptom-level indicators included in all confirmatory factor models are provided in Table S1.

Appendix G.3

Neuroimaging protocol

Imaging data were acquired using a Philips 3T Intera Quasar scanner and a Philips 3T Achieva Quasar Dual Scanner, with both scanners set to the same parameters (all analyses of brain structure included scanner type as a covariate). The Sydney Memory and Ageing Study (MAS) followed a standard imaging protocol, including: 1) a scout mid-sagittal cut for AC-PC plane alignment; and 2) 3D T1-weighted structural (T1w TFE – turbo field echo) MRI, acquired coronally with repetition time TR = 6.39 ms, echo time TE = 2.9 ms, flip angle = 8◦, matrix size = 256×256, field of view FOV = 256×256×190 mm3, and slice thickness = 1 mm with no gap between; yielding 1×1×1 mm3 isotropic voxels (Sachdev et al., 2010). The FreeSurfer (v7.1.0) processing pipeline was applied to T1-weighted scans for brain tissue segmentation (Fischl, 2012). The brain was segmented into 34 cortical regions per hemisphere and 9 subcortical regions per hemisphere (as well as the brain stem), using the Desikan–Killiany Atlas (Desikan et al., 2006).

Appendix G.4

Dementia diagnoses

Dementia status was determined via consensus diagnosis at each wave (Sachdev et al., 2010). Participants were assessed at fortnightly case conferences if they met the following criteria: 1) scored ≤ 1.5 standard deviations below normative data on a memory and non-memory measure; 2) scored ≤ 1.5 standard deviations below normative data on two non-memory measures; 3) showed reduced neuropsychological scores and a decline in informant-reported activities of daily living. Diagnoses were made by an expert panel of neuropsychiatrists, psychogeriatricians, and neuropsychologists based on thorough evaluation of relevant data (e.g., clinical, neuropsychological, laboratorial, and imaging data). Diagnoses were made according to DSM-4 criteria at each wave and by DSM-4 and DSM-5 criteria at waves six and seven; however, the present study only used diagnoses according to DSM-4 criteria in order to maintain consistency in measurement across follow-ups.

Appendix G.5

Model-specification

The latent structure of psychopathology was examined using confirmatory factor analysis (CFA) of symptom-level categorical indicators of mental illness at baseline. Four CFA models that are most commonly used to measure the latent structure of psychopathology were fit to the data. This included one-factor model, correlated-factors, bi-factor model, and higher-order models. For the one-factor model, all observed indicators of psychopathology were specified to load onto a single general factor of psychopathology. For the correlated factors model, observed indicators of psychopathology were specified to load onto three correlated factors (labelled internalizing, disinhibited-externalizing, and substance use). For the bi-factor model, observed indicators were specified to load onto a single general factor (labelled general psychopathology) and on one of three orthogonal (i.e., uncorrelated) specific factors (labelled internalizing, disinhibited-externalizing, and substance use). For the higher-order factor model, observed indicators were specified to load onto one of three specific factors (labelled internalizing, disinhibited-externalizing, and substance use) and these factors were specified to load onto a single higher-order general dimension of psychopathology. All models were estimated using the weighted least squares mean variance (WLSMV) and robust maximum likelihood (MLR) estimators in Mplus version 8.10 (Muthén & Muthén, 2017). For all models, the first factor loading was freely estimated and the means and variances of the latent factors were fixed to 0 and 1, respectively.

Appendix G.6

Assessment of model-fit

Confirmatory factor analysis models were first estimated using the Maximum Likelihood with Robust Standard Errors (MLR) estimator in Mplus version 8.10 (Muthén & Muthén, 2017). Models were directly compared using the Bayesian information criterion (BIC) and sample size adjusted BIC (ssaBIC). For both criteria, lower values indicate better model fit (Raftery, 1995). Models were also estimated using the weighted least squares mean variance (WLSMV) estimator to allow for assessment of absolute and incremental model fit, including the root mean square error of approximation (RMSEA; values < .05 indicating good model fit), the comparative fit index (CFI; values > 0.9 indicating good model fit), and the Tucker-Lewis index (TLI; values > 0.9 indicating good model fit).

As in **Chapter 3**, additional model-based estimates of reliability were calculated for the bi-factor model (using standardized factor loadings; Dueber, 2017), including the explained common variance (ECV), omega hierarchical (ωH) and omega hierarchical subscale (ωHS), and the percent uncontaminated correlations (PUC). Details regarding the definitions and recommended thresholds for these values was previously described in **Chapter 1** (Section

1.2.2) but are briefly reiterated here to provide a self-contained overview. ECV quantifies the proportion of shared variance among observed indicators that is attributable to the general factor relative to the specific factors included in the model (Reise et al., 2013). Values exceeding 0.70 suggest a reasonably strong general factor, while values above 0.85 are typically interpreted as evidence of essential unidimensionality (Rodriguez et al., 2016b). PUC refers to the proportion of item correlations that reflect variance solely from the general factor (i.e., uncontaminated by specific factors) with values greater than 0.70 similarly taken to support unidimensionality (Reise et al., 2013; Rodriguez et al., 2016a). Omega hierarchical (ωH) and omega hierarchical subscale (ωHS) estimate the proportion of variance in total and subscale scores that is attributable to the general and specific factors, respectively, after accounting for the influence of other latent dimensions (Bonifay, Reise, & Haviland, 2013; Reise et al., 2013). Values above 0.80 for ωH and above 0.75 for ωHS are commonly interpreted as indicating acceptable reliability (Reise et al., 2013; Rodriguez et al., 2016a). Finally, the H coefficient (H) reflects the extent to which a given factor is well-defined by its indicators and provides an index of its replicability across independent samples (Hancock & Mueller, 2001; Rodriguez et al., 2016a). H can be estimated for the general and specific factors in bifactor models and for lower-order factors in higher-order models, with values closer to 1 indicating stronger replicability; values above 0.70 are typically considered acceptable (Hancock & Mueller, 2001).

Appendix G.7

False discovery rate correction

Benjamini-Hochberg false discovery rate (FDR) was used to correct for multiple testing across sets of analyses, with an FDR threshold of 5% ($\alpha = 0.05$). When controlling for global brain structure, one set of analyses examined associations with GMV (i.e., global cortical and subcortical GMV, regional GMV in the frontal, parietal, temporal, and occipital lobes, regional GMV in the cerebellum and hippocampus) across waves for each set of BPVs representing the four transdiagnostic symptom dimensions at baseline (i.e., 32 analyses). An additional set of analyses examined cortical thickness (i.e., average global cortical thickness and average regional cortical thickness in the frontal, parietal, temporal, and occipital lobes) across waves for each set of BPVs representing the four transdiagnostic symptom dimensions at baseline (i.e., 20 analyses). Finally, one additional set of analyses examined dementia status for each set of BPVs representing the four symptom dimensions at baseline (i.e., 4 analyses). Follow-up tests of regional associations that did not control for global brain structure were treated as a separate set of analyses for FDR correction (i.e., 24 tests of regional GMV and 16 tests of regional cortical thickness). This same approach was followed for baseline analyses controlling for global brain structure (i.e., 32 analyses for GMV and 20 analyses for cortical thickness) and not controlling for global brain structure (i.e., 24 analyses for GMV and 16 analyses for cortical thickness). Finally, analyses examining associations with BPVs generated from the bi-factor model followed the same approach to FDR correction described above.

Appendix G.8

Deviations from the pre-registered analytic plan

There were two deviations from the pre-registered analysis that should be noted. Firstly, the pre-registered analysis stated that associations with *average* GMV for global and regional outcome measures would be examined. However, it was decided to examine associations with *total* GMV in order to ensure greater consistency with previous research investigating the relationship between gray matter structure and dimensions of psychopathology (Mewton et al., 2022; Romer et al., 2023; Snyder et al., 2017). Secondly, the pre-registered analytic plan stated that all models examining associations with specific/lower-order factors would be re-estimated whilst controlling for general psychopathology. These additional analyses were not necessary given that there were no statistically significant associations with any specific/lower-order symptom dimension.

Appendix G.9

Selection of the best-fitting model

Model-fit statistics and model-based reliability estimates for the four CFA models are provided in Table 4.2. The best-fitting model according to the BIC and ssaBIC was the bi-factor model (BIC = 28642.25; ssaBIC = 28267.32). The bi-factor model also demonstrated superior fit according to CFI, TLI and RMSEA indices (CFI = 0.950; TLI = 0.941; RMSEA = 0.040). The higher-order factor model (and the correlated-factors model by extension) demonstrated acceptable model fit (CFI = 0.926; TLI = 0.920; RMSEA = 0.047), whilst the one-factor model did not fit the data well (CFI = 0.686; TLI = 0.661; RMSEA = 0.097). In contrast to traditional model-fit statistics, evaluation of the standardized factor loadings for each model suggested that the higher-order model was superior to the bi-factor model. For the bi-factor model, standardized factor loadings for the general factor were non-significant for all indicators. Several indicators had negative factor loadings (i.e., 6/28) and more than half (i.e., 15/28) were relatively small in magnitude (i.e., factor loadings < 0.3). In addition, there were non-significant factor loadings for 13 of the 19 indicators of internalizing (i.e., all GDS items and most K10 items). For the one-factor model, standardized factor loadings for all indicators were positive in direction but four were non-significant and eight were small in magnitude (i.e., factor loadings < 0.3). In contrast, standardized factor loadings for the general and lower-order factors from the higher-order model (and the specific factors of the correlated-factors model by extension) were all significant, positive in direction, and > 0.3 in magnitude (with the exception of a single indicator of alcohol use). The standard errors of factor loadings were also substantially lower for most indicators of the higher-order/correlated-factors models compared to the bi-factor model, indicating greater precision in estimates for the higher-order model. Standardized factor loadings and standard errors for each of the four CFA models estimated using MLR are presented in Table 4.3 and those estimated using WLSMV are presented in Table S.3.

The imprecision of parameter estimates for the bi-factor model was further supported by model-based estimates of reliability (Table 4.2). The ECV value of 0.288 suggests a relatively weak general factor, accounting for only 28.8% of common variance among items in the dataset. Omega H values further revealed that general psychopathology accounted for 29.5% of the reliable variance in observed total scores after partialling out variance attributable to the specific factors. These values, in addition to the PUC value of 0.500, support the multidimensionality of the items used in the current study (i.e., ECV, Omega H, and PUC values all < 0.70). However, this multidimensionality was not reliably captured by the specific factors of the bi-factor model (i.e., ECV values ranged from 0.109 to 0.421 and omega HS was < 0.70 for the internalizing specific factor). Finally, H coefficient values indicated that the general and specific factors of the bi-factor model were well represented by their respective indicators (i.e., H coefficient values ranged from 0.764 to 0.962) but were lower than those observed for the higher-order model (i.e., H coefficient values ranged from 0.766 to 0.996). Therefore, although traditional fit indices supported the bi-factor model, the higher-order model was determined to provide the best fit to the data.

Appendix G.10

Unconditional linear mixed effect models

A series of post-hoc unconditional linear mixed effects models (i.e., without predictors included) were estimated to examine the trajectories of each brain structural outcome variable over time. All outcome measures were standardized prior to analysis and Benjamini-Hochberg false discovery rate (FDR) was used to correct for multiple testing across sets of analyses (i.e., 8 tests of GMV and 5 tests of cortical thickness). All models included random effects for the intercepts but no random effects for the slopes, which is consistent with the models used in the main analyses. Fixed effects indicated significant reductions in all brain structural outcome measures across waves (βs = -0.138 to -0.438; SEs = 0.015 to 0.047; $p < 0.001$), as expected in older adult samples. All fixed effects remained significant after false discovery rate (FDR) correction. The inter-class correlation coefficients (ICC) for these models ranged from 0.657 to 0.852, indicating substantial variability in baseline levels of total GMV and average cortical thickness between participants across all brain structural outcomes.

Appendix G.11

Results from analyses using Bayesian plausible values generated for the bi-factor model

All models were re-estimated using Bayesian plausible values (BPVs) for transdiagnostic symptom dimensions derived from the bi-factor model, following the exact methodology as described for primary, secondary, and post-hoc analyses. General and specific factors derived from the bi-factor model were not associated with any global or regional measures of GMV across waves. Substance use was associated with greater intra-individual change in cortical thickness within the parietal lobe at wave 2 (beta = 0.007; SE = 0.003; $p = 0.043$); however, this association did not survive FDR correction. No other symptom dimensions were associated with change in cortical thickness over time. General psychopathology was negatively associated with total cortical GMV at baseline (beta = -3644; SE = 1588.839; $p = 0.022$); however, this association did not survive FDR correction. There was no evidence of an association between general psychopathology and total subcortical GMV or average cortical thickness at baseline. No specific factors were associated with any baseline measure of global brain structure (i.e., total cortical GMV, total subcortical GMV, or average cortical thickness). When controlling for global brain structure (i.e., total GMV or average cortical thickness), general and specific factors were not associated with any baseline region of interest (ROI) measures. When not controlling for global brain structure, general psychopathology was negatively associated with baseline GMV in the frontal (beta = -1446; SE = 633.838; p = 0.023) and temporal (beta = -9220; SE = 406.836; p = 0.024) lobes. Neither association survived FDR correction. These associations are the same as those found for internalizing when derived from the higher-order model and likely reflect the fact that the general factor in the bi-factor model is defined primarily by internalizing items. General psychopathology was not associated with baseline GMV or cortical thickness in any other ROI. No specific factors were associated with any regional measure of baseline GMV or cortical thickness when not controlling for global brain structure. Finally, BPVs for general and specific symptom dimensions generated for the bi-factor model did not predict incident dementia. Results for all analyses involving transdiagnostic dimensions derived from the bi-factor model are provided in Tables S8-S12.

Table S1

Descriptions and response frequencies for symptom-level psychiatric indicators included in all confirmatory factor analysis models

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
Internalizing			
Keyed up or on edge	GAS	GAS1	No = 759; Yes = 270; Missing = 8
Worrying a lot	GAS	GAS2	No = 815; Yes = 215; Missing = 7
Irritable	GAS	GAS3	No = 861; Yes = 169; Missing = 7
Difficulty relaxing	GAS	GAS4	No = 884; Yes = 146; Missing = 7
Have you dropped many of your activities and interests?	GDS	GDS2	No = 787; Yes = 239; Missing = 11
Do you feel that your life is empty?	GDS	GDS3	No = 980; Yes = 47; Missing = 10
Do you often get bored?	GDS	GDS4	No = 939; Yes = 85; Missing = 13
Are you afraid that something bad is going to happen?	GDS	GDS6	No = 938; Yes = 91; Missing = 8

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
Do you feel happy most of the time?	GDS	GDS7	No = 89; Yes = 934; Missing = 14
Do you think it is wonderful to be alive now?	GDS	GDS11	No = 93; Yes = 933; Missing = 11
Do you feel pretty worthless the way you are now?	GDS	GDS12	No = 967; Yes = 59; Missing = 11
During the last 30 days, about how often did you feel tired out for no good reason?	K10	K101	None of the time = 368; A little of the time = 350; Some of the time = 252; Most of the time = 38; All of the time = 8; Missing = 21
During the last 30 days, about how often did you feel nervous?	K10	K102	None of the time = 768; A little of the time = 163; Some of the time = 81; Most of the time = 5; All of the time = 3; Missing = 17
During the last 30 days, about how often did you feel hopeless?	K10	K104	None of the time = 900; A little of the time = 88; Some of the time = 26; Most of the time = 1; All of the time = 1; Missing = 21

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
During the last 30 days, about how often did you feel restless or fidgety?	K10	K105	None of the time = 789; A little of the time = 154; Some of the time = 58; Most of the time = 7; Missing = 29
During the last 30 days, about how often did you feel depressed?	K10	K107	None of the time = 644; A little of the time = 278; Some of the time = 87; Most of the time = 6; All of the time = 2; Missing = 20
During the last 30 days, about how often did you feel that everything was an effort?	K10	K108	None of the time = 455; A little of the time = 405; Some of the time = 124; Most of the time = 24; All of the time = 9; Missing = 20
During the last 30 days, about how often did you feel so sad that nothing could cheer you up?	K10	K109	None of the time = 914; A little of the time = 86;Some of the time=16; Most of the time = 2; All of the time = 2; Missing = 17
During the last 30 days, about how often did you feel worthless?	K10	K1010	None of the time = 920; A little of the time = 65;Some of the time = 27; Most of the time = 5; All of the time = 1; Missing = 19

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
Disinhibited-externalizing			
Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle? (agitation/aggression screen)	NPI	NPIC	No = 926; Yes = 46; Missing = 65
Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others? (disinhibition screen)	NPI	NPIH	No = 945; Yes = 28; Missing = 64
Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self. (irritability/lability screen).	NPI	NPII	No = 906; Yes = 66; Missing = 65
Substance Use			

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
How often have you had a drink containing alcohol?	N/A	AFRQ	Not in last year = 130; Monthly or less = 167; 2-4 times per month = 168; 2-3 times per week = 135; 4-6 times per week = 144; daily = 293
How often do you have six or more standard drinks on one occasion?	N/A	A6	Never = 831; Less than monthly = 116; Monthly = 31; Weekly = 28; Daily or almost daily = 30; Missing = 1
How often have you been unable to remember what happened to you the night before because of drinking?	N/A	AMEM	Never = 839; Less than monthly to Daily or almost daily = 17; Missing=181
Has a relative, friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?	N/A	ACON	No = 815; Yes = 41; Missing = 181
Average number of cigarettes per day while smoking?	N/A	SPD	0 per day = 476; 1-9 per day = 164; 10-19 per day = 141; 20 or more per day = 232; Missing = 24

Indicators of psychopathology	Assessment Scale	Item label	Response frequencies
How old were you when you started smoking?	N/A	SST	Never started = 476; 18 years or older = 363; 13 to 17 years old = 168; 4 to 12 years old = 27; Missing = 3

Note. GAS, Goldberg Anxiety Scale; GDS, Geriatric Depression Scale; K10, Kessler 10; NPI, Neuropsychiatric Inventory; N/A, Not Applicable. This table lists the psychiatric indicators included in all confirmatory factor analysis models. GAS items 5-8 were only asked of participants who endorsed two of the first four GAS items and were thus not included in any measurement model. Missing items from the GDS and K10 were dropped due to zero cells in the bivariate correlation tables. Excluded items from the GDS include: 'Are you basically satisfied with your life?' (GDS1); 'Are you in good spirits most of the time?' (GDS5)' 'Do you often feel helpless?' (GDS8); 'Do you prefer to stay at home, rather than going out and doing things?' (GDS9); 'Do you feel that you have more problems with memory than most?' (GDS10); 'Do you feel full of energy?' (GDS13); 'Do you feel that your situation is hopeless?' (GDS14); 'Do you think that most people are better off than you are?' (GDS15). Excluded items from the K10 include: 'During the past 30 days, about how often did you feel so nervous that nothing could calm you down?' (K103); 'During the past 30 days, about how often did you feel so restless you could not sit still?' (K106).

Table S2

Baseline characteristics between those with complete and incomplete follow-up MRI data

	Complete MRI data (n = 194)	**Incomplete MRI data (n = 338)**	**P-value**
Sex			
Male	91 (46.9%)	151 (44.7%)	
Female	103 (53.1%)	187 (55.3%)	0.684
Age			
Mean (SD)	77.3 (4.11)	79.0 (4.88)	**< 0.001**
Education			
Mean (SD)	12.1 (3.58)	11.7 (3.60)	0.219
Total GMV (mm^3)			
Mean (SD)	56,2000 (53600)	54,8000 (51300)	**0.002**
Average cortical thickness (mm)			
Mean (SD)	2.44 (0.110)	2.42 (0.106)	0.121

Note. GMV, gray matter volume; MRI, magnetic resonance imaging. Baseline characteristics for those with complete and incomplete MRI follow-up data. Paired samples t-tests were used to compare groups on continuous variables and chi-square tests were used to compare groups on categorical variables. The results indicated that those with complete MRI follow-up data were more likely to be younger at baseline and to have larger total GMV at baseline, compared to those with incomplete MRI follow-up data.

Table S3

Standardized factor loadings and standard errors of the four confirmatory factor models estimated in the Sydney Memory and Ageing Study sample using weighted least squares mean variance

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Internalizing										
Keyed up or on edge	**0.393**	0.156	**0.742**	0.086	**0.647**	0.032	**0.647**	0.032	**0.554**	0.043
Worrying a lot	**0.361**	0.154	**0.726**	0.083	**0.619**	0.034	**0.619**	0.034	**0.551**	0.044
Irritable	0.220	0.099	**0.412**	0.070	**0.348**	0.048	**0.348**	0.048	**0.342**	0.049
Difficulty relaxing	**0.355**	0.130	**0.602**	0.086	**0.554**	0.041	**0.554**	0.041	**0.543**	0.045

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Dropped many activities and interests	**0.498**	0.042	-0.018	0.111	**0.464**	0.041	**0.464**	0.041	**0.449**	0.041
Feel that life is empty	**0.757**	0.055	-0.179	0.173	**0.708**	0.045	**0.708**	0.045	**0.719**	0.052
Often get bored	**0.574**	0.050	-0.064	0.139	**0.529**	0.047	**0.529**	0.047	**0.561**	0.049
Afraid that something bad is going to happen	**0.578**	0.078	**0.310**	0.134	**0.639**	0.039	**0.639**	0.039	**0.678**	0.042
Feel happy most of the time (reverse coded)	**0.649**	0.046	0.073	0.146	**0.637**	0.042	**0.637**	0.042	**0.643**	0.052
Think it is wonderful to be alive now (reverse coded)	**0.583**	0.050	-0.090	0.132	**0.532**	0.046	**0.532**	0.046	**0.566**	0.050
Feel pretty worthless the way you are now	**0.865**	0.062	-0.248	0.184	**0.794**	0.035	**0.794**	0.035	**0.804**	0.041

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	SE	λ	SE	λ	SE	λ	SE	λ	SE
Frequency of feeling tired out for no good reason	**0.692**	0.023	0.030	0.143	**0.666**	0.023	**0.666**	0.023	**0.640**	0.030
Frequency of feeling nervous	**0.564**	0.107	**0.498**	0.125	**0.685**	0.026	**0.685**	0.026	**0.684**	0.034
Frequency of feeling hopeless	**0.841**	0.027	0.080	0.18	**0.828**	0.022	**0.828**	0.022	**0.851**	0.025
Frequency of feeling restless or fidgety	**0.416**	0.098	**0.434**	0.096	**0.530**	0.038	**0.530**	0.038	**0.534**	0.045
Frequency of feeling depressed	**0.760**	0.048	0.219	0.16	**0.781**	0.021	**0.781**	0.021	**0.802**	0.022
Frequency of feeling that everything is an effort	**0.711**	0.023	0.046	0.150	**0.690**	0.023	**0.690**	0.023	**0.662**	0.031

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Frequency of feeling so sad that nothing could cheer you up	**0.760**	0.061	0.262	0.164	**0.792**	0.027	**0.792**	0.027	**0.832**	0.025
Frequency of feeling worthless	**0.852**	0.025	-0.027	0.180	**0.818**	0.024	**0.818**	0.024	**0.837**	0.029
Disinhibited-externalizing										
Refuses to cooperate or won't let people help/hard to handle	0.215	0.087	**0.684**	0.100	**0.782**	0.129	**0.782**	0.129	0.224	0.104
Acts impulsively without thinking/do or say things not usually done or said in public/embarrasses others	0.080	0.120	**0.793**	0.118	**0.643**	0.139	**0.643**	0.139	0.092	0.130

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Irritated and easily disturbed/moods very changeable/abnormally impatient	0.162	0.068	**0.631**	0.095	**0.706**	0.147	**0.706**	0.147	0.208	0.074
Substance use										
Frequency of having a drink containing alcohol	-0.016	0.039	**0.392**	0.031	**0.371**	0.032	**0.371**	0.032	0.033	0.042
Frequency of six or more standard drinks on one occasion?	-0.036	0.052	**0.617**	0.033	**0.580**	0.034	**0.580**	0.034	0.018	0.060
Frequency of being unable to remember what happened the night before because of drinking?	-0.022	0.14	**0.784**	0.081	**0.749**	0.08	**0.749**	0.080	0.033	0.150

Observed indicators of psychopathology	**Bi-factor model (general factor)**		**Bi-factor model (specific factors)**		**Higher-order model**		**Correlated-factors model**		**One-factor model**	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Relative, friend, doctor, or other health worker has expressed concerned about drinking or suggested cutting down	0.249	0.081	**0.700**	0.058	**0.748**	0.056	**0.748**	0.056	**0.334**	0.088
Average number of cigarettes per day while smoking	0.155	0.042	**0.899**	0.023	**0.914**	0.022	**0.914**	0.022	0.173	0.052
Age when started smoking	0.152	0.041	**0.943**	0.022	**0.955**	0.021	**0.955**	0.021	0.169	0.052
Standardized factor loadings of lower-order factors on the general factor										
Internalizing	-	-	-	-	**0.368**	0.106	-	-	-	-
Disinhibited-externalizing	-	-	-	-	**0.574**	0.183	-	-	-	-

Observed indicators of psychopathology	Bi-factor model (general factor)		Bi-factor model (specific factors)		Higher-order model		Correlated-factors model		One-factor model	
	λ	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**	**λ**	**SE**
Substance use	-	-	-	-	**0.322**	0.084	-	-	-	-

Note. WLSMV, weighted least squares mean variance. This table presents the standardized factor loadings and standard errors for the four dimensional models estimated in the Sydney Memory and Ageing Study sample. All models were constructed using confirmatory factor analysis (CFA) and estimated using WLSMV and DELTA parameterization in Mplus version 8.10 (Muthén & Muthén, 2017). Standardized factor loadings that are positive in direction and substantial in magnitude (i.e., > 0.3) are highlighted in bold. The exact wording used in assessing each psychiatric symptom is provided in the Appendix G (Table S1).

Table S4

Standardized results from analyses examining the relationships between transdiagnostic symptom dimensions derived from the higher-order model and global measures of gray matter structure

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General psychopathology												
BL Model	-1584	1831.194	0.387	-5179.59, 2011.32	-220.5	792.224	0.781	-1777.24, 1336.29	-0.002	0.006	0.798	-0.01, 0.01
LMM												
GP*Wave2	91.87	1265.72	0.942	-2393.52, 2577.27	109.3	538.22	0.839	-948.01, 1166.54	-0.001	0.004	0.85	-0.009, 0.007

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	SE	p	95% CI	β	SE	p	95% CI	β	SE	p	95% CI
GP*Wave4	380.4	1646.124	0.817	-2855.91, 3616.67	122.3	658.62	0.853	-1172.12, 1416.72	-0.003	0.005	0.606	-0.01, 0.007
Internalizing												
BL Model	**-3372**	**1493.334**	**0.024**	**-6299.69, -445.15**	23.01	610.432	0.970	-1173.62, 1219.63	-0.005	0.005	0.317	-0.01, 0.005
LMM												
INT*Wave2	-172.1	985.09	0.861	-2103.10, 1758.84	-169.6	412.37	0.681	-978.03, 638.75	0.001	0.003	0.784	-0.005, 0.007

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
INT*Wave4	1866	1245.75	0.134	-576.79, 4308.87	97.01	498.51	0.846	-880.33, 1074.35	-0.002	0.004	0.587	-0.009, 0.006
Disinhibited-externalizing												
BL Model	-759.8	1751.619	0.665	-4197.88, 2678.26	-198.8	769.149	0.796	1709.92, 1312.42	-0.00007	0.006	0.991	-0.01, 0.01
LMM												
DEXT*Wave2	54.46	978.38	0.956	-1866.16, 1975.08	198.8	415.05	0.632	-616.28, 1013.84	-0.00008	0.003	0.98	-0.006, 0.006

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
DEXT*Wave4	151.2	1240.21	0.903	-2285.78, 2588.09	163.2	497.07	0.743	-813.25, 1139.57	-0.001	0.004	0.705	-0.009, 0.006
Substance use												
BL Model	-2060	1635.682	0.208	-5266.22, 1146.73	-473	683.953	0.489	-1814.08, 868.04	-0.001	0.005	0.86	-0.01, 0.009
LMM												
SUB*Wave2	631.4	1057.53	0.55	-1441.56, 2704.39	-95.05	434.04	0.827	-945.84, 755.74	-0.004	0.003	0.287	-0.01, 0.003

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
SUB*Wave4	-444.7	1264.06	0.725	-2922.62, 2033.21	-0.576	526.83	0.999	-1033.39, 1032.23	-0.005	0.004	0.223	-0.01, 0.003

Note. BL, baseline; DEXT, disinhibited-externalizing; GP, general psychopathology; INT, internalizing; LMM, linear mixed models; SUB, substance use. BL Model refers to linear regression models predicting baseline gray matter volume (GMV). LMM refers to linear mixed models predicting intra-individual change in total GMV and cortical thickness across waves. In all models, pooled estimates of multiply imputed general and lower-order factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to False Discovery Rate (FDR) correction, with bold text indicating significant associations. No results were significant after FDR correction.

Table S5

Results from analyses examining whether transdiagnostic symptom dimensions derived from the higher-order factor model predict regional gray matter volume in the frontal, parietal, temporal, and occipital lobes

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
General factor																
BL Model 1	-25.47	354.048	-721.26, 670.32	0.943	-70.16	232.744	-527.29, 386.98	0.763	-110.248	235.375	-572.50, 352.01	0.640	-30.159	171.177	-366.27, 305.95	0.86
BL Model 2	-5160	720.14	-1929.96, 897.89	0.474	-4141	508.187	-1411.94, 583.84	0.416	-4191	466.361	-1334.78, 496.59	0.369	-158.707	248.773	-647.38, 329.96	0.524

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
LMM 1																
GP*Wave2	97.697	325.406	-541.29, 736.69	0.764	-5.1	184.065	-366.61, 356.41	0.978	-33.88	215.635	-456.43, 388.67	0.875	69.008	137.653	-201.38, 339.39	0.616
GP*Wave4	-1.904	428.483	-844.47, 840.66	0.996	-100.88	225.126	-543.24, 341.49	0.654	111.895	261.635	-402.33, 626.12	0.669	1.124	166.309	-325.66, 327.90	0.995
LMM 2																

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
GP*Wave2	7554	744.618	-1008.32, 1159.40	0.891	-2765	344.094	-703.22, 647.93	0.936	-5747	367.503	-779.52, 664.59	0.876	56.502	165.035	-267.68, 380.68	0.732
GP*Wave4	1190	744.618	-1345.17, 1583.09	0.873	-2350	425.144	-858.69, 811.69	0.956	1904	458.059	-710.27, 1090.97	0.678	20.781	201.713	-375.64, 417.19	0.918
Internalizing																
BL Model 1	-435.307	269.72	-964.06, 93.44	0.107	-124.49	184.939	-487.03, 238.03	0.501	-265.172	188.817	-635.31, 104.97	0.16	-78.644	140.394	-353.87, 196.58	0.575

	Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
BL Model 2	**-1332**	**585.206**	**-2479.35, -185.02**	**0.023**	-7548	408.386	-1555.34, 45.73	0.065	**-8305**	**375.023**	**-1565.63, -95.39**	**0.027**	-314.207	194.797	-696.06, 67.65	0.107
LMM 1																
INT*Wave2	194.282	252.988	-301.62, 690.19	0.443	-145.07	141.501	-422.44, 132.30	0.305	28.974	159.322	-283.32, 341.27	0.856	156.725	105.557	-50.20, 363.65	0.138
INT*Wave4	249.949	309.519	-356.85, 856.75	0.419	-133.148	170.603	-467.59, 201.29	0.435	301.818	197.7	-85.78, 689.42	0.127	-59.457	128.205	-310.81, 191.89	0.643

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
LMM 2																
INT*Wave2	5951	439.542	-855.62, 867.53	0.989	-2670	271.427	-799.04, 265.07	0.325	-8457	273.321	-620.34, 451.21	0.757	116.016	126.34	-131.65, 363.68	0.359
INT*Wave4	7639	557.113	-328.55, 1856.35	0.17	2291	331.701	-421.23, 879.35	0.49	6482	344.988	-28.28, 1324.75	0.06	62.228	156.707	-245.05, 369.50	0.691
Disinhibited-externalizing																

	Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
BL model 1	29.505	255.792	-472.75, 531.76	0.908	-12.542	182.151	-370.33, 345.25	0.945	-76.977	175.155	-420.79, 266.84	0.66	41.038	133.871	-221.84, 303.91	0.759
BL model 2	-1769	536.442	-1229.69, 875.79	0.742	-1573	385.721	-914.47, 599.92	0.684	-2069	360.57	-914.82, 501.02	0.566	-13.163	189.166	-384.65, 358.32	0.945
LMM 1																
DEXT*Wave2	24.433	250.514	-467.34, 516.20	0.922	18.004	149.219	-275.15, 311.16	0.904	-7.084	165.39	-331.90, 317.73	0.966	46.146	108.656	-167.27, 259.56	0.671

	Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
DEXT*Wave4	-118.939	307.462	-722.85, 484.97	0.699	-75.754	166.134	-401.95, 250.44	0.649	149.925	193.175	-229.46, 529.31	0.438	11.137	124.422	-233.19, 255.46	0.929
LMM 2																
DEXT*Wave2	1163	431.985	-836.26, 859.52	0.979	4604	272.097	-529.60, 538.81	0.987	-2287	282.189	-577.09, 531.36	0.935	37.991	127.38	-212.15, 288.13	0.766
DEXT*Wave4	-5477	535.274	-1106.11, 996.57	0.919	-3452	327.326	-677.38, 608.33	0.916	1961	360.445	-512.59, 904.78	0.587	21.672	155.563	-283.97, 327.31	0.889

	Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
Substance use																
BL model 1	181.418	620.237	-371.01, 733.84	0.52	-157.267	199.078	-547.57, 233.04	0.43	4.76	205.626	-398.42, 407.94	0.982	-172.84	147.284	-461.57, 115.89	0.147
BL model 2	-4816	614.725	-1686.61, 723.37	0.433	-6213	445.701	-1495.16, 252.55	0.163	-4128	400.095	-1197.05, 371.54	0.302	-346.042	207.008	-751.86, 59.77	0.095
LMM 1																

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
SUB*Wave2	329.196	269.335	-198.74, 857.14	0.222	132.228	153.594	-168.88, 433.33	0.389	-178.636	175.285	-522.26, 164.99	0.308	-1.847	110.567	-218.57, 214.88	0.987
SUB*Wave4	193.535	326.539	-446.61, 833.68	0.553	-148.979	178.774	-499.41, 201.45	0.405	-218.004	210.733	-631.16, 195.15	0.301	-3.779	137.44	-273.24, 265.68	0.978
LMM 2																
SUB*Wave2	4596	471.52	-464.63, 1383.89	0.33	1976	291.314	-373.47, 768.61	0.498	-1119	296.721	-693.57, 469.78	0.375	5.563	132.869	-254.88, 266.005	0.967

	Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
SUB*Wave4	7253	562.628	-1030.35, 1175.41	0.897	-2569	347.694	-938.52, 424.64	0.46	-3166	356.704	-1015.92, 382.72	0.375	-56.905	165.245	-380.89, 267.08	0.731

Note. BL, baseline; LMM, linear mixed models; GP, general psychopathology; INT, internalizing; DEXT, disinhibited-externalizing; SUB, substance use. BL Model 1 refers to linear regression models predicting baseline gray matter volume (GMV) and controlling for total GMV. BL Model 2 refers to linear regression models predicting baseline GMV without controlling for total GMV. LMM 1 refers to linear mixed models predicting intra-individual change in GMV across waves and controlling for total GMV. LMM 2 refers to linear mixed models predicting intra-individual change in GMV across waves without controlling for total GMV. In all models, pooled estimates of multiply imputed general and lower-order factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to False Discovery Rate (FDR) correction, with bold text indicating significant associations. No results were significant after FDR correction.

Table S6

Results from generalized linear models examining whether transdiagnostic symptom dimensions derived from the higher-order factor model are associated with regional cortical thickness in the frontal, parietal, temporal, and occipital lobes

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General factor																
BL Model 1	0.001	0.003	0.708	-0.005, 0.007	-0.001	0.004	0.783	-0.008, 0.006	-0.001	0.004	0.734	-0.009, 0.007	-0.000001	0.004	0.9998	-0.009, 0.008
BL Model 2	-0.001	0.008	0.94	-0.02, 0.01	-0.002	0.006	0.709	-0.01, 0.01	-0.003	0.008	0.681	-0.02, 0.01	-0.001	0.006	0.86	-0.01, 0.01
LMM 1																
GP*Wave2	0.00009	0.003	0.974	-0.005, 0.006	0.001	0.004	0.786	-0.006, 0.009	-0.001	0.005	0.811	-0.010, 0.008	0.001	0.005	0.881	-0.009, 0.110

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
GP*Wave4	-0.002	0.004	0.669	-0.008, 0.005	-0.001	0.005	0.85	-0.009, 0.008	0.004	0.006	0.53	-0.008, 0.015	-0.001	0.006	0.938	-0.01, 0.01
LMM 2																
GP*Wave2	-0.001	0.005	0.911	-0.011, 0.009	0.0003	0.005	0.96	-0.01, 0.01	-0.002	0.007	0.752	-0.01, 0.01	0.0002	0.006	0.972	-0.01, 0.01
GP*Wave4	-0.004	0.006	0.527	-0.016, 0.008	-0.003	0.006	0.629	-0.015, 0.009	0.001	0.009	0.944	-0.02, 0.02	-0.002	0.007	0.814	-0.01, 0.01
Internalizing																
BL Model 1	0.002	0.002	0.455	-0.003, 0.006	-0.001	0.003	0.832	-0.006, 0.005	-0.003	0.003	0.384	-0.009, 0.004	0.002	0.004	0.582	-0.005, 0.009
BL model 2	-0.003	0.006	0.559	-0.014, 0.008	-0.005	0.005	0.343	-0.014, 0.005	-0.008	0.006	0.185	-0.02, 0.004	-0.001	0.005	0.85	-0.01, 0.008

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 1																
INT*Wave2	0.001	0.002	0.586	-0.003, 0.006	-0.002	0.003	0.495	-0.008, 0.004	-0.001	0.004	0.795	-0.008, 0.006	0.004	0.004	0.382	-0.004, 0.012
INT*Wave4	-0.001	0.003	0.765	-0.006, 0.005	0.0003	0.004	0.931	-0.007, 0.008	0.005	0.005	0.247	-0.004, 0.014	-0.006	0.005	0.198	-0.016, 0.003
LMM 2																
INT*Wave2	0.002	0.004	0.543	-0.005, 0.010	-0.002	0.004	0.71	-0.009, 0.006	-0.00002	0.005	0.997	-0.01, 0.01	0.004	0.004	0.351	-0.005, 0.013
INT*Wave4	-0.003	0.005	0.564	-0.012, 0.007	-0.001	0.005	0.829	-0.011, 0.009	0.003	0.007	0.667	-0.01, 0.02	-0.007	0.005	0.228	-0.017, 0.004
Disinhibited-externalizing																

	Cortical Thickness															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	SE	p	95% CI	β	SE	p	95% CI	β	SE	p	95% CI	β	SE	p	95% CI
BL model 1	0.0004	0.002	0.871	-0.004, 0.005	0.001	0.003	0.851	-0.005, 0.006	-0.001	0.003	0.737	-0.007, 0.005	-0.000001	0.003	0.893	-0.006, 0.007
BL model 2	0.0003	0.005	0.955	-0.01, 0.01	0.0005	0.005	0.92	-0.009, 0.009	-0.001	0.006	0.85	-0.01, 0.01	0.0004	0.004	0.923	-0.008, 0.009
LMM 1																
DEXT*Wave2	-0.001	0.002	0.74	-0.005, 0.004	0.0004	0.003	0.908	-0.006, 0.006	0.00009	0.004	0.982	-0.007, 0.008	0.0003	0.004	0.951	-0.008, 0.008
DEXT*Wave4	-0.003	0.003	0.323	-0.008, 0.003	-0.002	0.004	0.664	-0.009, 0.006	0.005	0.005	0.351	-0.005, 0.014	0.001	0.005	0.861	-0.009, 0.011
LMM 2																
DEXT*Wave2	-0.001	0.004	0.85	-0.008, 0.007	0.0003	0.004	0.94	-0.008, 0.009	0.00002	0.005	0.996	-0.01, 0.01	0.0001	0.005	0.975	-0.009, 0.009

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
DEXT*Wave4	-0.004	0.005	0.374	-0.013, 0.005	-0.003	0.005	0.566	-0.012, 0.007	0.003	0.007	0.676	-0.01, 0.02	0.0002	0.005	0.97	-0.01, 0.01
Substance use																
BL model 1	0.002	0.002	0.316	-0.002, 0.007	-0.005	0.003	0.096	-0.0111, 0.0009	-0.001	0.004	0.739	-0.008, 0.006	-0.003	0.004	0.429	-0.01, 0.004
BL model 2	0.002	0.006	0.797	-0.01, 0.01	-0.006	0.005	0.272	-0.016, 0.005	-0.002	0.007	0.748	-0.01, 0.01	-0.004	0.005	0.476	-0.013, 0.006
LMM 1																
SUB*Wave2	0.002	0.002	0.35	-0.002, 0.007	**0.006**	**0.003**	**0.049**	**0.00003, 0.01288**	-0.005	0.004	0.184	-0.013, 0.002	-0.002	0.004	0.614	-0.010, 0.006
SUB*Wave4	0.003	0.003	0.38	-0.003, 0.008	0.001	0.004	0.831	-0.007, 0.008	-0.001	0.005	0.807	-0.010, 0.008	0.001	0.005	0.842	-0.009, 0.011

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 2																
SUB*Wave2	-0.001	0.004	0.735	-0.009, 0.007	0.003	0.004	0.474	-0.005, 0.012	-0.01	0.006	0.091	-0.021, 0.001	-0.004	0.005	0.336	-0.014, 0.005
SUB*Wave4	-0.002	0.005	0.643	-0.012, 0.007	-0.004	0.005	0.486	-0.014, 0.006	-0.007	0.007	0.295	-0.021, 0.006	-0.002	0.006	0.755	-0.013, 0.009

Note. BL, baseline; DEXT, disinhibited-externalizing; GP, general psychopathology; INT, internalizing; LMM, linear mixed models; SUB, substance use. Baseline Model 1 refers to linear regression models predicting baseline cortical thickness and controlling for average cortical thickness. Baseline Model 2 refers to linear regression models predicting baseline cortical thickness without controlling for average cortical thickness. LMM 1 refers to linear mixed models predicting intra-individual change in cortical thickness across waves and controlling for average cortical thickness. LMM 2 refers to linear mixed models predicting intra-individual change in cortical thickness across waves without controlling for average cortical thickness. In all models, pooled estimates of multiply imputed general and lower-order factor scores were entered as predictors. All models also controlled for age, sex, education, and MRI scanner. Bold text indicates significant associations prior to FDR correction. No results were significant after FDR correction.

Table S7

Results from analyses examining the relationships between transdiagnostic symptom dimensions derived from the higher-order model and total gray matter volume in the bilateral hippocampus and cerebellum

	Hippocampus				**Cerebellum**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
General factor								
BL Model 1	-3.552	41.16	-84.36, 77.26	0.93	182.685	408.528	-620.29, 985.67	0.66
BL Model 2	-22.41	48.45	-117.54, 72.72	0.64	-73.55	549.47	-1153.59, 1006.49	0.89
LMM 1								
GP*Wave2	11.89	34.95	-56.68, 80.46	0.73	146.58	337.11	-515.32, 808.47	0.66
GP*Wave4	-2.54	53.59	-108.02, 102.93	0.96	77.18	438.92	-785.67, 940.04	0.86
LMM 2								
GP*Wave2	11.06	36.46	-60.46, 82.58	0.76	128.2	416.8	-690.55, 946.95	0.76

	Hippocampus				Cerebellum			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
GP*Wave4	0.93	54.06	-105.43, 107.29	0.99	146.8	498.59	-832.82, 1126.39	0.77
Internalizing								
BL Model 1	13.6	34.24	-53.52, 80.72	0.69	436.41	309.67	-170.67, 1043.49	0.16
BL Model 2	-21.1	39.58	-98.69, 56.49	0.59	-35.69	412.42	-844.19, 772.79	0.93
LMM 1								
INT*Wave2	-4.48	29.59	-62.48, 53.51	0.88	155.38	269.19	-372.32, 683.09	0.56
INT*Wave4	-36.14	37.26	-109.21, 36.92	0.332	31.39	330.95	-617.52, 680.29	0.92
LMM 2								
INT*Wave2	-4.48	29.59	-62.48, 53.51	0.88	155.39	269.19	-372.32, 683.09	0.56
INT*Wave4	-36.14	37.26	-109.21, 36.92	0.33	31.39	330.95	-617.52, 680.29	0.92

	Hippocampus				Cerebellum			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
Disinhibited-externalizing								
BL Model 1	-18.65	32.37	-82.21, 44.91	0.565	71.19	296.41	-510.93, 653.31	0.81
BL Model 2	-26.56	37.63	-100.45, 47.33	0.48	-36.49	412.74	-847.43, 774.45	0.93
LMM 1								
DEXT*Wave2	10.11	28.65	-46.11, 66.33	0.72	176.82	262.34	-338.16, 691.81	0.5
DEXT*Wave4	4.25	36.56	-67.56, 76.07	0.91	171.55	325.5	-467.88, 810.99	0.59
LMM 2								
DEXT*Wave2	10.11	28.65	-46.11, 66.33	0.72	176.82	262.34	-338.16, 691.81	0.5
DEXT*Wave4	4.25	36.56	-67.56, 76.07	0.91	171.55	325.5	-467.88, 810.99	0.59
Substance use								

	Hippocampus				Cerebellum			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
BL Model 1	37.39	35.5	-32.19, 106.98	0.292	178.63	327.52	-463.47, 820.73	0.586
BL Model 2	11.78	41.54	-69.66, 93.22	0.777	-167.4	445.56	-1040.99, 706.20	0.707
LMM 1								
SUB*Wave2	18.74	32.42	-44.82, 82.29	0.56	-211.15	290.24	-780.14, 357.85	0.47
SUB*Wave4	13.29	39.94	-65.03, 91.62	0.74	-143.65	345.39	-820.79, 533.48	0.68
LMM 2								
SUB*Wave2	18.74	32.42	-44.82, 82.29	0.56	-211.15	290.24	-780.14, 357.85	0.47
SUB*Wave4	13.29	39.94	-65.03, 91.62	0.74	-143.65	345.39	-820.79, 533.48	0.680

Note. BL, baseline; DEXT, disinhibited-externalizing; GP, general psychopathology; INT, internalizing; LMM, linear mixed models; SUB, substance use. BL Model 1 refers to linear regression models predicting baseline gray matter volume (GMV) and controlling for total GMV. BL Model 2 refers to linear regression models predicting baseline GMV without controlling for total GMV. LMM 1 refers to linear mixed models predicting intra-individual change in GMV across waves and controlling for total GMV. LMM 2 refers to linear mixed models predicting intra-individual change in GMV across waves without controlling for total GMV. In all models, pooled estimates of multiply imputed general and lower-order factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to FDR correction, with bold text indicating significant associations. No results were significant after FDR correction.

Table S8

Results from logistic regression models predicting all-cause incident dementia across follow-up waves using transdiagnostic symptom dimensions derived from the higher-order and bi-factor models

Latent factors	**Higher-order factor model**				**Bi-factor model**			
	β	**SE**	**95% CI**	**p**	**β**	**SE**	**95% CI**	**p**
General psychopathology	0.04	0.07	-0.09, 0.18	0.570	0.02	0.058	-0.095, 0.135	0.731
Internalizing	0.02	0.05	-0.08, 0.12	0.730	0.0001	0.092	-0.182, 0.182	0.999
Disinhibited-externalizing	0.08	0.06	-0.03, 0.19	0.170	0.094	0.082	-0.068, 0.255	0.255
Substance use	-0.09	0.06	-0.19, 0.02	0.120	-0.097	0.058	-0.210, 0.017	0.095

Note. Dementia status was determined via consensus diagnosis from a multidisciplinary panel of experts at each wave of data collection using available clinical, neuropsychological, laboratory and neuroimaging data (see Sachdev et al., 2010). All participants were free of dementia at baseline. A single binary variable was used to indicate whether participants were diagnosed with dementia at *any wave* across 12 years of follow-up. Participants coded as having dementia at one wave and no dementia at subsequent waves (n = 7) were removed from the analysis. All models controlled for age, sex, and education.

Table S9

Results from analyses examining the relationships between transdiagnostic symptom dimensions derived from the bi-factor model and global measures of gray matter structure

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General factor												
BL model	**-3644**	**1588.839**	**0.022**	**-6760.018, -528.817**	-1543	629.228	0.806	-1387.942, 1079.354	-0.004	0.005	0.423	-0.013, 0.006
LMM												
GP*Wave2	-272.7	1025.004	0.79	-2282.1273, 1736.7953	-224.7	433.565	0.604	-1074.8196, 625.4273	0.001	0.003	0.778	-5485.099, 0.007
GP*Wave4	1880	1276.503	0.141	-623.1764, 4383.4465	-109	524.772	0.835	-920.0734, 1138.1065	-0.002	0.004	0.573	-100.093, 0.005

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
Internalizing												
BL model	-4498	2792.179	0.872	-5985.162, 5058.463	-2037	722.904	0.978	-13629.946, 1398.473	-0.001	0.006	0.861	-0.012, 0.010
LMM												
INT*Wave2	-14.38	1228.25	0.991	-2425.204, 2396.444	-44.71	557.264	0.936	-1139.777, 1050.358	0.0003	0.004	0.945	-0.007, 0.008
INT*Wave4	306.2	1544.243	0.843	-2727.280, 3339.619	20.95	627.496	0.973	-1211.505, 1253.400	-0.003	0.005	0.96	-0.010, 0.009
Disinhibited-externalizing												
BL model	2153	1848.751	0.907	-3415.802, 3846.357	-1080	755.252	0.886	-1591.574, 1375.595	0.002	0.006	0.791	-0.009, 0.013

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM												
DEXT*Wave2	-54.69	1365.246	0.968	-2737.771, 2628.398	302.1	550.338	0.583	-779.225, 1383.388	-0.002	0.004	0.954	-0.008, 0.008
DEXT*Wave4	-424.7	1706.21	0.804	-3780.725, 2931.299	17.42	667.831	0.979	-1295.378, 1330.211	-0.002	0.005	0.726	-0.011, 0.008
Substance use												
BL model	-1563	1687.588	0.355	-4871.602, 1746.498	-5816	670.013	0.385	-1895.259, 731.976	-0.001	0.005	0.918	-0.011, 0.009
LMM												
SUB*Wave2	764.4	1106.3	0.49	-1404.405, 2933.295	76.26	467.993	0.871	-841.381, 993.908	-0.004	0.004	0.27	-110.169, 0.003

	Total Cortical Volume				Total Subcortical Volume				Average Cortical Thickness			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
SUB*Wave4	-907.9	1358.197	0.504	-3571.340, 1755.608	53.72	568.258	0.925	-1060.807, 1168.244	-0.005	0.004	0.207	-138.840, 0.003

Note. BL, baseline; DEXT, disinhibited-externalizing; GP, general psychopathology; INT, internalizing; LMM, linear mixed models; SUB, substance use. Baseline Model refers to linear regression models predicting baseline gray matter volume (GMV) and cortical thickness. LMM refers to linear mixed models predicting intra-individual change in GMV across waves. In all models, pooled estimates of multiply imputed general and specific factor scores were entered as predictors. All models controlled for age, sex, education, and MRI scanner. All p-values are prior to False Discovery Rate (FDR) correction, with bold text indicating significant associations. No results were significant after FDR correction.

Table S10

Results from analyses examining the relationships between transdiagnostic symptom dimensions derived from the bi-factor model and regional gray matter volume in the frontal, parietal, temporal, and occipital lobes

	Total Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General psychopathology																
BL Model 1	-412.772	283.928	0.146	-969.480, 143.937	-76.689	195.74	0.695	-460.476, 307.098	-270.916	202.655	0.181	-688.311, 126.479	-83.591	149.47	0.576	-376.686, 209.503
BL Model 2	**-1446**	**633.838**	**0.023**	**-2688.987, -203.008**	-803.3	437.767	0.067	-1661.688, 55.082	**-922**	**406.836**	**0.024**	**-1719.823, -124.257**	-354.961	204.493	0.083	-755.889, 45.967
LMM 1																
GP*Wave2	196.553	272.096	0.470	-336.985, 730.091	-132.952	148.972	0.372	-425.029, 159.124	28.215	172.795	0.870	-310.615, 367.045	169.153	108.125	0.118	-42.814, 381.121

	Total Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
GP*Wave4	271.137	330.182	0.412	-376.405, 918.679	-128.998	174.848	0.461	-471.778, 213.783	274.902	210.195	0.191	-136.339, 687.143	-70.924	132.792	0.593	-331.303, 189.455
LMM 2																
GP*Wave2	-40.32	463.605	0.931	-949.247, 868.611	-287.4	283.542	0.311	-843.295, 268.474	-118.1	288.538	0.682	-683.802, 447.662	117.84	130.054	0.365	-137.125, 372.805
GP*Wave4	793	580.831	0.172	-346.251, 1932.175	239.7	342.798	0.485	-432.455, 911.790	625.5	351.148	0.075	-63.068, 1314.141	52.354	158.572	0.741	-258.568, 363.276
Internalizing																
BL Model 1	-73.387	402.856	0.856	-866.197, 719.423	-18.107	257.401	0.944	-524.189, 487.976	-14.624	253.82	0.954	-513.460, 484.213	8.909	213.993	0.967	-412.332, 430.151
BL Model 2	-201.3	1058.052	0.849	-2287.619, 1885.119	-108	723.255	0.881	-1533.889, 1317.808	-952.9	655.062	0.884	-1386.420, 1195.849	-24.618	366.757	0.947	-748.140, 698.905

	Total Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	SE	p	95% CI	β	SE	p	95% CI	β	SE	p	95% CI	β	SE	p	95% CI
LMM 1																
INT*Wave2	34.215	388.646	0.930	-730.547, 798.978	-9.277	212.64	0.965	-427.614, 409.060	-2.85	230.434	0.99	-455.908, 450.209	11.195	132.343	0.933	-248.620, 271.011
INT*Wave4	28.952	452.556	0.949	-861.492, 919.396	3.300	205.991	0.987	-401.022, 407.621	36.123	251.549	0.886	-458.013, 530.258	-20.394	170.453	0.905	-355.395, 314.608
LMM 2																
INT*Wave2	9.539	588.194	0.987	-1145.892, 1164.969	-26.68	364.684	0.942	-743.122, 689.766	-19.63	364.898	0.957	-736.449, 697.196	5.679	156.354	0.971	-301.238, 312.595
INT*Wave4	11.89	708.103	0.867	-1272.531, 1510.256	65.49	409.492	0.873	-738.554, 869.532	94.93	445.126	0.831	-779.899, 969.756	0.642	214.348	0.998	-420.893, 422.178
Disinhibited-externalizing																

	Total Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
BL Model 1	106.19	331.413	0.749	-544.712, 757.092	14.948	218.695	0.946	-414.351, 444.247	-44.914	227.693	0.844	-491.981, 402.154	59.13	170.614	0.729	-275.922, 394.182
BL Model 2	135.4	726.364	0.852	-1291.129, 1561.881	355.2	501.783	0.944	-949.787, 1020.836	-263.4	472.84	0.956	-955.037, 902.348	66.742	243.35	0.784	-411.226, 544.709
LMM 1																
INT*Wave2	-44.41	337.397	0.895	-707.192, 618.372	13.357	188.609	0.944	-357.161, 383.876	-6.41	212.011	0.976	-422.831, 410.011	17.72	134.651	0.895	-246.680, 282.121
INT*Wave4	-188.42	409.667	0.646	-993.576, 616.736	-12.745	219.703	0.954	-444.341, 418.850	120.125	257.403	0.641	-385.702, 625.952	40.269	172.788	0.816	-299.408, 379.946
LMM 2																
DEXT*Wave2	-47.35	611.908	0.938	-1249.959, 1155.251	10.45	378.027	0.978	-732.532, 753.437	-14.00	362.828	0.969	-726.714, 698.707	12.596	167.929	0.94	-317.318, 342.509

	Total Gray Matter Volume															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
DEXT*Wave4	-321.1	750.579	0.669	-1797.184, 1154.930	-10.37	438.059	0.813	-964.561, 757.250	39.55	475.306	0.934	-895.433, 974.526	6.416	209.33	0.976	-405.169, 418.000
Substance Use																
BL Model 1	274.918	306.172	0.369	-325.469, 875.305	-116.187	210.857	0.582	-529.659, 297.285	77.863	215.077	0.717	-343.885, 499.611	-181.136	156.682	0.248	-488.346, 126.075
BL Model 2	-311	671.969	0.644	-1628.666, 1006.650	-526.4	467.907	0.261	-1443.869, 391.121	-291.2	428.161	0.496	-1130.689, 548.299	-334.197	222.026	0.132	-769.559, 101.164
LMM 1																
SUB*Wave2	225.057	292.87	0.442	-349.224, 799.338	138.975	160.196	0.386	-175.111, 453.060	-167.714	183.342	0.36	-527.189, 191.761	-12.829	118.593	0.914	-245.342, 219.684
SUB*Wave4	89.851	341.152	0.792	-579.059, 758.761	-118.228	189.196	0.532	-489.181, 252.724	-276.009	214.587	0.198	-696.729, 144.712	-4.265	144.209	0.976	-287.069, 278.539

	Total Gray Matter Volume															
	Frontal lobes				Parietal lobes				Temporal lobes				Occipital lobes			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 2																
INT*Wave2	448.1	499.051	0.369	-530.341, 1426.490	268.5	305.916	0.38	-331.215, 868.299	-36.8	308.539	0.905	-641.706, 568.114	17.624	142.355	0.901	-261.488, 296.735
INT*Wave4	-150.7	599.8	0.802	-1326.791, 1025.429	-306.3	368.411	0.406	-1028.649, 416.137	-44.73	375.515	0.234	-1183.689, 289.108	-84.157	174.37	0.629	-426.144, 257.829

Note. BL, baseline; GP, general psychopathology; INT, internalizing; DEXT, disinhibited-externalizing; LMM, linear mixed models; SUB, substance use. BL Model 1 refers to linear regression models predicting baseline GMV and controlling for total gray matter volume (GMV). BL Model 2 refers to linear regression models predicting baseline GMV without controlling for total GMV. LMM 1 refers to linear mixed models predicting intra-individual change in GMV across waves and controlling for total GMV. LMM 2 refers to linear mixed models predicting intra-individual change in GMV across waves without controlling for total GMV. In all models, pooled estimates of multiply imputed general and specific factor scores were entered as predictors. All models also controlled for age, sex, education, and MRI scanner. Bold text indicates significant associations prior to FDR correction. No results were significant after FDR correction.

Table S11

Results from analyses examining the relationships between transdiagnostic symptom dimensions derived from the bi-factor model and total gray matter volume in the bilateral hippocampus and cerebellum

	Hippocampus				**Cerebellum**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General psychopathology								
BL Model 1	6.95	34.865	0.842	-61.396, 75.296	433.893	328.799	0.187	-210.871, 1078.657
BL Model 2	-32.999	40.359	0.414	-112.116, 46.117	-110.6	432.213	0.798	-958.029, 736.829
LMM 1								
GP*Wave2	1.461	31.309	0.903	-59.924, 62.847	111.41	281.239	0.692	-440.005, 662.826
GP*Wave4	-31.536	38.443	0.412	-106.927, 43.854	-4.025	340.939	0.991	-672.585, 664.534
LMM 2								
GP*Wave2	-6.224	32.378	0.848	-69.703, 57.256	-11.46	339.176	0.973	-676.545, 653.626

	Hippocampus				Cerebellum			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
GP*Wave4	-15.107	39.506	0.702	-92.575, 62.362	269.3	407.12	0.508	-529.072, 1067.668
Internalizing								
BL Model 1	0.774	51.514	0.988	-100.618, 102.166	48.693	550.58	0.93	-1037.046, 1134.433
BL Model 2	-4.183	49.257	0.932	-100.902, 92.536	-18.9	505.845	0.97	-1012.011, 974.218
LMM 1								
INT*Wave2	-0.296	49.863	0.995	-98.520, 97.929	6.254	348.486	0.986	-678.189, 690.697
INT*Wave4	0.1	50.597	0.998	-99.399, 99.598	-4.945	391.91	0.99	-774.294, 764.404
LMM 2								
INT*Wave2	-0.296	49.863	0.995	-98.520, 97.929	6.254	348.486	0.986	-678.189, 690.697
INT*Wave4	0.1	50.597	0.998	-99.399, 99.598	-4.945	391.91	0.99	-774.294, 764.404
Disinhibited-externalizing								

	Hippocampus				Cerebellum			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
BL Model 1	-24.517	41.486	0.555	-105.986, 56.952	-6.307	386.044	0.987	-764.703, 752.089
BL Model 2	-23.364	48.127	0.628	-117.871, 71.143	8.87	512.172	0.986	-997.156, 1014.896
LMM 1								
INT*Wave2	12.262	36.588	0.738	-59.548, 84.072	198.497	374.37	0.596	-537.436, 934.430
INT*Wave4	4.443	50.913	0.931	-95.693, 104.580	155.126	435.051	0.722	-700.066, 1010.318
LMM 2								
DEXT*Wave2	12.262	36.588	0.738	-59.548, 84.071	198.497	374.37	0.596	-537.436, 934.431
DEXT*Wave4	4.443	50.913	0.931	-95.693, 104.580	155.126	435.051	0.722	-700.066, 1010.318
Substance use								
BL Model 1	42.138	38.604	0.275	-33.562, 117.837	54.663	342.203	0.873	-616.278, 725.604
BL Model 2	19.514	44.817	0.663	-68.366, 107.393	-250.8	456.491	0.583	-1145.736, 644.231

	Hippocampus				Cerebellum			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 1								
SUB*Wave2	21.138	33.519	0.528	-44.578, 86.854	-194.84	304.98	0.523	-792.841, 403.161
SUB*Wave4	23.533	43.107	0.585	-61.045, 108.111	-94.531	364.003	0.795	-808.343, 619.280
LMM 2								
INT*Wave2	21.138	33.519	0.528	-44.578, 86.854	-194.84	304.98	0.523	-792.841, 403.161
INT*Wave4	23.533	43.107	0.585	-61.045, 108.111	-94.531	364.003	0.795	-808.343, 619.280

Note. BL, baseline; GP, general psychopathology; INT, internalizing; DEXT, disinhibited-externalizing; LMM, linear mixed models; SUB, substance use. BL Model 1 refers to linear regression models predicting baseline GMV and controlling for total GMV. BL Model 2 refers to linear regression models predicting baseline GMV without controlling for total GMV. LMM 1 refers to linear mixed models predicting intra-individual change in GMV across waves and controlling for total GMV. LMM 2 refers to linear mixed models predicting intra-individual change in GMV across waves without controlling for total GMV. In all models, pooled estimates of multiply imputed general and specific factor scores were entered as predictors. All models also controlled for age, sex, education, and MRI scanner. Bold text indicates significant associations prior to FDR correction. No results were significant after FDR correction.

Table S12

Results from generalized linear models examining whether transdiagnostic symptom dimensions derived from a bi-factor model are associated with regional cortical thickness in the frontal, parietal, temporal, and occipital lobes

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
General factor																
BL Model 1	0.002	0.003	0.518	-0.003, 0.006	-0.0004	0.003	0.899	-0.007, 0.006	-0.003	0.004	0.431	-0.010, 0.004	0.002	0.004	0.615	-0.005, 0.009
BL Model 2	-0.003	0.006	0.66	-0.014, 0.009	-0.004	0.005	0.475	-0.014, 0.007	-0.007	0.006	0.264	-0.019, 0.005	-0.001	0.005	0.912	-0.010, 0.009
LMM 1																
GP*Wave2	0.001	0.002	0.532	-0.003, 0.006	-0.002	0.003	0.497	-0.008, 0.004	-0.002	0.004	0.687	-0.009, 0.006	0.004	0.004	0.349	-0.004, 0.012

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
GP*Wave4	-0.001	0.003	0.825	-0.006, 0.005	0.001	0.004	0.876	-0.007, 0.008	0.005	0.005	0.282	-0.004, 0.014	-0.006	0.005	0.217	-0.017, 0.004
LMM 2																
GP*Wave2	0.003	0.004	0.509	-0.005, 0.011	-0.002	0.004	0.721	-0.009, 0.007	-0.001	0.006	0.916	-0.011, 0.010	0.005	0.005	0.324	-0.004, 0.014
GP*Wave4	-0.003	0.005	0.588	-0.013, 0.007	-0.001	0.005	0.859	-0.011, 0.009	0.002	0.007	0.719	-0.011, 0.015	-0.007	0.006	0.232	-0.018, 0.004
Internalizing																
BL Model 1	0.0001	0.003	0.963	-0.005, 0.006	-0.0002	0.007	0.973	-0.013, 0.013	-0.0003	0.006	0.953	-0.012, 0.011	0.001	0.005	0.902	-0.010, 0.011
BL model 2	-0.001	0.007	0.89	-0.01, 0.01	-0.001	0.009	0.896	-0.02, 0.01	-0.001	0.009	0.864	-0.02, 0.01	0.00003	0.007	0.996	-0.01, 0.01

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 1																
INT*Wave2	0.0003	0.003	0.928	-0.006, 0.006	-0.0005	0.004	0.903	-0.008, 0.007	-0.0002	0.005	0.976	-0.009, 0.009	0.00002	0.005	0.975	-0.009, 0.009
INT*Wave4	0.00007	0.005	0.989	-0.009, 0.009	0.0001	0.007	0.985	-0.014, 0.014	0.001	0.006	0.915	-0.010, 0.011	-0.001	0.007	0.875	-0.014, 0.012
LMM 2																
INT*Wave2	0.001	0.006	0.909	-0.010, 0.011	-0.0002	0.005	0.965	-0.011, 0.010	0.0002	0.007	0.98	-0.013, 0.013	0.0003	0.006	0.952	-0.011, 0.011
INT*Wave4	-0.0002	0.008	0.982	-0.016, 0.015	0.00001	0.007	0.999	-0.013, 0.013	0.0003	0.009	0.968	-0.017, 0.017	-0.001	0.007	0.88	-0.014, 0.012
Disinhibited-externalizing																

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
BL model 1	-0.0002	0.003	0.949	-0.005, 0.005	0.001	0.004	0.843	-0.006, 0.007	-0.0005	0.004	0.911	-0.008, 0.007	0.0001	0.005	0.975	-0.009, 0.009
BL model 2	0.001	0.007	0.83	-0.01, 0.01	0.002	0.006	0.738	-0.009, 0.014	0.001	0.008	0.868	-0.01, 0.02	0.001	0.006	0.847	-0.01, 0.01
LMM 1																
DEXT*Wave2	-0.001	0.003	0.728	-0.007, 0.005	-0.00008	0.004	0.986	-0.008, 0.008	0.001	0.005	0.879	-0.009, 0.011	0.00004	0.005	0.995	-0.010, 0.010
DEXT*Wave4	-0.003	0.004	0.451	-0.009, 0.004	-0.001	0.005	0.77	-0.011, 0.008	0.003	0.006	0.597	-0.009, 0.015	0.002	0.006	0.709	-0.010, 0.015
LMM 2																
DEXT*Wave2	-0.001	0.005	0.809	-0.011, 0.009	-0.0002	0.006	0.977	-0.012, 0.011	0.001	0.007	0.935	-0.014, 0.015	-0.0001	0.006	0.98	-0.012, 0.011

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
DEXT*Wave4	-0.004	0.006	0.465	-0.016, 0.007	-0.003	0.006	0.644	-0.015, 0.009	0.001	0.009	0.894	-0.017, 0.019	0.001	0.007	0.838	-0.012, 0.014
Substance use																
BL model 1	0.002	0.003	0.499	-0.003, 0.007	-0.005	0.003	0.149	-0.011, 0.002	-0.0003	0.004	0.945	-0.008, 0.007	-0.003	0.004	0.425	-0.011, 0.005
BL model 2	0.001	0.006	0.846	-0.01, 0.01	-0.005	0.006	0.364	-0.016, 0.006	-0.001	0.007	0.901	-0.01, 0.01	-0.004	0.005	0.493	-0.014, 0.007
LMM 1																
SUB*Wave2	0.002	0.003	0.418	-0.003, 0.007	**0.007**	**0.003**	**0.043**	**0.0002, 0.0137**	-0.005	0.004	0.254	-0.013, 0.003	-0.002	0.005	0.621	-0.011, 0.007
SUB*Wave4	0.003	0.003	0.286	-0.003, 0.009	0.002	0.004	0.654	-0.006, 0.009	-0.003	0.005	0.513	-0.013, 0.006	0.003	0.005	0.634	-0.008, 0.013

	Cortical Thickness															
	Frontal lobes				**Parietal lobes**				**Temporal lobes**				**Occipital lobes**			
	β	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**	**β**	**SE**	**p**	**95% CI**
LMM 2																
SUB*Wave2	-0.002	0.004	0.659	-0.011, 0.007	0.003	0.005	0.459	-0.006, 0.012	-0.01	0.006	0.115	-0.022, 0.002	-0.005	0.005	0.34	-0.015, 0.005
SUB*Wave4	-0.002	0.005	0.683	-0.012, 0.008	-0.003	0.006	0.594	-0.014, 0.008	-0.01	0.007	0.176	-0.024, 0.004	-0.001	0.006	0.917	-0.012, 0.011

Note. BL, baseline; GP, general psychopathology; INT, internalizing; DEXT, disinhibited-externalizing; LMM, linear mixed models; SUB, substance use. BL Model 1 refers to linear regression models predicting baseline cortical thickness and controlling for average cortical thickness. BL Model 2 refers to linear regression models predicting baseline cortical thickness without controlling for average cortical thickness. LMM 1 refers to linear mixed models predicting intra-individual change in cortical thickness across waves and controlling for average cortical thickness. LMM 2 refers to linear mixed models predicting intra-individual change in cortical thickness across waves without controlling for average cortical thickness. In all models, pooled estimates of multiply imputed general and specific factor scores were entered as predictors. All models also controlled for age, sex, education, and MRI scanner. Bold text indicates significant associations prior to FDR correction. No results were significant after FDR correction.

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Appendix H

Supplementary materials for Chapter 5

Appendix H.1

Assessment of model-fit

Traditional indices of absolute and incremental model-fit were evaluated. This included the Comparative Fit Index (CFI), Tucker Lewis Index (TLI), and Root Mean Square Error of Approximation (RMSEA). CFI and TLI values > 0.9 and RMSEA values < 0.08 were considered to indicate acceptable model-fit (Hu & Bentler, 1999; Marsh et al., 2004). H coefficient (H) values for the lower-order factors (Dueber, 2017) were also estimated, providing an index of the degree to which variance in the lower-order factors was captured by their respective indicators and the likelihood that factor estimates will replicate across studies (Rodriguez et al., 2016). H coefficient values range from 0 to 1, with higher-values indicating greater reliability and replicability for a given factor (Hancock & Mueller, 2001; Rodriguez et al., 2016). Note that H coefficient values can be calculated for the lower-order factors in a higher-order model but not for the higher-order factor. H values greater than 0.7 are typically interpreted to indicate sufficient reliability of a given factor (Hancock & Mueller, 2001). Finally, model parameters (e.g., the significance, direction, and magnitude of the standardized factor loadings and the magnitude of the standard errors) were evaluated to assess the interpretability of the model (Forbes et al., 2021).

Table S1

Results for multigroup measurement invariance testing and differences in latent means for the higher-order model

		Chi-square (df)	CFI	RMSEA
Configural invariance model		180,419.555 (3416)	**0.934**	**0.044**
First-order metric/scalar invariance model		166,058.179 (3717)	**0.940**	**0.040**
Second-order metric/scalar invariance model		164,535.453 (3723)	**0.940**	**0.040**
		Latent mean differences across age groups		
Age groups	**Latent factors**	**Standardized estimates**	**Standard errors**	**p-values**
60-64 years old (n= 28,988)				
	Internalizing	**-0.262**	**0.039**	**< 0.001**
	Addictions and substance use	**-0.236**	**0.079**	**0.003**
	Thought disorder	**-1.022**	**0.062**	**< 0.001**

	Cognitive dysfunction	**4.604**	**0.043**	**< 0.001**
	General	**-0.352**	**0.054**	**< 0.001**
65-69 years old (n= 35,922)				
	Internalizing	**-0.524**	**0.036**	**< 0.001**
	Addictions and substance use	**-0.446**	**0.076**	**< 0.001**
	Thought disorder	**-1.357**	**0.059**	**< 0.001**
	Cognitive dysfunction	**4.133**	**0.036**	**< 0.001**
	General	**-0.734**	**0.051**	**< 0.001**
70-78 years old (n= 24,695)				
	Internalizing	**-0.639**	**0.039**	**< 0.001**
	Addictions and substance use	**-0.767**	**0.082**	**< 0.001**

Thought disorder	**-1.411**	**0.061**	**< 0.001**
Cognitive dysfunction	**4.674**	**0.044**	**< 0.001**
General	**-0.899**	**0.056**	**< 0.001**

Note. CFI, Confirmatory Fit Index; RMSEA, Root Mean Square Error of Approximation; df, degrees of freedom. The total sample size for these analyses was N = 109,296 and participants were stratified by age into four categories, including: 55-59 years old (n = 19,681), 60-64 years old (n = 28,988), 65-69 years old (n = 35,922), and 70-78 years old (n = 24,695). All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus (version 8.10; Muthén & Muthén, 2017). Further information regarding model-specifications for each invariance test are provided in detail in **Chapter 3** (Appendix F.4; Hoy, Forbes et al., 2025). In the current study, analyses were restricted to participants that were aged 55-78 years old at the time of completing the online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. All models controlled for years of education. Change in CFI values between the configural and lower-order metric/scalar invariance models were within the recommended thresholds, as were changes in CFI values between the lower- and higher-order metric/scalar invariance model (Cheung & Rensvold, 2002; Meade et al., 2008), indicating that the model is invariant across age groups. Differences in latent means for the lower-order factors were examined using the lower-order metric/scalar invariance model and differences in latent means for the higher-order factor were examined using the higher-order metric/scalar invariance model. Latent mean differences were examined by fixing the lower- or higher-order factors to 0 in the reference group (i.e., participants aged 55-59 years old). All latent mean difference tests were statistically significant.

Table S2

Model-fit statistics for structural equation models examining associations with polygenic scores for Alzheimer's Disease and dementia status across the four age groups

	CFI	TLI	RMSEA
Structural equation models			
Model 16	**0.940**	**0.942**	**0.039**
Model 17	**0.940**	**0.942**	**0.039**
Model 18	**0.941**	**0.942**	**0.038**
Model 19	**0.938**	**0.940**	**0.040**
Model 20	**0.938**	**0.940**	**0.040**
Model 21	**0.938**	**0.940**	**0.039**
Model 22	**0.939**	**0.940**	**0.039**
Model 23	**0.939**	**0.941**	**0.039**
Model 24	**0.940**	**0.941**	**0.039**
Model 25	**0.938**	**0.940**	**0.040**
Model 26	**0.939**	**0.941**	**0.039**
Model 27	**0.939**	**0.941**	**0.039**
Model 28	**0.939**	**0.941**	**0.039**
Model 29	**0.939**	**0.941**	**0.039**
Model 30	**0.940**	**0.942**	**0.038**

Note. CFI, Comparative Fit Index; TLI, Tucker Lewis Index; RMSEA, Root Mean Square Error of Approximation. This table presents the model-fit statistics for the 15 structural equation models (SEMs) estimated to examine associations with polygenic scores for Alzheimer's Disease (AD-PGS) and all-cause incident dementia across the four age-stratified subsamples. Model 16 is the SEM regressing the binary all-cause incident dementia variable on the general higher-order factor . Model 17 is the SEM regressing the general higher-order factor on the AD-PGS. Model 18 is the SEM examining indirect effects of the AD-PGS on dementia status via their influence on levels of the general higher-order factor. Models 19-22 are the SEMs regressing incident dementia on internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. Models 23-26 are the SEMs regressing internalizing, addictions and substance use, thought disorder, and cognitive dysfunction on the AD-PGS, respectively. Models 27-30 are the SEMs examining indirect effects of the AD-PGS on dementia status via their influence on levels of internalizing, addictions and substance use, thought disorder, and cognitive dysfunction, respectively. For SEMs examining associations with the higher-order factor, the second-order metric/scalar invariant model (in which higher-order means were free to vary) was used. For SEMs examining associations with the lower-order factors, the first-order metric/scalar invariance model (in which lower-order means were free to vary) was used. All models were estimated in Mplus (version 8.10; Muthén & Muthén, 2017), using weighted-least squares (WLSMV) estimation and DELTA parameterization. All SEMs controlled years of education.

Table S3

Model-fit statistics for multivariable structural equation models examining associations between lower-order dimensions, polygenic scores for Alzheimer's Disease and dementia status

	CFI	TLI	RMSEA
Structural equation models in the full sample			
Model S1	**0.935**	**0.931**	**0.040**
Model S2	**0.935**	**0.931**	**0.040**
Model S3	**0.935**	**0.931**	**0.040**
Structural equation models across age groups			
Model S4	**0.939**	**0.941**	**0.039**
Model S5	**0.940**	**0.941**	**0.039**
Model S6	**0.940**	**0.941**	**0.039**

Note. CFI, Comparative Fit Index; RMSEA, Root Mean Square Error of Approximation; TLI, Tucker-Lewis Index. This table presents the model-fit statistics for the six structural equation models (SEMs) estimated to examine *multivariable* associations between the lower-order factors, polygenic scores (PGSs) for Alzheimer's Disease and all-cause incident dementia in older adults from the UK Biobank. In all models, each of the four lower-order factors were entered simultaneously as predictors, outcomes, or mediators. Model S1-S3 were conducted in the full sample. In Model S1, dementia status was regressed on each of the lower-order factors simultaneously. In Model S2, each of the lower-order factors were simultaneously regressed on the Alzheimer's disease PGS. Model S3 examined indirect effects of PGSs for Alzheimer's disease on dementia status via their influence on levels of the four lower-order factors. Models S4-S6 repeat these three analyses across the four different age groups (i.e., 55-59, 60-64, 65-69, 70-78 years old) using the lower-order metric/scalar invariance model. All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus (version 8.10; Muthén & Muthén, 2017). Analyses were restricted to participants that were aged 55-78 years old at the time of completing the online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. All models in the full sample controlled for age and years of education and all models by age group controlled for years of education only. All models demonstrated acceptable fit to the data based on absolute and incremental indices of model-fit.

Table S4

Multivariable associations between the lower-order dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and incident dementia examined in the full sample

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
Model S1	Main effects	Internalizing	-	Incident dementia	**0.136**	**0.021**	**< 0.001**
		Addictions and substance use	-	Incident dementia	0.037	0.025	0.243
		Thought disorder	-	Incident dementia	-0.054	0.030	0.140
		Cognitive dysfunction	-	Incident dementia	**0.191**	**0.021**	**< 0.001**
Model S2	Main effects	AD-PGS	-	Internalizing	0.004	0.003	0.275

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
			-	Addictions and substance use	-0.002	0.005	0.626
			-	Thought disorder	-0.011	0.005	0.062
			-	Cognitive dysfunction	**0.033**	**0.004**	**0.001**
Multivariable mediation model							
Model S3	Direct effect	AD-PGS	-	Incident dementia	**0.192**	**0.010**	**< 0.001**
	Indirect effect	AD-PGS	Internalizing	Incident dementia	0.001	0.001	0.275

SEM	Effect type	Explanatory variable(s)	Mediator(s)	Outcome variable(s)	β	SE	p-value
	Indirect effect	AD-PGS	Addictions and substance use	Incident dementia	-0.0002	0.0004	0.650
	Indirect effect	AD-PGS	Thought disorder	Incident dementia	0.001	0.001	0.275
	Indirect effect	AD-PGS	Cognitive dysfunction	Incident dementia	**0.006**	**0.001**	**< 0.001**
	Total effect	AD-PGS	All lower-order dimensions	Incident dementia	**0.199**	**0.010**	**< 0.001**

Note. AD-PGS, Alzheimer's disease polygenic score; SEM, structural equation model. This table presents the results of multivariable analyses examining associations between lower-order dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia in the full sample. In all SEMs, each of the four lower-order factors were entered simultaneously as predictors, outcomes, or mediators. In Model S1, dementia status was regressed on each of the lower-order factors simultaneously. In Model S2, each of the lower-order factors were simultaneously regressed on PGSs for Alzheimer's disease. Model S3 examined indirect effects of PGSs for Alzheimer's disease on dementia status via their influence on levels of the four lower-order factors. All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus (version 8.10; Muthén & Muthén, 2017). Analyses were restricted to participants that were aged 55-78 years old at the time of completing the online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. All models controlled for age and years of education. All p-values for main and indirect effects are False Discovery Rate (FDR) corrected. Significant associations are reported in bold text. Effect sizes for binary dementia outcomes are presented as probit regression coefficients rather than odds ratios, as WLSMV estimation in Mplus models categorical outcomes using a probit link function.

Table S5

Multivariable associations between the lower-order factors of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and incident dementia examined across the four age groups

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
Multivariable associations with lower-order dimensions							
Model S4							
55-59 years old	Main effects	Internalizing	-	Incident dementia	-0.034	0.096	0.727
		Addictions and substance use	-	Incident dementia	0.132	0.057	0.081
		Thought disorder	-	Incident dementia	**0.233**	**0.082**	**0.026**
		Cognitive dysfunction	-	Incident dementia	0.070	0.093	0.550
60-64 years old	Main effects	Internalizing	-	Incident dementia	0.100	0.054	0.137

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
		Addictions and substance use	-	Incident dementia	0.058	0.062	0.444
		Thought disorder	-	Incident dementia	-0.075	0.071	0.437
		Cognitive dysfunction	-	Incident dementia	**0.325**	**0.053**	**< 0.001**
65-69 years old	Main effects	Internalizing	-	Incident dementia	**0.141**	**0.036**	**< 0.001**
		Addictions and substance use	-	Incident dementia	-0.004	0.039	0.947
		Thought disorder	-	Incident dementia	-0.010	0.050	0.942
		Cognitive dysfunction	-	Incident dementia	**0.157**	**0.033**	**< 0.001**
70-78 years old	Main effects	Internalizing	-	Incident dementia	**0.177**	**0.033**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
		Addictions and substance use	-	Incident dementia	0.040	0.037	0.449
		Thought disorder	-	Incident dementia	**-0.125**	**0.048**	**0.023**
		Cognitive dysfunction	-	Incident dementia	**0.236**	**0.030**	**< 0.001**
Model S5							
55-59 years old	Main effects	AD-PGS	-	Internalizing	0.009	0.008	0.478
			-	Addictions and substance use	0.011	0.011	0.537
			-	Thought disorder	0.008	0.011	0.550
			-	Cognitive dysfunction	0.022	0.010	0.478

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
60-64 years old	Main effects	AD-PGS	-	Internalizing	0.003	0.007	0.758
			-	Addictions and substance use	-0.018	0.009	0.113
			-	Thought disorder	-0.014	0.009	0.249
			-	Cognitive dysfunction	**0.031**	**0.008**	**< 0.001**
65-69 years old	Main effects	AD-PGS	-	Internalizing	0.013	0.006	0.871
			-	Addictions and substance use	0.004	0.009	0.871
			-	Thought disorder	-0.019	0.009	0.058
			-	Cognitive dysfunction	**0.035**	**0.007**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
70-78 years old	Main effects	AD-PGS	-	Internalizing	0.006	0.007	0.461
			-	Addictions and substance use	-0.005	0.011	0.718
			-	Thought disorder	-0.014	0.011	0.364
			-	Cognitive dysfunction	**0.051**	**0.009**	**< 0.001**
Multivariable mediation model with lower-order dimensions							
Model S6							
55-59 years old	Direct effect	AD-PGS	-	Incident dementia	**0.132**	**0.048**	**0.006**
	Indirect effects	AD-PGS	Internalizing	Incident dementia	-0.001	0.001	0.693
			Addictions and substance use	Incident dementia	0.001	0.001	0.570

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
			Thought disorder	Incident dementia	0.002	0.003	0.550
			Cognitive dysfunction	Incident dementia	0.002	0.002	0.550
	Total effect	AD-PGS	All lower-order dimensions	Incident dementia	**0.136**	**0.048**	**0.005**
60-64 years old	Direct effect	AD-PGS	-	Incident dementia	**0.103**	**0.034**	**0.002**
	Indirect effects	AD-PGS	Internalizing	Incident dementia	0.0004	0.001	0.758
			Addictions and substance use	Incident dementia	-0.001	0.001	0.444
			Thought disorder	Incident dementia	-0.012	0.009	0.444
			Cognitive dysfunction	Incident dementia	**0.010**	**0.003**	**0.005**

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
	Total effect	AD-PGS	All lower-order dimensions	Incident dementia	**0.114**	**0.033**	**0.001**
65-69 years old	Direct effect	AD-PGS	-	Incident dementia	**0.187**	**0.019**	**< 0.001**
	Indirect effects	AD-PGS	Internalizing	Incident dementia	0.0003	0.001	0.871
			Addictions and substance use	Incident dementia	0.00001	0.0001	0.947
			Thought disorder	Incident dementia	0.0002	0.001	0.947
			Cognitive dysfunction	Incident dementia	**0.005**	**0.002**	**0.002**
	Total effect	AD-PGS	All lower-order dimensions	Incident dementia	**0.193**	**0.019**	**< 0.001**
70-78 years old	Direct effect	AD-PGS	-	Incident dementia	**0.231**	**0.015**	**< 0.001**

SEM	Effect type	Explanatory variable(s)	Mediators	Outcome variable(s)	β	SE	p-value
	Indirect effects	AD-PGS	Internalizing	Incident dementia	0.001	0.001	0.461
			Addictions and substance use	Incident dementia	-0.0002	0.001	0.876
			Thought disorder	Incident dementia	0.002	0.001	0.429
			Cognitive dysfunction	Incident dementia	**0.015**	**0.003**	**< 0.001**
	Total effect	AD-PGS	All lower-order dimensions	Incident dementia	**0.246**	**0.015**	**< 0.001**

Note. AD-PGS, Alzheimer's disease polygenic score; SEM, structural equation model. This table presents the results of multivariate analyses examining associations between lower-order dimensions of psychopathology and cognitive dysfunction, polygenetic risk for Alzheimer's disease, and all-cause incident dementia across age groups. Participants were stratified by age into four categories, including: 55-59 years old, 60-64 years old, 65-69 years old, and 70-78 years old. Structural Equation Models (SEMs) were estimated using the lower-order metric/scalar invariance model. In all SEMs, each of the four lower-order factors were entered simultaneously as predictors, outcomes, or mediators. In Model S4, dementia status was regressed on each of the lower-order factors simultaneously. In Model S5, each of the lower-order factors were simultaneously regressed on the

Alzheimer’s disease PGS. Model S6 examined indirect effects of PGSs for Alzheimer’s disease on dementia status via their influence on levels of the four lower-order factors. All models were estimated using the weighted least squares mean variance (WLSMV) estimator and DELTA parameterization in Mplus (version 8.10; Muthén & Muthén, 2017). Analyses were restricted to participants that were aged 55-78 years old at the time of completing the online cognitive assessments, free of dementia at the time of completing both the cognitive and mental health assessments, and of European ancestry. All models controlled for years of education. All p-values for main and indirect effects are False Discovery Rate (FDR) corrected. Significant associations are denoted in bold text. Effect sizes for binary dementia outcomes are presented as probit regression coefficients rather than odds ratios, as WLSMV estimation in Mplus models categorical outcomes using a probit link function.

Supplementary References

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Appendix I

Mplus and R code for Chapters 3-5

Samples of the analysis code, including Mplus input files and R Scripts for analyses conducted across each empirical chapter are provided in the links below:

Chapter 3: https://osf.io/hdxqp/files/osfstorage

Chapter 4: https://osf.io/uhds9/files/osfstorage

Chapter 5: https://osf.io/wrk7c/files/osfstorage

Appendix J

Ethical approval for the UK Biobank and Sydney Memory and Ageing Study (MAS) data

Chapters 3-5 of this thesis involve secondary analysis of existing data from the UK Biobank and the Sydney Memory and Ageing (MAS) study, for which formal ethical approval is not required. Access to the Sydney MAS was approved by the MAS Governance Committee and Centre for Healthy Brain Ageing (CHeBA) Research Bank (reference number: APIDM_00096). Access to the UK Biobank was approved by the UK Biobank Access Management Team (reference number: 316382). Details regarding data availability, collection, and ethical approval are provided below.

UK Biobank. Individual level data from the UK Biobank is not publicly available due to legal and ethical restrictions on data sharing. Researchers can apply for access to the UK Biobank data through their official application process (http://www.ukbiobank.ac.uk/register-apply/). UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. All participants provided written and informed consent.

Sydney Memory and Ageing Study. Individual level data from the Sydney MAS is also not publicly available due to ethical and legal restrictions on data sharing. Researchers can apply for access to the Sydney MAS data via the MAS Governance Committee (https://cheba.unsw.edu.au). Ethics approval was obtained from the Human Research Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service. All participants provided written and informed consent.