Food for Thought: Investigating Adolescent Nutrition, Health Behaviours, and Mental Health and Their Association with the Onset of Chronic Inflammation

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BscHons Nutrition, Exercise and Health

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Abstract

Chronic inflammation plays an important role in disease aetiology, but our understanding of its prevalence and associated risk factors in adolescents is limited – a population with worsening health behaviours and disease rates.
This thesis aims to investigate the global prevalence of chronic inflammation in adolescents and understand how health behaviours, mental health and socio-demographic factors associate with inflammation and disease in Australian adolescents.

Study 1 is a meta-analysis of chronic inflammation prevalence in adolescents worldwide. Results indicate inflammation levels in this population is approaching the threshold for chronic inflammation, and that those who are overweight/obese are more likely to meet this threshold. **Study 2** examines in a large cohort of Australian adolescents how multiple health behaviours, mental health, and socio-demographic variables associate with 11 non-communicable diseases/developmental conditions. Almost half (46%) of adolescents have one or more of these diseases/conditions and tobacco, alcohol, ultra-processed food intake and poor mental health are associated with each of these. **Study 3** examines associations between adolescent-perceived parental monitoring and dietary intake. Results reveal a complex relationship, with higher parental monitoring associated with increased vegetable and lower ultra-processed food intake, but also insufficient fruit and excessive sugar-sweetened beverage intake. **Study 4** is the first to test the feasibility of assessing inflammatory markers via dried blood spot collection in a school setting. Results establish feasibility and find associations between diet and inflammation largely align with the adult literature, indicating adolescents are not immune to the biological impacts of poor dietary intake.

Overall, this thesis advances the fields of prevention and epidemiology by identifying modifiable targets for adolescent health, laying the foundations for future causal analysis.

Statement of Originality

This thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (Medicine) at The University of Sydney.

This is to certify that to the best of my knowledge; the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

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 used have been acknowledged.

Bridie Osman
19.09.24

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- Paul Ramsay Foundation Health4Life Initiative Postgraduate Research Scholarship
- Research Training Program (RTP) Fee offset (domestic Australia higher degree by research student)

Author attribution statement

This thesis contains six chapters and four publications. One paper is published in the Maternal & Child Nutrition (Chapter 4). Two publications (Chapter 3 and 5) are currently under review with the Australian and New Zealand Journal of Public Health and Public Health Nutrition, respectively. On all publications, I am the corresponding and lead author.

The author attribution for each chapter is detailed below, using initials: Bridie Osman (BO), Matthew Sunderland (MS), Maree Teesson (MT), Felice Jacka (FJ), Louise Thornton (LT), Katrina E Champion (KEC), Tracy Burrows (TB), Emily Hunter (EH), Nicola C Newton (NCN), Lauren A Gardner (LAG), Wolfgang Marx (WM), Rachel Visontay (RV), Emma Devine (EKD), Siobhon O' Dean (SO), Isabelle Lynch (IL), Karis Fox (KF), Kelly McLeod (KM).

Chapter 2: BO led the development of this paper. BO, MS, MT, FJ, WM, and LT designed the study protocol. BO completed database searches based on guidance from a research librarian at The University of Sydney. Title and abstract screening were conducted by BO, and full-text articles were screened by BO, with 10% double screened by EH & KM. Data extraction and risk of bias assessments were conducted by BO, EH and IL and 80% were checked by BO and IL. BO ran the statistical analysis under the guidance of MS, and BO and MS interpreted the results. BO wrote the initial manuscript; all authors reviewed the manuscript and approved the final version. Acknowledgments are also given to non-authors: IL, KF, KM for contributing during volunteer placements to data screening, extraction, and supplementary file preparation for this study.

Chapter 3: BO led the development of this paper. MS, LT, FJ, MT were involved in conceptualization. KEC and NCN secured funding and KEC led the development of the overall Health4Life RCT. LAG and BO were responsible for ethics. BO was the primary lead in recruitment and data collection for this study and was responsible for the inclusion of measures to assess non-communicable disease and developmental conditions. Data were directly accessed and verified by BO and MS, who developed the statistical methodology, with further input from TS, SO and EKD. BO conducted formal analysis with support from MS and EKD. BO wrote the original manuscript, and all authors were involved in the review.

Chapter 4: BO led the development of this paper. BO, LT, TB, MS, LG, KC and MT were involved in conceptualization. KEC and NCN secured funding and KEC led the development of the overall Health4Life RCT with oversight from NCN. KC, LAG and BO were responsible for ethics. BO was the primary lead in recruitment and data collection for this study which SS & EH assisted with. BO ran the statistical analysis and interpretation under the guidance of MS. MT & NCN oversaw project management. BO wrote the original manuscript, and all authors were involved in the review.

Chapter 5: BO led the development of this paper. BO led and MS, LT and MT contributed to the formulation of the research question and design of this study. BO was responsible for the ethics applications and governance with review from MS, FJ, LT and MT. BO built the study protocol and supporting documents and was responsible for recruitment. TB supplied the AES-FFQ for dietary intake examination. BO was responsible for ensuring LT and EH completed training required to attend data collection days. BO was responsible for participant data collection with assistance from LT and EH. BO conducted the analysis of data with assistance from SO & MT. BO wrote the original manuscript and all authors reviewed the article.

I confirm that all of the work in this thesis is my own, and any contribution made by others has been explicitly acknowledged.

Signature placeholder

Bridie Osman, 18th September 2024

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

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18th September 2024

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- I hope nothing more than to have made you all proud.

Table of Contents

List of abbreviations

SES – Socio-economic status

SCI – Systematic chronic inflammation

DBS – Dried blood spot

UPFs – Ultra-processed foods

IBS – Irritable bowel syndrome

ADHD – Attention deficit hyperactivity disorder

ADD – Attention deficit disorder

NAFLD – Non-alcoholic fatty liver disease

CVD – Cardiovascular disease

T2D – Type 2 diabetes

T1D - Type 1 diabetes

CRP – C-reactive protein

hsCRP – High sensitivity C-reactive protein

TNF-a – Tumor necrosis factor alpha

HPA – Hypothalamic-pituitary-adrenal axis

BMI – Body mass index

IL-6 – Interleukin-6

IL-b – Interleukin-b

SCFAs – Short chain fatty acids

MD – Mediterranean diet

AIHW - Australian Institute of Health and Welfare

BPA – Bisphenol

TMAO - Trimethylamine-N-oxide

AGEs - Advanced glycation end products

PUFAs - Omega-3 fatty acids

RCT – Randomised controlled trial

NR – Not reported

SD – Standard deviation

IQR – Interquartile range

JBI – The Joanna Briggs Institute of Prevalence Critical Appraisal Tool

WHO – World Health Organization

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO - International Prospective Register of Systematic Reviews

PICO - Population, interventions, comparators, and outcomes

IBD – Inflammatory bowel disease

MHBC - Multiple health behaviour change

NSW – New South Wales

WA – Western Australia

QLD – Queensland

CONSORT - Consolidated Standards of Reporting Trials

FAS-III - Family Affluence Scale-III

SSB – Sugar-sweetened beverages

PA – Physical activity

MVPA - Moderate-to-vigorous physical activity

SDQ - Strengths and difficulties questionnaire

PHQ - Patient health questionnaire

PROMIS-A - Patient-reported outcomes measurement information system for anxiety

IBS-SSS - IBS severity scale

CI – Confidence interval

OR – Odds ratio

AES-FFQ – Australian Eating Survey® food frequency questionnaire

FFQ – Food frequency questionnaire

FAS – Family affluence scale

SOPs – Standard operating procedures

STROBE-Nut - STrengthening the Reporting of OBservational studies in Epidemiology – Nutritional Epidemiology

ARFS - Australian recommended food score

NPAAC - The National Pathology Accreditation Advisory Council

Dissemination, funding and awards during candidature

Publications arising from this thesis

Published/Accepted

1. **Osman, B.,** Champion, K.E., Thornton, L., Burrows, T., Smout, S., Hunter, E., Sunderland, M., Teesson, M., Newton, N. C., & Gardner, L. A. (2024). Exploring the association between adolescent-perceived parental monitoring on dietary intake. *Maternal & Child Nutrition*, e13650. https://doi.org/10.1111/mcn.13650
2. **Osman, B.,** Teesson, M., Marx, W., Thornton, L., Jacka, F., Hunter, E., Visontay, R., Sunderland, M. (2023, March 30 - preprint). Elevated rates of systemic inflammation among adolescents pervade geography and time: A systematic review and meta-analysis of global mean C-reactive protein levels. *Open Science Framework* https://doi.org/10.31219/osf.io/ut584

Under review

3. **Osman, B.,** Sunderland, M., Devine, E., Thornton, L., Jacka, F., Teesson, M., Prevalence of non-communicable diseases and developmental conditions in 5014 Australian adolescents, and their correlations with diet, other lifestyle behaviors, and mental health. *Australian and New Zealand Journal of Public Health*
4. **Osman, B.,** Burrows, T., O'Dean, S., Sunderland, M., Jacka, F., Thornton, L., Teesson, M., C-reactive protein: associations with dietary intake in adolescents and feasibility of collection via dried blood spot in Australian schools. *Public Health Nutrition.*

Additional publications during my candidature

5. Battista, K., Smout, S., Patte, K.A., Gardner, L.A., Newton, N.C., **Osman, B**., Chapman, C., Leatherdale, S.T., Champion, K.E. Sociodemographic and lifestyle factors associated with adolescent mental ill-health: A decision tree analysis. *Prevention Science* (Under review).
6. Thornton, L., Corliss, C., Deen H., Teesson, M., Champion, K.E., Partridge, S.R., Heinsch, M., Spring, B., Gardner, L.A., Rickwood, D., Sunderland M., Newton, N., Zaman, S., Redfern, J., **Osman, B.,** Wilson, J., Watt, M., Kay-Lambkin, F. The Triple E Project: A factorial randomised controlled trial to enhance engagement with eHealth approaches to improve health risk behaviours among adolescents. *BMC Public Health.* **24**, 2697 (2024). https://doi.org/10.1186/s12889-024-20124-5.
7. O'Dean, S.*, Smout, S.*^, Sunderland, M., Slade, T., Gardner, L.A., Chapman, C., Thornton, L., **Osman, B.,** Hunter, E., Egan, L., Teesson, M.T., Newton, N.C., Champion, K.E. (2024),

Adolescent behavioural intentions: Secondary outcomes from a cluster randomised controlled trial of the Health4Life school-based lifestyle modification intervention. *Canadian Journal of Public Health*. *Joint first authors, (2024) https://doi.org/10.17269/s41997-024-00955-w.

8. O'Dean, S., Sunderland, M., Newton, N., Gardner, L., Teesson, M., Chapman, C., Thornton, L., Slade, T., Hides, L., McBride, N., Kay-Lambkin, F.J., Allsop, S.J., Lubans, D., Parmenter, B., Mills, K., Spring, B., **Osman, B.,** Ellem, R., Smout, S., McCann, K., Hunter, E., Catakovic, A. and Champion, K. (2024), The Health4Life e-health intervention for modifying lifestyle risk behaviours of adolescents: secondary outcomes of a cluster randomised controlled trial. *Medical Journal Australia*, 220: 417-424. https://doi.org/10.5694/mja2.52279
9. Champion, K. E., Newton, N. C., Gardner, L. A., Chapman, C., Thornton, L., Slade, T., Sunderland, M., Hides, L., McBride, N., O'Dean, S., Kay-Lambkin, F., Allsop, S., Lubans, D. R., Parmenter, B., Mills, K., Spring, B., **Osman, B**., Ellem, R., Smout, S., … Mewton, L. (2023). Health4Life eHealth intervention to modify multiple lifestyle risk behaviours among adolescent students in Australia: A cluster-randomised controlled trial. *The Lancet Digital Health,* 5(5), e276–e287.
10. Visontay, R., Mewton, L., Sunderland, M., Bell, S., Britton, A., **Osman, B.,** North, H., Mathew, N., Slade, T. A comprehensive evaluation of the longitudinal association between alcohol consumption and a measure of inflammation: Multiverse and vibration of effects analyses, *Drug and Alcohol Dependence,* Volume 247, 2023, 109886, ISSN 0376-8716, https://doi.org/10.1016/j.drugalcdep.2023.109886.
11. Smout, S., Gardner, L. A., Champion, K. E., **Osman, B.,** Kihas, I., Thornton, L., Teesson, M., Newton, N. C., & Burrows, T. (2023). Prevalence and correlates of addictive eating behaviours in a large cohort of Australian adolescents. *Australian & New Zealand Journal of Psychiatry*, 000486742311652.
12. Leary, M., Pursey, K. M., Verdejo-Garcia, A., Smout, S., McBride, N., **Osman, B.,** Champion, K. E., Gardner, L. A., Jebeile, H., Kelly, E. V., Thornton, L., Teesson, M., & Burrows, T. L. (2022). Socio-Demographic, Self-Control, Bullying, Parenting, and Sleep as Proximal Factors Associated with Food Addiction among Adolescents. *Behavioral Sciences,* 12(12), 488.
13. Thornton, L., **Osman, B.,** Champion, K.E., Green, O., Wescott, A.B., Gardner, L.A., Steward, C., Visontay, R., Whife, J., Teesson, M., Parmenter, B., Birrell, B., Bryant, Z., Chapman, C., Lubans, D., Van de Ven, P., Torous, J., Sunderland, M., and Slade, T (2022). How well can your smartphone measure what you eat, drink and smoke? A systematic review

of the measurement properties of smartphone approaches to assess diet, alcohol use and tobacco use, *JMIR*.

14. Gardner LA, Debenham J, Newton NC, Chapman C, Wylie FE, **Osman B**, Teesson M, Champion KE. Lifestyle risk behaviours among adolescents: a two-year longitudinal study of the impact of the COVID-19 pandemic. *BMJ Open*. 2022 Jun 1;12(6):e060309. doi: 10.1136/bmjopen-2021-060309. PMID: 35649588; PMCID: PMC9170793.
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16. Thornton L, Brown HM, **Osman B,** Stewart C, Whife J, Champion KE, Gardner LA, McBride N, Allsop S, Spring B, and Teesson M. Factors associated with adolescents' engagement with a Healthy Lifestyles app. *Procedia Computer Science*. 206, C (2022), 56–67. https://doi.org/10.1016/j.procs.2022.09.085
17. Leary M, Pursey KM, Verdejo-Garcia A, Smout S, McBride N, **Osman B**, Champion KE, Gardner LA, Jebeile H, Kelly EV, Thornton L, Teesson M, Burrows TL. Socio-Demographic, Self-Control, Bullying, Parenting, and Sleep as Proximal Factors Associated with Food Addiction among Adolescents. Behav Sci (Basel). 2022 Dec 1;12(12):488. doi: 10.3390/bs12120488. PMID: 36546971; PMCID: PMC9774808.
18. Thornton, L., Gardner, L.A., **Osman, B.,** Green, O., Champion, K.E., Bryant, Z., Teesson, M., Kay-Lambkin, F., The Health4Life Team and Chapman, C (2021). A multiple health behaviour change, self-monitoring, mobile app for adolescents: Development of the Health4Life app. *JMIR mHealth and uHealth.*

Presentations arising from this thesis

National

1. **Osman, B.,** Burrows, T., O'Dean, S., Sunderland, M., Jacka, F., Thornton, L., Teesson, M., C-reactive protein: associations with dietary intake in adolescents and feasibility of collection via dried blood spot in Australian schools. *Oral presentation at The Australasian Society of Behavioural Medicine.* Gold Coast, Australia, February 2025 (accepted).
2. **Osman, B.,** Burrows, T., O'Dean, S., Sunderland, M., Jacka, F., Thornton, L., Teesson, M., Feasibility and pilot study: Associations between dietary intake, mental health, and

inflammation in Australian adolescents. *Poster presentation at Society for Mental Health Research.* Sydney, Australia, November 2024 (accepted).

3. **Osman, B**., Teesson, M., Marx, W., Thornton, L., Jacka, F., Hunter, E., Visontay, R., Sunderland, M. Elevated rates of systemic inflammation among adolescents pervade geography and time: A systematic review and meta-analysis of global mean C-reactive protein levels. *Oral presentation at The Australian Society for Behavioural Health and Medicine.* Geelong, Australia, February 2023.
4. **Osman, B.,** Burrows, T., Champion, K., Hunter, E., Gardner, L., Smout, S., Thornton, L., Sunderland, M., Are adolescent-perceived parental control and monitoring associated with adolescent dietary intake? *Oral presentation at The Academy of Child and Adolescent Health, 'Gamechangers in Adolescent Health Conference', Sydney, Australia* April 2022
5. **Osman, B.,** Champion, K., Thornton, L., The Health4life eHealth initiative, 24-month findings. *Invited oral presentation* at The Matilda Centre Seminar, Sydney, Australia, September 2022
6. **Osman, B**., Teesson, M., Thornton, L., Sunderland, M., Jacka, F. *Invited oral presentation* at The Food and Mood Centre, Deakin (virtual), Australia, June 2021

International

7. **Osman, B.,** Burrows, T., O'Dean, S., Sunderland, M., Jacka, F., Thornton, L., Teesson, M., C-reactive protein: associations with dietary intake in adolescents and feasibility of collection via dried blood spot in Australian schools. *Oral presentation at The European Health Psychological Society.* Cascais, Portugal, September 2024.
8. **Osman, B.,** Sunderland, M., Teesson, M., Devine, E., Jacka, F., Moreno, L., Thornton, L. Prevalence of medical conditions and associations with diet, other lifestyle behaviours and mental health in 5,015 Australian adolescents. *Oral presentation at The Nutrition Society Conference.* Liverpool, UK, July 2023.
9. **Osman, B.,** Sunderland, M., Jacka, F., Thornton, L., Teesson, M. Food for thought: Investigating adolescent nutrition, health behaviours, and mental health and their association with the onset of chronic inflammation. Orl presentation at the growth, exercise, nutrition and development (GENUD) research group. Zaragoza, Spain, May 2023.

Additional presentations arising during my candidature

National

10. **Osman, B.,** Champion, K., Gardner, L.A., O'Dean, S., Newton, N., Thornton, L., Chapman, C., Slade, T., McBride, N., Stewart, C., Hunter, E., Sunderland, M., Hides, L., Lubans, D., Allsop, S., Smout, S., and Teesson, M., Web-based intervention targeting multiple risk behaviours and mental health in Australian school students: Process evaluation of the Health4Life Initiative. *Poster presentation at Society for Mental Health Research.* Sydney, Australia, November 2024 (accepted).
11. Smout, S., Gardner, L. A., Champion, K. E., **Osman, B.,** Kihas, I., Thornton, L., Teesson, M., Newton, N., Burrows, T., Prevalence and correlates of addictive eating behaviours in a large cohort of Australian adolescents. Poster presentation at the Australasian Professional Society on Alcohol and other Drugs (APSAD) conference. October 9-12, 2022, Darwin, Northern Territory, Australia.
12. Barrett E, Champion K, Gardner L, Smout S, Rowe A-L, Osman B, McBride N, Mills K, Teesson M, Newton N. The prevalence and correlates of trauma among Australian school students in NSW, QLD and WA. Oral presentation at the Trauma Aware Schooling Conference. Brisbane (Sept 2022).
13. **Osman, B.,** Thornton, L., Champion, K.E., Green, O., Wescott, A.B., Gardner, L.A., Steward, C., Visontay, R., Whife, J., Teesson, M., Parmenter, B., Birrell, B., Bryant, Z., Chapman, C., Lubans, D., Van de Ven, P., Torous, J., Sunderland, M., and Slade, T., How well can your smartphone measure what you smoke? A systematic review of the measurement properties of smartphone approaches to assess tobacco use. Oral Presentation at The Society for Mental Health Research, Hobart, Australia, March 2022.
14. Gardner, L.A., Debenham, J., Newton, N.C., Wiley, F., **Osman, B.,** Teesson M., Champion, K.E. The Impact of the COVID-19 Pandemic on Six Key Lifestyle Risk Behaviours in Australian Adolescents. Oral Presentation at Australasian Society of Behavioural Health and Medicine 2022 Conference, Virtual, Australia, February 2-4 2022.
15. Smout, S., Gardner, L. A., **Osman, B**., Burrows, T., Leary M. Food addiction, mental health and substance-use during a transition period: Data from 6,700 Australian 12/13-year-olds. *Oral presentation, the World Congress of Epidemiology,* Melbourne, Australia, September 3-6 2021.
16. **Osman, B.,** Champion, K.E., Teesson, M., Gardner, L., Kay-Lambkin, F., Chapman, C., Thornton, L., Slade, T., Sunderland, M., Mills, K., Parmenter, B., Lubans, D., Hides, L., McBride, N., Allsop, S., Spring, B.J., McGowan, C., Bauer, J., Barrett, E., Stapinski, L., Mewton, L., Birrell, L., Quinn, C., Smout, S., Newton, N.C (2019). A cluster randomised controlled trial evaluating a school-based eHealth intervention to prevent six key risk factors for chronic disease among Australian adolescents: The Health4Life Study. Poster Presentation

at the Society of Mental Health Research 41st Annual Meeting, Melbourne, Australia, November 27-29 2019.

17. Champion, K. E., Teesson, M., Newton, N. C., Kay-Lambkin, F., Chapman, C., Thornton, L., Slade, T., Mills, K., Sunderland, M., Allsop, S., Hides, L., McBride, N., Bauer, J., Parmenter, B., Spring, B., Lubans, D., Gardner, L. A., McGowan, C., Cornell, S., Osman, B., Smout, S. & The Health4Life Team. An eHealth school-based intervention to reduce chronic disease risk factors: Study Protocol of the Health4Life Initiative. Oral Presentation at the Australasian Professional Society on Alcohol & other Drugs (APSAD), Hobart, Australia, November 10-13 2019.

International

18. Thornton, L., Osman, B., Stewart, C., Whife, J., Brown, H., Champion, K. E., Gardner, L.A., McBride, N., Allsop, S., Spring, B., & Teesson M. Factors associated with adolescents' engagement with a Healthy Lifestyles app. Oral Presentation at ISRII 2022 Conference, Pittsburgh, United States, 19-21 September 2022.
19. Gardner, L.A., Champion, K.E., Teesson, M., Gardner, L.A., Chapman, C., Thornton, L., Slade, T., Sunderland, M., Allsop, S., Hides, L., McBride, N., Kay-Lambkin, F., McCann, K., Parmenter, B., Lubans, D., Spring, **B, Osman.,** McCann, K., Smout, S., Ellem, R., Whife, J., Stewart, C & The Health4Life Team. A cluster randomised controlled trial of an eHealth intervention to prevent multiple lifestyle risk behaviours among Australian adolescents: Results from the Health4Life Study. Oral Presentation at Lisbon Addictions 2022 Conference, Lisbon, Portugal, 23-25 November 2022.
20. Champion, K.E., Newton, N., Kay-Lambton, F., Chapman, C., Thornton, L., Slade, T., Mills, K., Sunderland, M., Allsop, S., Hides, L., McBride, N., Parmenter, B., Spring, B.J., Lubans, D., Gardner, L., **Osman, B**., McCann, K., Smout, S., Ellem, R., Rakunathan, V., Whife, J., Stewart, C & H4L Team. An eHealth intervention to prevent multiple lifestyle risk factors among Australian adolescents: The Health4Life Initiative. *Oral presentation, The International Congress of Behaviour Medicine (ICBM)*, June 7-11 2021.

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Osman, B. (2023) Professional staff development fund to attend the Australasian Society of Behavioural Medicine annual conference, Adeliade $828

Osman, B. (2023) Professional staff development fund to complete a 1-day project management course $675

Osman, B. (2024) The University of Sydney Postgraduate Research Support Scheme $1000

Awards

Individual awards

2022 – Scholarship to attend Australian & New Zealand Mental Health Association's international mental health conference

2023 – Matilda Centre higher degree by research student research excellence award

Team awards

2023 – University of Sydney Faculty of Medicine and Health Makers and shapers awards – outstanding research (team award)

Leadership and advocacy activities arising during candidature

2022 - Macquarie PACE student – 72 hours mentorship

2021 – present: assist with supervising and training Health4Life research staff

2021 – present: The Society of Mental Health Research

2021 – present: The Academy of Child and Adolescent Health

2021 – 2023: The Nutrition Society, UK

2022 – present: The Australian Society for Behavioural Medicine

2024 – present: The European Health Psychology Society

2024 – present: Public health association Australia

Units of study and other training completed during candidature

Introduction to Biostatistics – One unit of study (master's level), University of Sydney, 2021

Managing Wellbeing and Recognising Vicarious Trauma – 1-day workshop (Blue knot foundation).

Grant development workshop – *2-day workshop,* The Matilda Centre, 2022

Food and Water Security – One unit of study (master's level), The University of Sydney, 2022

Grant development workshop – *2-day workshop,* The Matilda Centre, 2023

Grant development workshop – *2-day workshop,* The Matilda Centre, 2024

Chapter 1 - General introduction

"If someone wishes for good health, one must first ask oneself if he is ready to do away with the reasons for his illness. Only then is it possible to help him" Hippocrates – the 'father of medicine' 460BC-377BC.

Preface

Modifiable health behaviours, mental health and sociodemographic factors are integral determinants of health. These factors contribute substantially to the rise in chronic disease prevalence worldwide and pose a significant public health burden, yet they are poorly understood in adolescents. The increasing rates of mental disorders and non-communicable diseases observed over the past decade have emphasised the urgency in better understanding the onset of these conditions and who is at higher risk, with the aim of helping to assist in responding to the issue.

In adult populations, associations between modifiable health behaviours (e.g. poor nutritional intake, physical inactivity, increased screen time, unhealthy sleep, increased alcohol, tobacco intake - otherwise known as 'the Big 6' health behaviours), poor mental health, low socio-economic status (SES) and higher rates of chronic inflammation have been demonstrated. Chronic inflammation is an immune response, known to become pathologic and ultimately play an integral role in the aetiology of chronic disease. As such, chronic inflammation can ultimately be used to quantify the biological health impacts of lifestyles. Despite our growing understanding of chronic inflammation and the immune system, governed by the gut microbiome in adults, our knowledge of chronic inflammation in adolescence is disproportionately lacking. Limited research has been conducted examining associations between inflammation and modifiable health behaviours, mental health, and sociodemographic factors in adolescent populations (10-19 years old). This is despite the fact that adolescents experience high rates of specific non-communicable diseases and developmental conditions, such as asthma, irritable bowel syndrome (IBS), eczema, hay fever, and attention deficit hyperactivity disorder (ADHD) than older cohorts. The lack of understanding of inflammation at this life stage to be a missing resource within preventative public health.

Critically, the 'Big 6' health behaviours, parenting influences, mental health and socio-demographics also frequently co-occur and interact. Thus, furthering our understanding of the relationships between these factors and inflammation in adolescents has the potential to identify

possible modifiable targets for prevention, which could halt the trajectory of lifelong chronic disease.

This thesis makes a substantive contribution to epidemiological research by improving our current understanding of chronic inflammation and disease in adolescents. More specifically, through a series of four empirical chapters. this thesis:

- Systematically reviews and meta-analyses the global prevalence of systematic chronic inflammation in the global population of adolescents for the first time, in sub-groups at higher risk of inflammation, and determines changes in prevalence of chronic inflammation over time.
- Determines the prevalence of non-communicable diseases and developmental conditions, in the largest cohort of 14-15-year-old Australian adolescents to date, and their associations with common risk behaviours (poor dietary intake, sleep, physical inactivity, sedentary recreational screen time, alcohol and tobacco intake), mental health, SES and sex.
- Establishes associations between adolescent-perceived parental monitoring and dietary intake for the first time in Australia, in a national sample of 12-13-year-olds.
- Assesses the feasibility and examines associations between total diet quality, percentage energy from core and non-core food groups, and high sensitivity C-reactive protein (a marker of inflammation) collected via dried blood spot (DBS), in a sample of Australian 15–16-year-olds.

1.1 Research context

To set the context, existing research on common and emerging public health concerns in adolescents, specifically noncommunicable diseases, developmental conditions and poor mental health are first reviewed. Second, evidence for inflammation in the aetiology of these diseases and conditions, as well its implication for future chronic diseases is reviewed. Finally, potentially modifiable pro-and-anti-inflammatory factors and their current prevalence in adolescence is presented.

1.1.0 Prevalence of noncommunicable diseases, developmental conditions, and mental disorders, and their co-occurrence in adolescents

The need for greater understanding and more effective prevention of non-communicable diseases, developmental conditions and mental disorders in Australian adolescents is clearly

highlighted by their high prevalence in Australia and throughout the developed world[1]. Adolescence is a critical period where the onset of many noncommunicable diseases, developmental conditions and mental disorders can occur. The most prevalent noncommunicable diseases and developmental conditions in adolescents comprise atopic conditions such as asthma, eczema, food allergies and hay fever, as well as other conditions such as IBS, poor mental health and ADHD. Rates of these conditions have been rising worldwide[2] with particularly high rates reported in westernized countries[3].

Looking first to two of the most pervasive atopic conditions, asthma and eczema; asthma, in particular, has rapidly increased over recent decades and is currently the most common chronic disease in this age group, with 11.8% of Australian females and 9% of males aged 15-24-years-old living with asthma in 2021[1]. Asthma is also responsible for one of the highest hospitalization rates in adolescents[4]. Similarly, global eczema rates have increased over the past decade in upper income countries[5], with an average of 6% of children and adolescents currently having symptoms[5]. Quality of life for eczema sufferers often declines, generally worsening when 15 years or older, during and post-puberty[6]. Both conditions are heterogeneous inflammatory conditions, and whilst genetic susceptibility is a significant precursor to diagnoses, oxidative stress caused by environmental and behavioural factors is also acknowledged as a mechanism in their pathogenesis[7-9].

Outside of prevalent atopic conditions, another priority is IBS as onset is most common during adolescence[10, 11] and its symptomology can have a profound impact on daily life, including recurrent abdominal pain or cramping, gas or bloating and altered bowel movements. IBS is a functional gastrointestinal disorder, which in 2016, affected 23% of the child and adolescent population in the USA[12] and its incidence is expected to be on the rise, similar to trends observed in adult populations[13]. Children and adolescents experiencing IBS are likely to have impaired quality of life[14], experience psychological distress and social isolation[15, 16] and have reduced school attendance[17]. Roughly 30% of adolescent IBS patients can expect symptoms to proceed into adulthood[18, 19] impacting the physical, educational, and social lives of sufferers[20].

Mental health conditions such as depression and anxiety have increased in prevalence in recent years in adolescents with 1 in 7 (14%) aged 4-17 estimated to have experienced a mental illness in 2021[21]. In Australia the most common mental illnesses in adolescents are anxiety disorders

(7%) and major depressive disorder (3%)[21], which can persist over time with roughly 7% of 15-17-year-olds having a long-term mental health condition (2021)[22]. Similarly, rates of the developmental condition ADHD have also been increasing substantially recently, with current estimates of prevalence at 7% in the adolescent population [21].

Such chronic diseases commonly co-occur, and these comorbidities are associated with worse health outcomes and difficulties in clinical management. The most prevalent comorbidities are experienced in adolescents with obesity, being more likely to have IBS[23], 1.7 times more likely to have asthma, 26.1 times more likely to have non-alcoholic fatty liver disease, and 4.4 times more likely to have high blood pressure than their healthy weight counterparts[24]. In Australia alone, 30% of adolescents with a mental illness generally experience 2 or more mental illnesses in a 12-months period[21]. Poor mental and physical health are not solitary and commonly interact, both able to play a role in maintaining or exacerbating an inflammatory or disease state[25].

1.1.1 Global burden of disease

Experiencing non-communicable diseases, developmental conditions or mental disorders at a young age lays the foundations for more severe and high-burden chronic condition manifestation in later life. In adults, chronic diseases (e.g., cardiovascular disease, cancer, obesity, type 2 diabetes) are the number one cause of death [26-29], currently causing 3 in 5 deaths worldwide. The burden of both cancer and cardiovascular disease (CVD) has significantly increased over the past decade (11.5% increase for CVD and 14.7% for cancers in 2019)[30], imposing increasing physical, mental, social, and economic impacts worldwide. CVD alone costs Australia's economy $5.6 billion per year (2015-16)[31]. Chronic diseases significantly reduce an individual's likelihood of being able to work,[32] be independent and live a fulfilling life, resulting in a further cycle of physical and mental ill health[33]. Comorbidities are ubiquitous: 80% of Australians over the age of 65 reported having three or more chronic conditions [34-36], and across the whole Australian population 1 in 4 had two or more chronic diseases in 2014-15[37]. Critically, the World Health Organization predicts that depression and stress-related disorders will be the most widespread health problems by 2030, followed closely by inflammatory conditions such as allergies, autoimmune diseases and diseases associated with low-grade inflammation[38]. Due to its integral role in the aetiology of each of these diseases, chronic inflammation can offer important insights into these burgeoning public health issues.

1.1.2 Chronic inflammation in the aetiology of disease

The immune system is diverse and complex and recent scientific advances into its functioning have led to an improved understanding of the pathogenesis of chronic disease[39]. The most profound finding is that chronic disease is characterized by elevated inflammatory markers[40-43]. Inflammation is a process initiated by the immune system to attack invading bacteria or viruses, a crucial component of the body's natural immune response. Acute inflammation is a short-term, defensive response to an immediate injury or invading pathogen (e.g., an infection, swelling surrounding an injury or an allergic reaction) to help restore homeostasis. Less adaptive however, systemic low-grade chronic inflammation (SCI) occurs when inflammatory processes are regularly triggered by environmental and behavioural stressors, resulting in inflammatory substances continuously circulating the body.

The main process by which SCI occurs involves cells initially detecting harmful stimuli, triggering inflammatory pathways (adipocytes and macrophages), and releasing a cascade of inflammatory markers such as cytokines (i.e. interleukin-6 'IL-6', interleukin-b 'IL-b', tumor necrosis factor-a 'TNF-a'), inflammatory enzymes and proteins (C-reactive protein), which subsequently recruit inflammatory cells to target the harmful stimuli. SCI can also occur as a result of oxidative stress, caused by antioxidant defence systems which can also increase production of other inflammatory cytokines[44]. Furthermore, inflammatory cytokines are important coordinators of an immune response due to their pro- or anti-inflammatory properties. The major anti-inflammatory cytokines are interleukin (IL)-1 receptor antagonist, IL-4, IL-16, IL-10 and IL-13[45].
In practice C-reactive protein (CRP) is the most used measurement of inflammation[46], as a rapidly responding central component of the innate immune response.

1.1.2.1 Chronic inflammation as a precursor to disease

As a result of known immunological processes, cytokines, inflammatory proteins, enzymes and oxidative stress are biomarkers that can determine inflammatory levels and ultimately disease states [47-49]. Prolonged SCI can become pathologic, causing substances such as CRP to be perpetually circulating in the blood and coming into regular contact with vital organs, causing tissue damage[50] and further activating oxidative stress processes[51]. SCI is a precursor to many chronic diseases[52], including CVD[53], cancers[54], type 2 diabetes (T2D)[55], depression[56] and Alzheimer's Disease[57]. CRP itself is known to significantly contribute in

multiple ways to atherogenesis and plaque build-up[58], increasing the risk of cardiovascular incidents[59].

1.1.2.2 Chronic inflammation in adolescents

Systemic low-grade chronic inflammation can manifest asymptomatically, with the potential to be present for decades prior to chronic disease diagnosis. Meanwhile, SCI can have a detrimental biological effect on DNA, organ cells, and blood vessel cells, and contribute to neuron damage. The magnitude of this issue in adolescents is unclear due to the lack of evidence on the prevalence and impacts of chronic inflammation at this life stage. An increasing body of literature is emerging showing that adolescents and children are in fact experiencing low-grade inflammation at high rates, sometimes akin to the inflammatory levels experienced in adult populations[60-62].

A young person with SCI can experience symptoms such as abdominal and chest pain, fatigue with the potential to progress into longer term fatigue, joint pain and fever, stunted growth, anaemia, and body aches[63]. Given that, for example, approximately 30% of adolescents experience fatigue[64] and 30-50% of adolescents experience body aches[65], it is possible that SCI is more prevalent than known. SCI can be measured in adolescents by biomarker retrieval, with a CRP level of ≥2mg/L-10mg/L indicating low-grade inflammation in this age group. This could offer an early indication of general long-term health, as CRP levels in young people can independently predict adult CRP levels[66], alongside adulthood metabolic syndrome[67]. It is therefore vital to understand any modifiable risk factors for inflammation, as these offer an opportunity to prevent or improve an inflammatory or disease state.

1.2 Modifiable causes of inflammation

Modifiable risk factors for SCI, such as the Big 6 heath behaviours (dietary intake, physical activity, sleep, screen time, alcohol and tobacco use) and mental health provide an opportunity to better understand and improve the health trajectories of vulnerable populations such as adolescents. Furthermore, the Big 6 health behaviours and mental health are commonly interrelated, which is both an important epidemiological consideration and a preventive one, affording the opportunity for multiple health behaviour change frameworks to be adopted to

encourage the most efficient preventive programmes. Despite this, literature rarely examines health behaviours and mental health concurrently.

The current thesis will predominantly focus on the Big 6 modifiable health behaviours, mental health and their association with inflammation. This body of work will also explore two notable socio-demographic factors, sex and SES, as they have the potential to impact inflammation as well as moderate the Big 6 health behaviours. The prevalence of the Big 6 across three Australian states in 12.5-year-olds (2019) is displayed in Figure 1. These behaviours, mental health, sex and SES will be explored in more detail below.

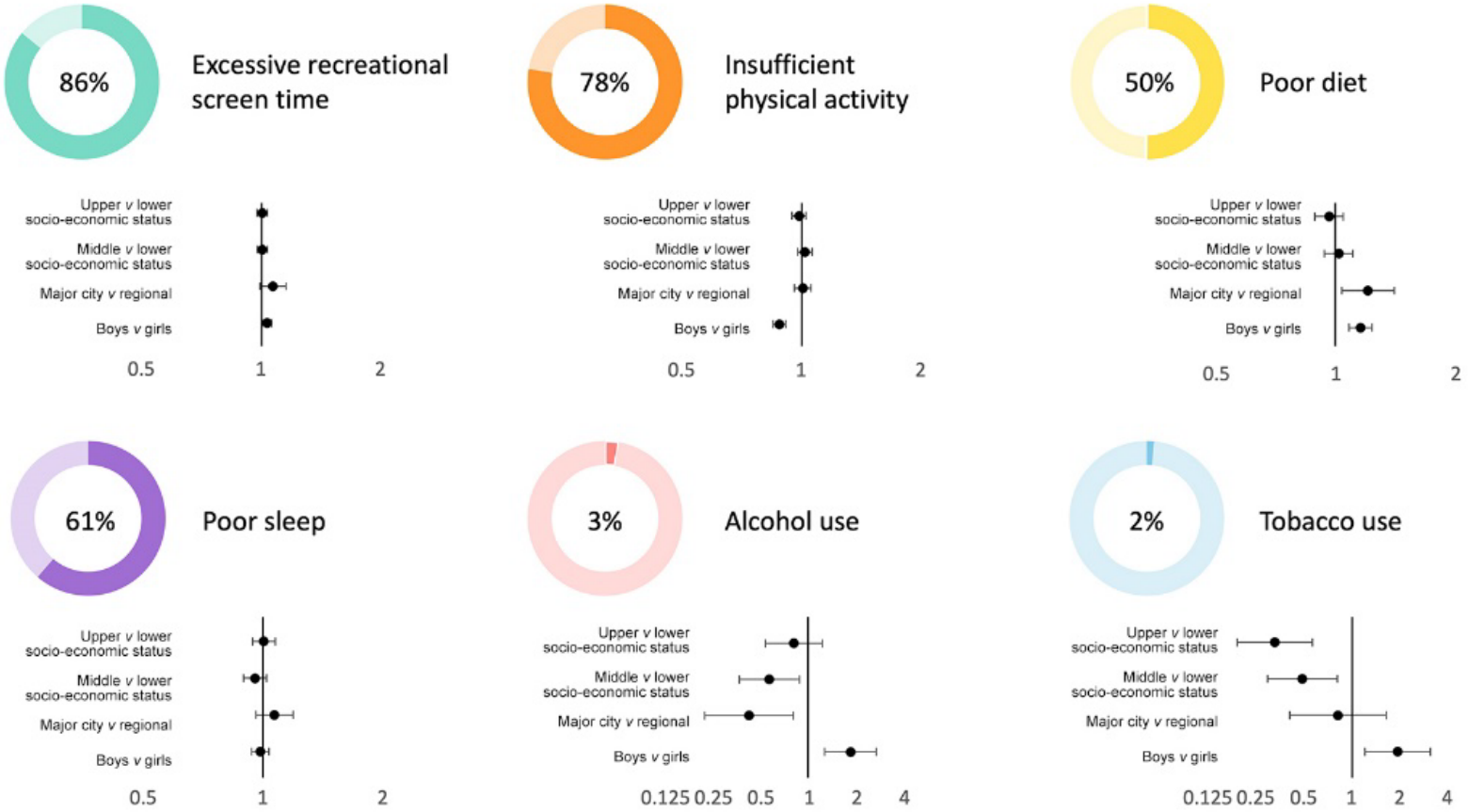


Figure 1 - Prevalence of the Big 6 modifiable health behaviours (alcohol intake, screen time, sleep, exercise, dietary intake and tobacco use) in 12-13-year-olds Australian adolescents 2019[68].

1.2.0 The Big 6 health behaviours

1.2.0.1 Nutritional intake

Nutritional intake is well recognised for its potential to cause inflammation [69, 70], via specific foods (e.g., ultra-processed foods [UPFs] and sugar-sweetened beverages [SSBs]) modulating key pathways that induce an inflammatory response[71] (Table 1). On-going consumption of these inflammation-inducing foods leads to stubborn SCI that can prove difficult to eradicate. Diet is so vital to health that the Global Burden of Disease Study ranks it as the 5th biggest contributor to disability-adjusted life years[72]. Table 1 provides a summary of key pro-inflammatory nutritional components and their current rates of consumption in adolescents.

Table 1- Consumption of nutritional intake components and their individual relationships with inflammation.

	Components	Foods	Inflammatory impacts	Consumption in adolescents
Macronutrients and minerals	Unhealthy fats	**Saturated fat**– some meats, fried foods, margarine spreads, pastries, pies, snacks. **Trans-fat**– naturally in some meats, milk. **Hydrogenated trans-fat**- industrially processed products, fried foods, margarine.	**Saturated fats** ↑ inflammation through toll-like receptor 4 within the brain's hypothalamus and increase risk of CVD[73-76]. **Trans fats increase**↑ inflammatory markers (hsCRP, IL6 and TNF-a)[77-79], by enabling an endoplasmic reticulum stress response and subsequent inflammatory cascades (notably to a greater extent than saturated fats)[80], and increases the risk of CVD[81, 82]. Overconsumption of **all unhealthy fats** can lead to unhealthy weight gain, posing a secondary independent risk for chronic inflammation, discussed in more detail later in this chapter.	Saturated fat consumption is highly prevalent in Australia, posing considerable risk. The latest national Australian Institute of Health and Welfare (AIHW) survey (2011-2012)[83] found fat and saturated fat accounted for 14% of overall energy intake (9–19-year-olds). The most recent global data in adolescents is from the USA (2017-20) showing saturated fats accounted for 11.9% of daily energy intake[84]. There is no recent trans-fat data. Large observational studies in children and adolescents support a direct association between higher plasma saturated fat levels and low-grade inflammation[85, 86].
	Sugar	**Sugars or high fructose corn syrup**[87-89] - candys or SSB. **Refined carbohydrates**[90-93] - white bread, pasta, cakes, pastries.	**Sugary foods** have a high glycaemic index - raising blood glucose significantly and rapidly[94]; increased glucose prompts increased insulin levels and subsequently ↑ a proinflammatory state[95], resulting in heightened CRP and IL-6[96-98]. Furthermore, increased intake of sugary items such as **SSB** are associated with unhealthy weight gain[99], an independent proinflammatory risk factor.	The AIHW data (2011-12)[83] found adolescents were consuming 12-13% of their average energy intake from added sugars. SSB popularity in adolescents has risen considerably in recent decades[68, 99-101]. There have been some reductions in added sugar consumption from 2001-2018 in the USA, due to replacements with artificial sweeteners (independently pro-inflammatory, explained in more detail later), however consumption is still above the dietary recommendations[102].
	Sodium	Table **salt**, deli, or cured meats, UPFs i.e. potato chips, fries and sauces.	**High sodium** intake increases adipose tissue mass[103]; impacts the innate immune system by ↑ tissue inflammation and exacerbates autoimmune disease[104, 105]. Some pro-inflammatory properties can be attributable to overarching diets associated with higher sodium (energy dense, SSB or FFQ)[106, 107]. Research has established positive associations between sodium intake and obesity independent of SSB and energy	The AIHW data (2011-12)[83] found adolescents were consuming on average 2,761mg of sodium a day, rising well above the adequate intake of 460-920mg per day. Sodium intake in adolescents is positively associated with both inflammation and adiposity at this age [110]. More current data is needed on the rates of adolescent sodium intake.

			intake[108, 109].	
Foods	UPFs	Hyperpalatable, nutrient poor products. Chemically modified substances extracted from foods, & additives (aspartame, cyclamate, sucralose, potassium or stevia) enhancing durability, taste, texture and appearance with minimal or no inclusion of a whole food[111]- ready meals, carbonated soft drinks, pre-packed snacks i.e. chips, bars, cakes, refined breakfast cereals[112].	Individual components of UPFs impact the gut and ↑ inflammation in various ways. **Nutritional profiles** are the key concern, generally high in inflammatory ↑ free sugars, trans and saturated fats and sodium, simultaneously low in anti-inflammatory properties[113]. **Additives and chemicals** are non-nutritive components of UPFs ↑inflammation[114]. **Sweeteners** contribute to an inflammatory cascade[115, 116] by their modulation of microbiota[117, 118], specifically intestinal microbiota, by enhancing and supporting proinflammatory bacteria and initiating the formation of endotoxins[115, 116], however data is varied and limited. Sweeteners are also associated with increased CVD risk[119]. **Emulsifiers** also facilitate an inflammatory cascade[120], contributing to intestinal dysbiosis by increasing intestinal permeability and promoting a proinflammatory state[118, 121]. Similarly, data is varied and limited[118, 122]. **Harmful chemicals** such as acrylamide are associated with inflammation[123]. Acrolein, caused by lipid oxidation has also been association with higher rates of hsCRP [124, 125]. Both chemicals are commonly present in many UPFs. **Phthalates and bisphenol (BPA)** are chemicals of growing concern because exposure (through their migration from food packaging onto consumed UPFs) increases the production of inflammatory cytokines, IL-1, IL-6 and TNF-1[126-129]. There are also correlations between phthalates and systematic markers of oxidative stress from urinary samples in adults[130, 131]. Both substances are classified as endocrine disruptors and it is through this endocrine disruption that an inflammatory response is thought to be triggered[132], linking them directly to the development of CVD, diabetes, and obesity[133, 134]. **The altered physical properties of processed food products**	Currently UPFs are in abundance, involving a wide range of ready to eat products. The percentage of dietary energy consumed from UPFs in an average Australian diet is 42%, and 58% in the USA, compared to 10% and 25% in Italy and South Korea[142]. The AIHW data (2011-12) found adolescent UPF intake was higher than UPF intake from any other age bracket accounting for 41% of daily energy intake. There has been an influx in usage of sweeteners in UPFs, particularly non-caloric ones[119] to reduce added sugar intake, however these pose their own threat to health. Minimal research has been conducted on phthalate consumption in adolescents however one such study conducted on Western-European adolescents found that those with detectable exposure to phthalates through urinary samples had significant associations with diagnoses of asthma[143]. In fact, many studies have found that both phthalates and BPA substances are present in the urine of people with high UPF consumption[113, 129, 144, 145]. In adolescents there is a clear relationship between increased consumption of UPFs and increased body fat being an independent risk factor for inflammation (covered in more detail later in this chapter)[146, 147].

			as a whole can result in a higher glycaemic load and reduced gut-brain satiety signalling, resulting in overconsumption[135]. Multiple meta-analyses have found direct associations between UPF intake and chronic disease incidence in adults[136-141].	
	Meats	**Animal meat products** - particularly processed and red meats[148-150], including smoked meat, sausages or beef[151].	Different meat sources impact the body in various ways due to distinct micro/macro nutrient profiles, and chemical and physical structures. High meat consumption is significantly associated with an increased risk of diseases such as colorectal cancer and CVD[152, 153]. **Red meat's** proinflammatory properties are multifaceted. Firstly, they are higher in saturated fat and sodium than other meat sources, resulting in ↑ inflammation. They contain and induce production of harmful toxins when consumed, alongside sulphates, haem iron and overarching alterations of the gut microbiota including generation of Trimethylamine-N-oxide (TMAO), each of which contributes to ↑ inflammatory response[152]. Elevated levels of TMAO specifically have further been linked with atherosclerosis, congestive heart failure and cardiovascular mortality[154]. **Smoked or processed meats** pose an extra independent proinflammatory risk. When meats are cooked or smoked in high temperatures, compounds called advanced glycation end products (AGEs) are formed[155]. Consumption increases accumulation of AGEs in the body resulting in oxidative stress and inflammation[156]. High levels of AGEs have been linked to diabetes, kidney failure, Alzheimer's Disease, premature aging and CVD[157]. **White meat** such as chicken also causes generation of TMAO in the gut microbiota however correlations are weaker, partly due to lower content of saturated fats and its ability to help maintain gut homeostasis by increasing lactobacillus or A.muciniphila levels[152].	The AIHW classify processed meats as a dietary risk factor contributing 1.4% to ill health in Australia[83]. Further, this data found adolescent males (14-18-year-olds) consumed the largest amounts of processed meats (0.6 serves per day) out of all age groups in Australia. Red meat consumption made up over 40% of Australian adolescent meat consumption and in general, adolescents consume 0.5 serves of other non-lean meat per day (i.e. higher fat mince)[83].

Whole diets	Western ised diet	From an epidemiological and public health perspective, evaluating **diets as a whole** allows for the exploration of their biobehavioural effect in large population cohorts, ultimately helping to inform public health nutrition messaging and even national dietary guidelines. The westernised diet is largely deemed pro-inflammatory, consisting of high proportions of calorie-dense and nutrient poor UPFs, and red and processed meats, whilst being low in fruits, vegetables, healthy fats and grains. This contrast with the Mediterranean or Nordic diets favoured for their anti-inflammatory properties, both explained further later in this chapter. When reviewing observational studies, individuals that adhere to a higher westernised diet tend to have increased intestinal permeability and subsequent inflammatory markers[122, 158]. Whilst those who adhered to a more Mediterranean diet[159, 160] display no such association.	High proportions of the world's population already consume the harmful westernised diet. Concerningly more countries are converging to consuming more westernised foods as they grow economically[161], which could encourage further detrimental physical and economic burdens globally.

1.2.0.2 Physical inactivity and sedentary recreational screen time

Globally, 81% of adolescents are deemed insufficiently physically active[162], based on the criteria from the WHO recommended guidelines of 60 minutes or more of daily, moderate-to-vigorous physical activity for adolescents[163]. Similarly, Figure 1 illustrates that in Australia 78% of adolescents are deemed insufficiently physically active and 86% partake in excessive sedentary recreational screen time. The AIHW estimates physical inactivity is responsible for 2.6% of the total disease burden in Australia (2017)[83].

It is well documented that physical inactivity is directly linked to the prevalence of chronic diseases such as cancer[164], T2D[165], dementia[166], depression[165] and CVD[167]. There are two distinct ways in which physical inactivity induces an inflammatory response: firstly, independent of obesity status, age, smoking and gender, muscle disuse can result in IL-6 resistance, which in turn leads to elevated circulating levels of IL-6 and CRP[168, 169]. Like CRP, IL-6 is a marker of inflammation and a cytokine that regulates bodily processes and in general circulating levels of IL-6 in the blood are damaging and associated with increased risk of chronic diseases[169].

The second most described inflammatory risk factor caused by physical inactivity is its ramifications for visceral fat accumulation and subsequent activation of a network of inflammatory pathways[170], explained in more depth within the 'obesity' section of this chapter. Ultimately, high rates of physical inactivity result in increased visceral fat, generally accompanied by fatigue, muscle wasting, and chronic inflammation. Concerningly, deconditioned muscles and inflammation further diminish cardiovascular performance and subsequently the ability to perform physical activity, leading to an unhealthy cycle of sedentarism[171].

Less scientific research has been conducted in adolescents surrounding physical inactivity and inflammation. One noteworthy meta-analysis identified that when obese children and adolescents increased their physical activity levels (without coinciding dietary interventions), their adiponectin, leptin and inflammatory markers (IL-6, CRP and TNF-a) improved[172]. Alongside the health impacts of sedentarism, recreational screen time promotes a scale of independently pro-inflammatory properties such as increased social media use (potentially moderated by self-esteem)[173], cyberbullying[174], body image dissatisfaction[175, 176], impacts on mental health[177] and sleep disruptions[178].

1.2.0.3 Unhealthy sleep

Global data suggests that unhealthy sleep patterns are prevalent in adolescents, with only 32%-86% meeting the respective sleep guidelines of their country[179]. In Australia, 61% of adolescents are getting poor sleep[68] (Figure 1). Unhealthy sleep patterns (too short-or -long sleep durations) are linked to chronic disease prevalence in later life[180-182], therefore it is unsurprising that there is a direct link between unhealthy sleep and elevated CRP[183-185]. Sleep is vital for human health and has many functions, with one of the main ones being its support of a neurally integrated immune system to prepare for injury or infectious threats. Current lifestyles are more susceptible to continuous 'social threats' which consequently can cause increased population sleep disturbances[186]. These alterations in sleep or circadian rhythms can cause inflammatory production or immune cell redistribution, dysregulating the overall immune system[186], processes that are governed by the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA)[186].

The relationship between poor sleep and low-grade inflammation in adolescents is yet to be clearly defined – the limited research conducted in adolescents has identified short sleep duration[187, 188] and greater variability of sleep duration as being significantly associated with higher CRP[189]. Further research found inflammatory associations with short sleep durations in younger adolescents but not older adolescents[189]. Furthermore, unlike in the adult literature[190], studies are yet to find a significant relationship between sleep quality and inflammation in adolescents[189]. These findings could suggest that sleep duration is most important as a younger adolescent, and as a person develops into late adolescence and adulthood, sleep quality becomes more important.

Socio-economic status (SES) and race also seem to be important moderators in the sleep-inflammatory relationship: whilst findings are limited, two studies established that adolescents from higher SES[189] or who are white[191] are more sensitive to the influence of inadequate sleep on elevated CRP levels compared to their peers. These relationships could be attributable to low-SES youth having higher CRP at baseline (described in the 'SES' section in this chapter), suggesting that physiological responses may be dampened by their extra stressors[192] or a ceiling effect (that already elevated levels have less room to be exacerbated by poor sleep)[189]. The adult literature also displays discrepancies, suggesting sleep-inflammatory relationships are moderated by covariates such as gender[193], disease state[194] or body mass index (BMI)[195].

In addition, the inflammatory-sleep relationship is considered bidirectional: those experiencing higher levels of inflammation have more fragmented sleep, rapid eye movement sleep or decreased sleep duration[196]. However, adolescent data supporting this bidirectional relationship is currently lacking. The sleep–inflammatory relationship can be further exacerbated by the consequences of poor sleep causing reduced physical activity, poorer dietary intake and worsened mood[197], each of which can contribute in their own way to increased inflammatory markers (see respective chapters).

1.2.0.4 Alcohol and tobacco

The AIHW estimates smoking contributes 9% of the total disease burden in Australia, with alcohol use contributing 4.6% (2017)[83]. As displayed in Figure 1, the prevalence of alcohol (3%) and tobacco use (2%) in 12-13-year-old Australians is still relatively low. Prevalence of alcohol and tobacco use in adolescents has generally been declining in most high-income countries since 1999, however alcohol's decline has stabilised in recent years (since 2015) and smoking is beginning to increase again [198-202]. Importantly, adolescence is a critical period during which individuals primarily experiment with alcohol or smoking for the first time[198-200]. Mechanistically, alcohol can initiate gut dysbiosis[203] and gut bacterial overgrowth[204], heightening the release of endotoxins which in turn activates immune cells, increasing inflammation[205]. There is a clear positive correlation between increased alcohol consumption and increased levels of inflammatory markers[206, 207], along with evidence of damage to the gut[208], which is the immune system regulator.

Tobacco smoking triggers oxidative stress through reactive oxygen species, causing DNA damage and initiating an inflammatory response[209]. Tobacco smoke also heightens exposure to endotoxins (lipopolysaccharides), one of the most prolific inflammatory molecules, resulting in a well-recognised relationship between tobacco smoke inhalation and inflammation[210, 211]. These detrimental effects can be burdensome even at a young age, with adolescents exposed to environmental tobacco smoke in the household being significantly more likely to be diagnosed with asthma[212]. Tobacco contains nicotine (also found in vapes or e-cigarettes), one of many harmful chemicals within cigarettes and vapes, which is similarly toxic and activates neutrophiles that initiate an inflammatory response[213]. The addictive nature of nicotine and alcohol, coupled with increased peer pressure and risk-taking behaviours during adolescence, creates heightened concern for inflammation caused by these behaviours in this age group[214].

However, as exposure to these two risk factors is generally higher in adulthood, there is disproportionately less research conducted in adolescents.

1.2.1 Overweight or obesity – a risk factor for The Big 6

Child and adolescent obesity is a considerable public health issue, currently deemed an epidemic by the World Health Organisation and known as 'globesity'[215, 216]. A recent global review of obesity found that among school age children and adolescents, obesity was more likely than thinness in 67% of girls from 133 countries and 63% of boys from 125 countries[217]. In Australia the AIHW estimates that being overweight or obese contributes 7% of total disease burden in Australia (2017). In 2011-12, one-third (30%) of Australian adolescents were overweight or obese[83], with this prevalence now expected to be higher. Overweight and obesity heightens risks of conditions such as asthma[218], T2D and depression[219] during adolescence.

Evidence supports the relationship between unhealthy weight gain or obesity and chronic inflammation, primarily due to the role of increased adiposity with all-cause mortality[220]. White adipose tissue such as visceral fat, subcutaneous fat, and bone marrow fat are made up of adipocytes (white fat cells). Adipocytes produce adipokines, which can be pro- (leptin and TNF-alpha) and anti-inflammatory (adiponectin) and are initiators of different metabolic and physiological signalling cascades. They are responsible for regulating fatty acid oxidation, glucose uptake and insulin signalling along with other metabolic and energy-producing processes[221]. Unhealthy weight gain (increased white fat cells) causes inflamed or dysfunctional adipocytes[222] and as a result heightens production of pro-inflammatory adipokines such as TNF-alpha, leptin, and IL-6[223, 224]. Moreover, anti-inflammatory cytokines such as adiponectin are reduced with excessive adipose tissue[223], together forming an optimum environment for systemic inflammation. Figure 2 illustrates the immune differences between lean and obese adipose tissue. The impact of white adipose tissue is so great that it is thought to be responsible for at least 40% of circulating IL-6 at rest, on average [170, 225].

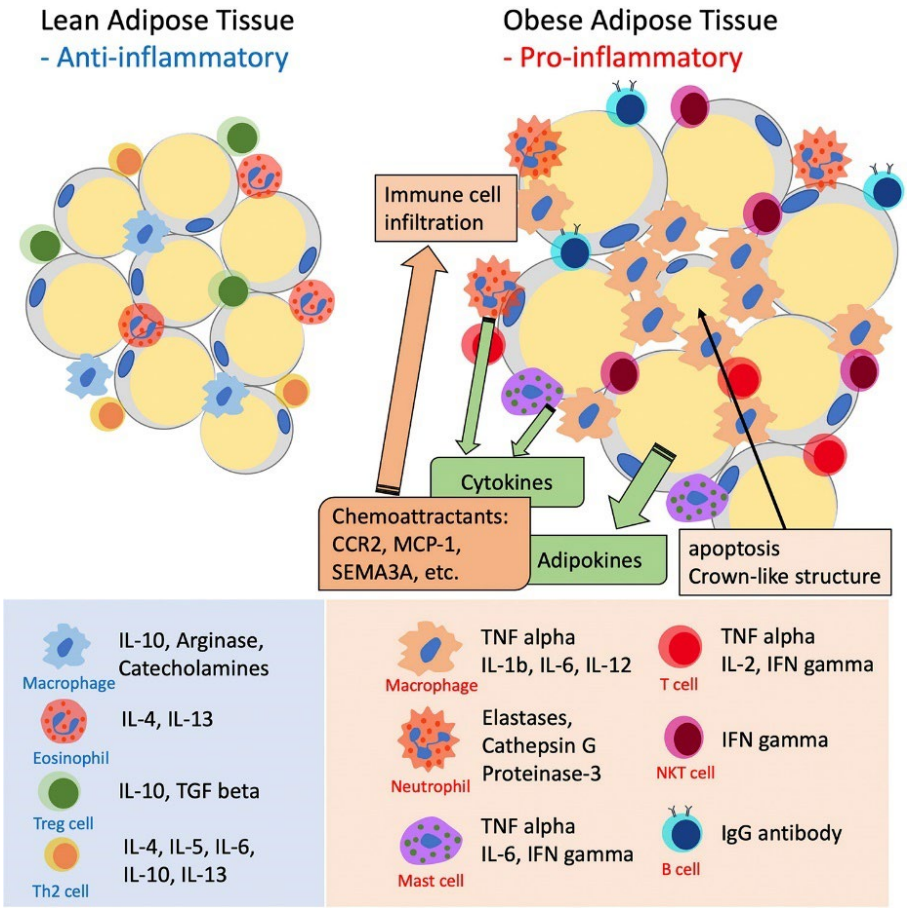


Figure 2 - The anti-inflammatory and pro-inflammatory immunological differences between lean and adipose tissue[226].

Whilst literature is lacking compared to adult research, it is established that in children with obesity or who are overweight, adiponectin levels are lower and leptin levels higher when compared to healthy weight children[227]. A recently published meta-analysis found that reducing excess body fat in children or adolescents who are overweight or obese significantly reduced inflammation through various improved biomarkers, including increased adiponectin (anti-inflammatory) and decreased leptin and TNF-Alpha (pro-inflammatory)[215].

1.2.2 Parental monitoring

A further modifiable component contributing to the Big 6 health behaviours in adolescents is how a child is parented. Parenting plays a particularly integral role in adolescent dietary intake, and as such is a potential contributor to the globesity epidemic and an indirect risk factor for chronic inflammation. One important element of food parenting practices is 'structure' (e.g., monitoring and modelling behaviours)[228], otherwise known as parental monitoring. Parental

monitoring refers to a parent's awareness of their child's whereabouts and knowledge of their activities and friendships[229, 230], along with the child's contribution and voluntary descriptions of their free time activities. It is well established that low levels of parental monitoring are associated with riskier health behaviours such as use of alcohol[231] and tobacco or drugs[232] in adolescents. However, in relation to examining parental monitoring influences on dietary intake, a substantial proportion of the literature only focuses on child cohorts[233, 234], a developmental stage when there is a lack of independence and children are still generally under constant caregiver supervision. The limited literature in adolescents suggests similar associations between high parental monitoring and healthier adolescent dietary intake[235-237], however there is a lack of data in large Australian cohorts as well as examining adolescent-perceived parental monitoring and associations with specific dietary variables.

A better understanding of parental monitoring of adolescents is crucial given the increased independence of behaviours and choices during this transition period. This is particularly true when compared with other parenting constructs such as parental control (placing limits and restrictions on behaviours and insistence on compliance)[238], which may be more necessary prior to adolescence and the development of functional decision-making skills.
Furthermore, the ability for parental monitoring to positively or negatively impact an adolescent's health behaviours, and the potential to modify this, makes it a potential behaviour target for consideration in future behaviour change research.

1.2.3 Mental health

Shifting away from the Big 6, approximately half of all mental disorders start between late adolescence and early adulthood and can predict future psychopathology in adulthood[239, 240]. The prevalence of mental conditions in adolescents is at a historic high: in Australia between 2012-15 and 2017-18 the proportion of young people reporting having a long-term mental or condition increased from 19% to 26%[241]. Further, poor mental health, particularly stress and depression, are related to chronic inflammation in adults[56, 69, 242-244], with evidence of similar relationships emerging in adolescents[245-247]. Mechanisms underpinning these independent and collaborative relationships are depicted in Figure 3.

Adolescent depression links to inflammation have been the most explored mental health concern to date, with multiple large meta-analyses and longitudinal studies finding positive associations

between depression and both concurrent and future inflammation[248, 249]. There is less literature available on the links between adolescent anxiety and inflammation. One study found significant associations between generalised anxiety disorder and inflammation in adolescents[250], however associations were attenuated when other health-related covariates, demographics or substance use were controlled for. One meta-analysis including nine studies on inflammatory associations with anxiety in adolescents found results were only approaching significance[251], and important limitations caused by study quality rendered these findings provisional. Considering the strong correlations between anxiety and inflammation in adult populations[252-254], the pathophysiological implications of stressor exposure (Figure 3) and the lack of research in adolescents, there is a clear justification for future research.

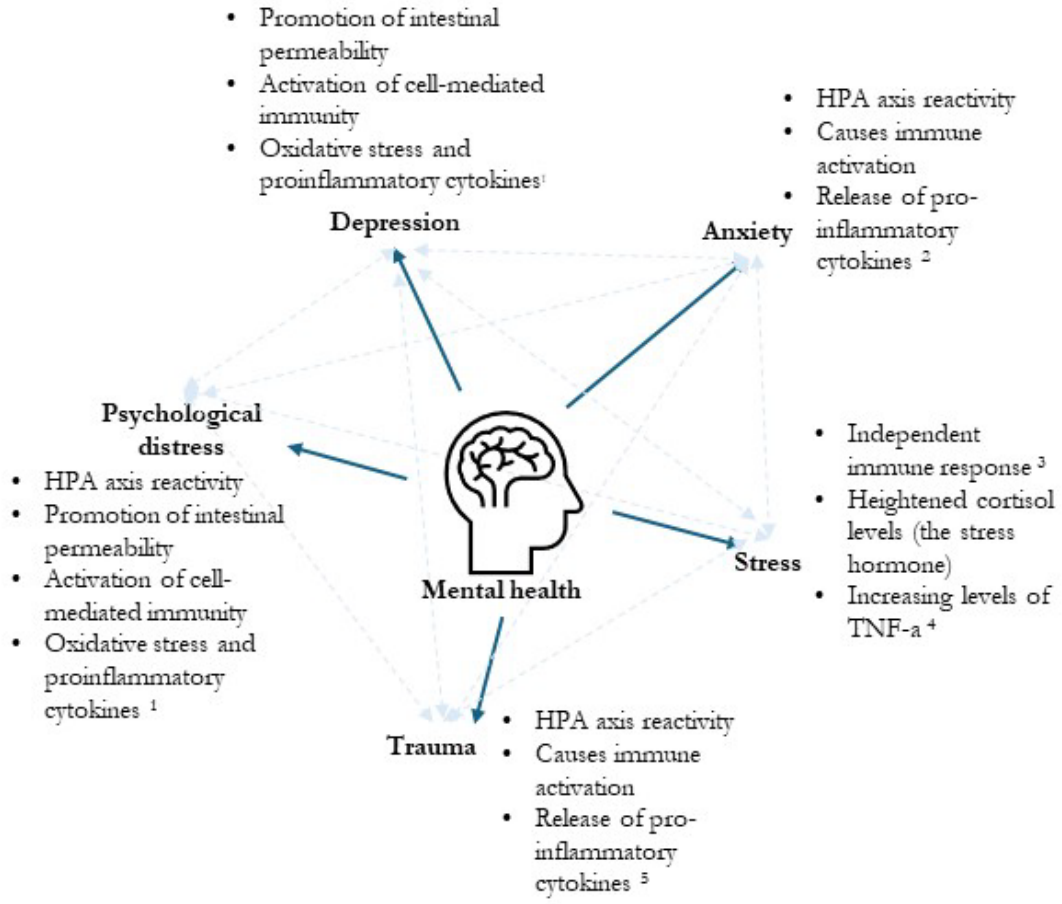


Figure 3 – Independent and collaborative immunological pathways causing an inflammatory response because of individual mental health conditions.

[1] Berk, M., et al., *So depression is an inflammatory disease, but where does the inflammation come from?* BMC Medicine, 2013. **11**(1): p. 200.
[2] Haroon, E., C.L. Raison, and A.H. Miller, *Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior.* Neuropsychopharmacology, 2012. **37**(1): p. 137-62
[3] Knight, E.L., et al., *Perceived stress is linked to heightened biomarkers of inflammation via diurnal cortisol in a national sample of adults.* Brain, Behavior, and Immunity, 2021. **93**: p. 206-213.
[4] Carvalho, K.M.B., et al., *Does the Mediterranean Diet Protect against Stress-Induced Inflammatory Activation in European Adolescents? The HELENA Study.* Nutrients, 2018. **10**(11).
[5] Baumeister, D., S.L. Lightman, and C.M. Pariante, *The Interface of Stress and the HPA Axis in Behavioural Phenotypes of Mental Illness*, in *Behavioral Neurobiology of Stress-related Disorders*, C.M. Pariante and M.D. Lapiz-Bluhm, Editors. 2014, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 13-24.

Similarly, a meta-analysis of 187 studies looking at associations between psychological distress in children, adolescents and adults found significant positive correlations with inflammation, although these were weak during childhood, stronger during adolescence and strongest during adulthood[255]. Finally, childhood trauma is significantly associated with lifelong heightened inflammatory levels and a susceptibility to a more sensitive inflammatory response to stressors[256].

Mental health, along with sleep, is somewhat unique amongst the other contributors to inflammation escribed in this thesis in that there is established evidence of its bidirectional relationship with inflammation[257]. Studies suggest inflammation itself is also a significant predictor of future mental health[258]. This is supported by four longitudinal studies within a meta-analysis finding that inflammation (CRP or IL-6) significantly predicted future depression[248]. Mechanistically, this can be explained by inflammatory cytokines in the brain impacting the HPA axis, hippocampal neurogenesis and neurotransmission whilst activating the sympathetic system[259]. This ultimately alters the brain's structure and function and leads to cognitive changes producing depressive symptoms[56]. Whilst research is limited, this relationship is thought to be so significant that studies suggest a therapeutic treatment for anxiety and fear-based disorders could be sought by targeting inflammation[260].

1.3 Socio-demographic associations with inflammation

1.3.0 Socio-economic status

Socio-economic status is based upon an individual's education, income, job and access to social and health resources. In Australia 24% of low-income households had children aged 0-14years-old (2017-18), and a further 11% of households with children had jobless families (2019)[261]. Low SES is increasingly being linked with elevated levels of inflammation[262-264], predisposing individuals to higher disease risk and potentially furthering health disparities. The cause of this remains ambiguous, however a body of research conducted in adults provides evidence for a link between lower parental education and inflammation[255], and an increased likelihood of adverse mental health[265], stress[266] and trauma[267, 268], each individually being associated with greater inflammation[269-271]. Limited research has focused on the adolescent population; however, findings are beginning to emerge depicting similar correlations predisposing young

people from low SES backgrounds to higher inflammation[272-274]. Further, low SES and ethnic minority youth are more likely to experience poverty[255, 275] or discrimination[192], both independent sources of elevated inflammation. Low SES cohorts are also more likely to be exposed to other risk factors such as environmental pollutants and chemical exposures (including phthalates), both of which are inflammatory inducing and known for heightening the risk of developing asthma in adolescents[143, 276, 277]Furthermore, health disparity research suggests that exposure to a stressor can exert stronger harmful impacts on those with more socio-cultural disadvantage[278], meaning that the same inflammatory risk factor could have more deleterious impacts on those from low SES compared to their counterparts. There is a substantial gap in the literature focusing on this relationship in young people, which is imperative in future research.

1.3.1 Sex

Hormonal differences between males and females play an integral role in an inflammatory response and underlying inflammatory levels. Research shows female (oestrogen), and male (androgens) hormones modulate elements of the immune system, where oestrogen generally acts as a stimulator of an immune response and androgens generally as a natural immunosuppressant[279-281]. This is one of the elements thought to contribute to the higher prevalence of autoimmune conditions in females[282] and an important consideration when understanding inflammatory health in the general population. Aside from hormonal differences, male and female adolescents are often parented differently specifically, males are expected to experience lower parental monitoring than females[283]. Literature suggests lower parental monitoring is associated with poorer health behaviours therefore these sex differences could result in a male's being predisposed to worse inflammation inducing health behaviours. Despite this, there is very limited research conducted on these associations in adolescents, a vital consideration due to the hormonal shift humans experience during puberty. This direct impact of hormones on inflammation indicates substantially more consideration is required during adolescence, where pre-pubertal males could be at higher risk of inflammation which could shift to post-puberty females being at higher risk.

1.4 Anti-inflammatory properties

When considering the impacts of lifestyles and socio-demographic factors on population health, it is equally important to consider their potential anti-inflammatory properties alongside their

harms. Anti-inflammatory substances fight to reduce inflammation and can help to restore a pro/anti-inflammatory equilibrium if a balanced, healthy lifestyle is met. It is valuable to recognise that whilst unhealthful lifestyles adopted in modern day exacerbate an inflammatory response, the natural processes of ageing also slowly reduce immune system functionality, subsequently increasing low-grade inflammation in the elderly[284], heightening the significance of anti-inflammatory behaviours throughout life. This area of research is continuing to emerge and the information we know about essential anti-inflammatory components are explored in more detail below.

1.4.0 Nutrition

The anti-inflammatory potential of a healthy diet is so significant that it is thought that at least six of the top 10 leading causes of death are preventable or at least clinically improved through dietary means[285]. The most impactful individual anti-inflammatory components of dietary intake are described in detail in Table 2. Factors contributing to healthy dietary intake in adolescents are the three main constructs of food parenting practices: coercive control (e.g. restriction, pressure to eat), structure (e.g. monitoring, modelling) and autonomy support (e.g. encouragement, education)[228]. Increased parental monitoring, referring to open channels of communication, child's contribution in decision making and parents awareness of but not control over decisions, in particular is expected to have the most favourable outcomes on an adolescents dietary intake[286].

Table 2 – Nutritional intake components and their individual anti-inflammatory relationship.

	Components	Foods	Anti-inflammatory impacts	Consumption in adolescents
Macro/micronutrients and minerals	Fibre	Complex carbohydrates in plants, (soluble, insoluble and varying degrees of viscosity and fermentability). **Soluble fibres**-oats, seeds/nuts, legumes, vegetables etc., are the fermentable fibres. **Insoluble fibres**-wholegrains, root vegetables, beans.	Generally, **soluble fibres** are broken down into biproducts such as short chain fatty acids (SCFA) and result in increased bacterial diversity and improve the intestinal barrier (butyrate specifically)[287], increasing good bacteria in the gut microbiome and ↓ inflammation[288]. Furthermore, fibre's anti-inflammatory potential is attributed to healthy weight maintenance or weight loss by playing an important role in satiety, by impacting prebiotic fibres metabolised by gut microbiomes (decreases ghrelin and increases leptin)[289]. Studies found participants consuming a low vs high fibre diet only reached the same satiety levels when the low fibre diet reached 689kcal/day more than the high fibre diet[290]. Consuming varied fibrous foods regularly offers the opportunity for a diverse bacterial environment in the gut, strengthening overall immunity, correlating with ↓ inflammation and a reduction in many chronic diseases[291].	AIHW data (2011-12) found adolescents were consuming 4-5.5 portions of grains per day out of the recommended 7, with 75-95% of the adolescent population consuming below the recommended serves (depending on sex). As such, boys were generally consuming 80% of their adequate intake of fibre per day and girls at 88%. This inadequate fibre intake within the western adolescent diet poses a risk for gut health.
	Healthy fats	**Polyunsaturated fats** contain **omega 3**-oily fish, flax, chia seeds, walnuts, soybeans. **omega 6**-walnuts, tofu, eggs, safflower oil, hemp, sunflower seeds. **Monounsaturated fats** contain **omega 9** -olive oil, almonds, avocado or peanut oil, cashews[292, 293].	'Healthy fats' are essential for human health, both as an energy source and aiding healthy bodily functions. **Omega 6** and **3** are essential fatty acids and the optimum ratio of **omega-6/omega-3** consumption (4:1) is associated with decreased risk of many chronic diseases[294]. **Omega 6** is a primary source of energy for the body but can be detrimental if consumed in excess, such as in the western diet. **Omega 3's** have impressive anti-inflammatory properties[295] and are directly linked to reducing mental health conditions such as anxiety[295] or depression[296] and reduce the risk of chronic diseases such as rheumatoid arthritis[297] and other chronic diseases[298]. **Omega-3's** are also substrates for the production of lipid compounds that form the physical feedback signal to stop inflammation and initiate tissue repair[299].	Data on healthy fat consumption in adolescents is scarce, the most recent Australian data from the Raine study (2011) found adolescents were consuming one-third of the optimum consumption of health fats (omega-3 fatty acids or PUFAs) and exceeding the recommended amount of saturated fat by one-third[300]. Research has found that adolescents with higher intakes of PUFA/SFA ratio had a negative correlation with CRP[301]. Other adolescent literature is mainly limited to cross-sectional designs, predominantly within the context of a whole Mediterranean diet but show great promise for future research[302].

	Micron utrients	**Potassium**-bananas, cooked spinach. **Magnesium**-avocados, nuts. **Zinc-**tofu, legumes. **Phosphorus**-mushrooms, yogurt. **Niacin**-peanuts, wheat flour. **Vitamins C**-bell peppers, kiwi fruit. **D-**eggs, mushrooms. **B12**-eggs, almonds.	Micronutrients are constituent elements of a healthful diet. Whilst different micronutrients are processed, function and aid bodily systems in varying ways it is valuable to elucidate those that have the most anti-inflammatory properties. **Polyphenols, potassium, magnesium, zinc, phosphorus, niacin** and **vitamins C, D** and **B12** offer the most anti-inflammatory properties out of all micronutrients[113]. **Polyphenols** can directly ↓ inflammation and play a vital role in preventing or slowing the progression of chronic diseases such as diabetes, cancers, CVD, neurodegeneration and obesity[303, 304]. Many of these micronutrients supply the body with crucial antioxidants and become the first line of defence against disease.	Varied, balanced diets rich in fruits, vegetables, healthy fats, dairy and fish is needed to reach optimum micronutrient levels, likely unfeasible in Australian adolescents who are generally not meeting national dietary guidelines and consuming high rates UPFs and sugars[83]. The Raine study found adolescents (17-year-olds) were deficient in calcium, magnesium, folate, vitamin D and E[305], and further research found zinc and iron deficiencies in Australian adolescents[306]. Given micronutrients' anti-inflammatory properties and role in vital bodily functions, further public health efforts for understanding and improving balanced diets in adolescent is needed.
Foods	Vegetab les and fruits	**Vegetables**-leafy greens (lettuce, spinach), cruciferous (cabbage, cauliflower), marrow (pumpkin, zucchini), root (potato, sweet potato), plant stem (celery, asparagus), allium (onion, garlic), legumes (lentils, soybeans, chickpeas). **Fruits**, **herbs** and **spices.**	Firstly, **vegetables** and **fruits** are some of the primary sources of fibre within diets. Secondly, they are high in antioxidants which offer vital immune defences by neutralising oxidative stress and removing free radicals from the body. As such, antioxidants can reduce the deleterious effects of aging and poor health behaviours and have many neuro-protective effects, decreasing the risk of many chronic diseases[304]. Finally, **vegetables** and **fruits** contain a variety of the anti-inflammatory micronutrients previously discussed, notably contribution rich sources of polyphenols. **Herbs** and **spices** also offer a range of polyphenols, antioxidants and other healthful properties, contributing to overall health and promoting bodily functions. Turmeric is a powerful anti-inflammatory **spice**, alongside ginger, cinnamon and garlic. Consuming an abundance of different vegetables and fruits allows for the best opportunity of a variety of polyphenols, antioxidants, vitamins and fibre lending to the most gut bacteria diversity and therefor stronger immunity.	The AIHW data (2011-12) found adolescents were consuming on average 2 out of the 5 recommended portions of vegetables a day, and 1.5 out of the 2 recommended portions of fruit. The same data found an astonishing 100% of the adolescent population were below the recommended serves of vegetables and 66% for fruit[83]. The AIHW classify low vegetable intake as a dietary risk factor contributing 1.4% to ill health and fruit 2.0% in Australia [83].

	Fish	**Oily fish:** Salmon, sardines, tuna, bass, trout. **White fish:** Cod, haddock, plaice, pollock.	**Oily fish** are the most prominent example of the anti-inflammatory properties of healthy fat consumption. The impressive immunological profile of **oily fish** showcases a richness in omega-3 fatty acids (PUFAs), tryptophan, taurine, vitamin A, and melatonin each with anti-inflammatory properties[299, 307]. PUFAs have such strong links with reducing chronic diseases that one such study found improved outcomes to critically ill ICU patients when tube-fed continuous infusions of fish oil[299]. It's also important to acknowledge that the high protein content in fish lends itself to higher satiety, reducing the opportunity for overconsumption and therefore excess weight gain.	Adolescent PUFA consumption and associations with adolescent inflammation is mentioned in the 'healthy fats' section above. Average fish consumption in Australian adolescents is largely unknown, the AIHW data (2011-12) classified fish within a broader 'lean meat' variable (lean meat, poultry, eggs and plant base alternatives) and found on average adolescents were consuming between 1.2-1.7 serves per day of total lean meat, significantly below the recommended 2.5 serves per day.
Whole diets	Mediterranean diet (MD) and Nordic diet.	The **mediterranean diet (MD)** has become a focal point in public health nutrition due to its extensive anti-inflammatory properties. Generally, the **MD** is high in fruits, vegetables and legumes (fibre and vitamins), olive oil and fish (healthy fats) and low in red and processed meats and refined foods. After discussing the anti-inflammatory attributes of each of these **MD** constituents, it is unsurprising to find an abundance of observational and interventional studies showing ↓ inflammatory markers in those with a greater adherence to the **MD**[308]. As a result, research consistently shows an effective reduction on the risk of chronic diseases and overall mortality when adhering to the **MD**[309, 310], including robust longitudinal studies showing a 25% lower risk of developing CVD over 12 years[311], and 23% lower risk of premature death in comparison to those with lower adherence[312]. A recent meta-analysis including 23 RCTs of 'healthful' dietary patterns (**MD**, DASH, vegan, **Nordic**) found the **MD** was significantly more anti-inflammatory than the other dietary patterns[313]. Whilst most research has been conducted on the **MD**; the **Nordic** diet also shows great anti-inflammatory potential. The **Nordic** diet is similar to the **MD** being high in whole grains, olive oil, fish and low in saturated fats, red and processed meats. A review of both observational and interventional studies found ↓ inflammatory markers in almost all of those adhering to a healthy Nordic diet[314].		Rates of adolescent adherence to the Mediterranean diet worldwide vary significantly across and within countries. All studies included in a recent umbrella review[315] into the adherence to the MD in children and adolescents and associations with multiple outcomes found increased adherence had an inverse relationship with pro-inflammatory markers, a protective role in childhood asthma and positive associations with health-related quality of life, increased physical activity and decreased sedentary time. From a public health perspective, it is advantageous to determine and utilise healthy whole dietary patterns as this can simplify national nutritional messaging and adherence.

1.4.1 Other health behaviours and mental health

1.4.1.0 Sleep

Only 39% of the Australian adolescent population are expected to have healthy sleep patterns[68]. Healthy sleep duration and quality enhance immune system functioning, predominantly through the HPA axis and sympathetic nervous system[186]. Healthy sleep simultaneously accommodates a normal functioning HPA axis which in turn activates optimum levels of circulating cortisol, not only decreasing the production of inflammation[316] but also promoting an antiviral immune response[317]. Healthy sleep is so impactful to an immune response that studies have found treating sleep disorders can significantly reverse levels of inflammation[318]. Indeed, focusing on this sleep-immune regulation shows promise to redirect a misaligned inflammatory transcriptional programme, subsequently assisting in accommodating the social threats we perceive in modern society[186]. Despite this, there is a lack of research conducted on the anti-inflammatory influences of sleep within adolescents, where all previous research has been conducted in adults.

1.4.1.1 Physical activity

Unlike other health behaviours, exercise's relationship with the immune system is predominantly centred around its anti-inflammatory potential. The anti-inflammatory properties of exercise are multi-faceted, initiated by both the brain, muscles, adipose tissue and lymphoid organs, detailed in Figure 4. There are three prolific anti-inflammatory pathways. Firstly, exercise immediately initiates the release of anti-inflammatory cytokines[319] such as IL-6 (when released from active muscle tissue[320]), causing higher circulating levels of adiponectin and lower levels of circulating pro-inflammatory adipokines[168, 170]. Further cytokines and myokines offer longer-term exercise induced benefits (such as endothelial function and fat distribution) enabling ongoing indirect anti-inflammatory effects[321, 322].

Secondly, molecules that bond toll-like receptors are reduced in those who exercise, causing a downregulation of toll-like receptor-4[170] and inflammasomes[323], both of which initiate an inflammatory response. Alongside inflammation prevention, skeletal muscle can excrete proteins that counter-balance the adipokine-pro-inflammatory effects and therefore help restore homeostasis when the immune system is faced with external stressors[321, 324]. It is therefore unsurprising that the term 'exercise as medicine' has been adopted by some, as studies find exercise can ameliorate symptoms from many chronic diseases[325].

Finaly, exercise increases the capacity of skeletal muscle to oxidize fatty acids, through a process called lipolysis. Exercise-induced lipolysis utilises circulating free fatty acids to provide fuel for working muscles to accommodate contraction[326], both during a single exercise session or as a result of regular exercise[326]. The increased oxidation of free fatty acids result in decreased overall lipid storage inside cells, fat accumulation and cell lipotoxicity[327]. Indeed, the utilisation of free fatty acids from increased skeletal muscle capacity through regular exercise prevents excess adipose tissue and ameliorates changes in adipose tissue immune cell profiles that would otherwise signal pro-inflammatory pathways[168]. As such, young people who adhere to physical activity guidelines are significantly less likely to become overweight or obese[328], and a recent meta-analysis found that reducing body fat in children and adolescents with obesity significantly reduced inflammatory markers[215]. Outside of the adult literature, there is insufficient availability of scientific research on the anti-inflammatory or protective potential of physical activity in the adolescent population.

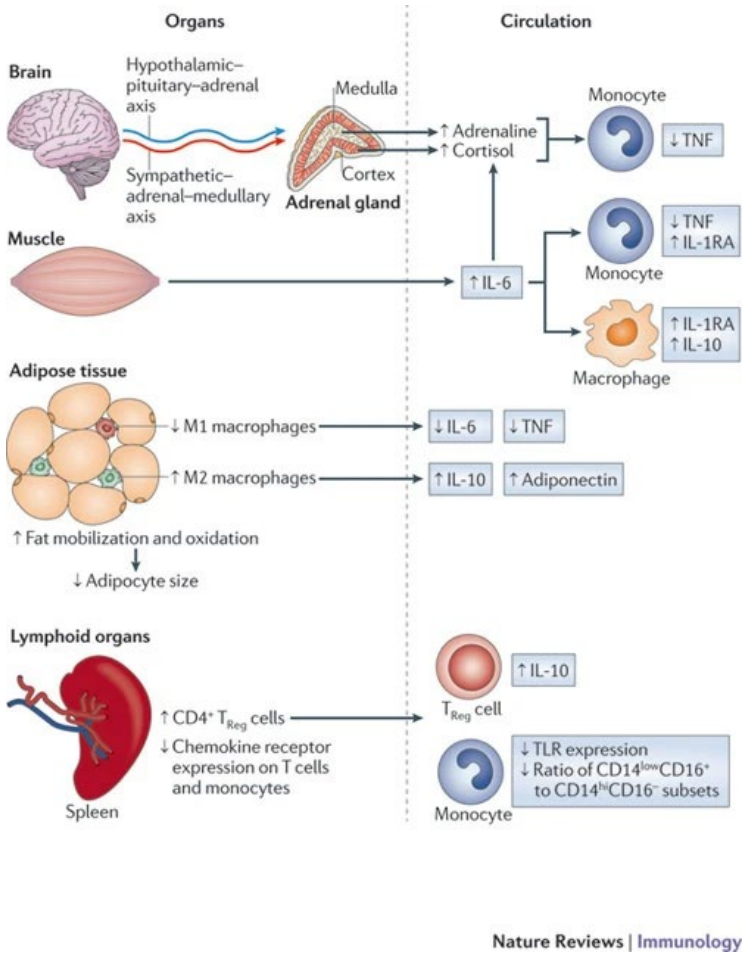


Figure 4 - Potential mechanisms contributing to the anti-inflammatory effects of exercise[170].

1.4.1.2 Mental health

Most literature focuses on the association between poor mental-health and inflammation. Evidence is emerging of the anti-inflammatory potential of complementary health interventions such as meditation and mindfulness. Mindfulness aims to work on processes to calm the central nervous system and improve well-being. The meditative process is argued to regulate stress response pathways by modulating the HPA axis and autonomic nervous system which then influences the production of proinflammatory processes, by inhibiting them when stressors are present[329]. This has translated to real world settings where meditation has been successful in modulating stress and stress hormones[330, 331], inflammatory disorders[332, 333] and pain management[334, 335]. One such RCT found that mindfulness-based therapy significantly reduced CRP levels in inflammatory bowel disease patients at a 6-month follow up compared to controls[336]. However, there is some indication that mindfulness, used in a preventative approach is not effective, from a large UK RCT finding no significant effect of within school mindfulness at the one year follow up[337]. Importantly, this study came with some significant limitations, such as low programme adherence and changes to the follow up protocol caused by the pandemic.

Notably, minimal good quality research has been conducted in adolescents. A recently updated large meta-analysis (66 RCTS) found mindfulness-based programmes improved symptoms of anxiety but not depression, or sustained benefits at follow up[338] (contrary to its original meta-analysis of 33 RCTs which also found depression improvements). The literature included in the review typically had low study quality and low adherence to the trials, and findings suggest that potentially benefits of mindfulness may only be sustained if the mindfulness practice itself is sustained, but ultimately more high-quality studies are needed. Incorporating meditative practices into a healthy lifestyle could be beneficial to equip the general population with regulative practices when inevitable physical and psychological stressors arise, helping to reduce the immunological impacts.

1.5 Multiple health behaviours

In real world settings it is important to acknowledge that these health behaviours and mental health operate in a complex and dynamic system, much of the time directly impacting each other. Worldwide, more than 80% of adolescents engage in two or more health risk behaviours and more than 35% engage in three or more[339]. For example, an estimated 81% of 11-17 year olds do not meet recommended physical activity levels worldwide[162], and one reason for not

partaking in physical activity is poor sleep, which can subsequently lead to poor dietary intake, each of which can contribute to poor mental health. Alongside these broader relationships, interrelation is present even at smaller molecular levels, for example, vitamin D receptors are expressed in key brain areas, and as such can overlap with the pathophysiology of depression, alongside playing a role in circadian rhythms and sleep[56]. Furthermore, poor health behaviours in adolescents commonly track into adulthood, increasing the risk for lifelong ill health[340]. The interrelationship between multiple health behaviours suggests the Big 6 and mental health should be considered in unison[341, 342], ultimately allowing for concurrent targeting of risk behaviours that offer an efficient solution for improving adolescent health and preventing future disease.

Despite the importance of understanding multiple health behaviours, most research simply examines one or two health behaviours at a given time and there is a lack of data from large adolescent cohorts, both cross-sectionally and longitudinally, and none specifically in Australia. To our knowledge only four studies have examined multiple health behaviours (five or more of the Big 6), including one study recently conducted in Korea[343], one multi-national study[344] (37 countries), and two from Canada[345, 346]. Whilst promising that the literature is advancing, these studies leave some significant gaps due to limitations in their design. Firstly, all studies categorised their health behaviours as either meeting/not meeting the national health guidelines or engaging in high/moderate/low levels of behaviours, resulting in a loss of sensitivity and nuance to smaller differences, particularly as most adolescents do not meet the national health guidelines[162, 347]. Secondly, only two studies accounted for sex and SES[343, 345], whilst the remaining studies only accounted for sex as a covariate. No studies examined their statistical interactions with multiple health behaviour associations, missing key determinants of health. Finally, whilst important health behaviour associations were found in these four studies, determinants of health, lifestyles and national health guidelines vary between countries and cultures indicating there is a significant gap in the literature from an Australian perspective.

1.6 Summary of knowledge gaps

The knowledge gaps identified in the sections above, and which this thesis aims to address, have been summarised in Table 3.

Table 3 - Summary of knowledge gaps.

1. Knowledge gap regarding current prevalence of immunological health (chronic inflammation, non-communicable diseases and developmental conditions) and behavioural health in adolescents
To date, no studies worldwide have examined the prevalence of low-grade inflammation in the general population of adolescents. This is an important gap, as there is a lack of understanding of biobehavioural health impacts in early life. • Limited research has explored sub-groups that are at higher risk of low-grade inflammation, needed to guide future prevention interventions and halt trajectories towards chronic disease. There is minimal data on the prevalence of common and emerging non-communicable diseases and developmental conditions in adolescents within Australia. • Some of the common atopic conditions have up-to-date data in Australia (i.e. asthma), however most other non-communicable disease and developmental condition prevalence data is lacking or dated. Most importantly, prevalences are generally explored individually and rarely in unison with other diseases or conditions, or health behaviours. There is insufficient up-to-date knowledge of the prevalence of multiple poor health behaviours (the Big 6) and mental health conditions in Australian adolescents. • Previous research is from outside of Australia, does not examine all of the Big 6 and mental health, and utilises categorical variables for mental health and health behaviours (mostly based on 'meeting' or 'not meeting' national guidelines), resulting in data lacking in sensitivity. • Parenting is key to adolescent behaviours. Parental monitoring may be a significant factor contributing to an adolescent's diet, yet there has been no research in Australia to date examining adolescent-perceived parental monitoring on dietary intake, needed to improve our understanding of the most effective parenting practices.
2. Knowledge gaps regarding health behaviour and mental health's associations with chronic inflammation, non-communicable diseases and developmental conditions in adolescents
To my knowledge, to date no studies have examined the associations between whole lifestyles (multiple health behaviours and mental health) and non-communicable diseases and developmental conditions in adolescents. This is a missed opportunity to guide future public health and prevention attempts. • Previous literature has examined one or two health behaviours or mental health variables generally with a singular non-communicable disease or developmental condition, largely in small, targeted cohorts. • Within the available literature some health behaviours are particularly lacking in evidence such as sleep, tobacco, and alcohol. • Larger population samples are required to enable a real-world view of the public health issues currently faced in Australia. Specific to nutritional intake, most previous research examining the associations between particular dietary variables and inflammation has been conducted in adults. Much of the minimal adolescent research only includes inflammation as a covariate with their main study focus on other variables. There is a key gap as to whether specific dietary variables have pro and anti-inflammatory effects on young people. Exploring if adolescents succumb to the same deleterious immunological impacts from dietary intake as adults will strengthen the argument to improve dietary intake during this life stage, and policies exposing adolescents to harmful foods.
3. Knowledge gaps regarding socio-demographic associations with chronic inflammation, noncommunicable disease and developmental conditions in adolescents

Currently there is scarce data examining the associations between SES and immunological health in adolescents, despite adult research distinguishing important relationships.

- The sleep-inflammatory relationship specifically is proven to be moderated by SES and many other inflammation inducing health behaviours can be worse in low SES cohorts (the Big 6, trauma and stress).

In adult literature it is known that sex hormones can have varying pro-and-anti-inflammatory affects, however this has not been explored in adolescents. It is therefore important to improve our understanding during a time when hormonal shifts occur to determine those at higher risk.

- Furthermore, it is known that parents generally monitor adolescent females more than males, a parenting factor expected to correlate with more favourable dietary outcomes. However, this has not been explored from an adolescent's perspective and in relation to specific dietary variables.

4. Knowledge gaps in the feasibility of adolescent biobehavioural research

To my knowledge, to date no studies have utilised dried blood spots (DBS) to retrieve hsCRP in adolescents outside of a medical setting in Australia.

- DBS are well used in countries such as the USA and UK, however there is limited usage in Australia and subsequent resources to support this, despite their ease of use and strong validity of results.

One reason for the lack of biobehavioural research in adolescents could be the difficulties (ethics, costs, resources) in collecting bio samples from this cohort. DBS feasibility exploration is needed to gauge its usefulness, affordability, non-invasiveness, and accessibility in retrieving biomarkers from adolescents in real world settings, broadening access to rural/remote or low SES communities.

1.7 Overview and aims of thesis

This thesis attempts to contribute knowledge to the existing gaps in literature discussed above and to investigate the relationship between adolescent nutrition, other health behaviours and mental health with the onset of chronic inflammation. The overarching purpose of this thesis is to contribute valuable preventative biobehavioural health insights about a vulnerable population, to advise future public health messaging and policies, and contribute to the prevention of lifelong disease and the physical, mental, and economic burdens that accompanies it.

1.7.0 Thesis structure

To achieve this purpose, this thesis is broken down into four empirical chapters (chapters 2-5) and the findings and implications are summarised in the discussion (chapter 6). A brief overview of each chapter is provided below.

Chapter two is the first study to critically analyse, via a systematic review and meta-analysis, the existing evidence of the prevalence of systemic chronic inflammation (SCI) via C-reactive protein levels (mg/L) in the general population of adolescents worldwide. Ninety-one studies with 37,347 participants were included in this meta-analysis, and it details SCI prevalence changes over time (past 10 years) as well as subgroup analyses of data based on specific demographics: body weight, sex, country-level SES and region. The aim of this review was to establish a clearer understanding of the prevalence of systemic chronic inflammation in the general population of adolescents, something unknown before now.

Chapter three is the first study in Australia to analyse the prevalence of common and emerging non-communicable diseases and developmental conditions in adolescents (i.e., IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D, Type 1 Diabetes [T1D], ADD/ADHD and autism/Aspergers), and their associations with multiple health behaviours (diet, physical activity, sleep, screen time, alcohol use and tobacco use), and mental health. I assisted in gathering self-report data from a representative cohort of 5014 Australian adolescents, across three states (New South Wales, Queensland and Western Australia) and used multi-variable logistic regressions to estimate the associations between variables. Interaction terms were used within regression models to assess whether any associations between common and emerging conditions and health behaviours or mental health differed depending on sex and SES. The aim of this study was to probes trajectories as well as current health behaviour and non-communicable disease and developmental condition information. Secondly, to assist future research efforts and public health messaging, by identifying potential covariates that should be prioritised to prevent the onset of chronic inflammatory diseases.

Chapter four is the first study in Australia to examine associations between adolescent-perceived parental monitoring and dietary intake. Specifically, this study explores four key dietary variables: intake of fruit, vegetables, SSB, and UPF. Further, this study is the first of its kind in controlling for key demographic factors linked with parental monitoring, including gender and SES, which is critical to informing tailored prevention and intervention approaches. The study included a large sample (N=6053) of 12-13-year-old adolescents across New South Wales, Western Australia and Queensland. The aim of these study was to better understand dietary associations with a key social determinant of health from an adolescent's perspective, during a transitional developmental phase to help inform future parenting interventions.

Chapter five is the first study to assess the feasibility of collecting inflammatory markers via dried blood spot collection in adolescents within a school setting. It presents associations between specific dietary variables, dietary grouping (core and non-core foods) and a global dietary score with the inflammatory marker hsCRP in a small sample of Australian adolescents (N=20). Correlations between dietary variables, BMI and hsCRP were explored and sample size calculations are presented to contribute to the currently limited literature. The aim of this study was to gather pilot data to guide future research of dietary associations with inflammatory markers in adolescents and to assess a non-burdensome, cost effective and valid tool to collect inflammatory markers in adolescents, to encourage future biobehavioural research in adolescents.

Chapter six contains the general discussion of the combined findings from chapters 1-5 of this thesis. Further, the implications of this thesis, suggestions for future directions and conclusions are discussed.

Chapter 2: Elevated rates of systemic inflammation among adolescents pervade geography and time: A systematic review and meta-analysis of global mean C-reactive protein levels.

Preface

This chapter describes the first study to examine the prevalence of systemic chronic inflammation (via C-reactive protein 'CRP') in the adolescent population worldwide, changes in CRP levels overtime and subgroups at heightened risk of systemic chronic inflammation. In Chapter 1 it was identified that whilst there is an increasing understanding of immunological experiences causing inflammation in adults, there is an unwavering need for a better understanding of inflammatory levels experienced during adolescence. Emerging literature indicates that adolescents are indeed experiencing low-grade inflammation however, the lack of data synthesis reporting clear mean levels of inflammation historically and at present, diminishes our ability to determine the current scale of this health issue, track population changes in the future and determine population means of CRP. This chapter addresses this gap by summarising observational data from the general population to determine the global estimate of CRP among adolescents, via a large meta-analysis. It also fills the gap by offering novel findings on changes in levels of CRP overtime (past 10 years) and identifies sub-groups that are at risk of higher inflammatory levels.

This chapter is available at:

1. **Osman, B**., Teesson, M., Marx, W., Thornton, L., Jacka, F., Hunter, E., Hunter, E., Visontay, R., Sunderland, M. (2023, March 30). Elevated rates of systemic inflammation among adolescents pervade geography and time: A systematic review and meta-analysis of global mean C-reactive protein levels. https://doi.org/10.31219/osf.io/ut584
2. **Osman, B.,** Teesson, M., Marx, W., Thornton, L., Jacka, F., Hunter, E., Visontay, R., Sunderland, M. (2023, March 30 - preprint). Elevated rates of systemic inflammation among adolescents pervade geography and time: A systematic review and meta-analysis of global mean C-reactive protein levels. *Open Science Framework*. https://doi.org/10.31219/osf.io/ut584

(Supplementary materials are available in Appendix 1)

2.0 Abstract

Introduction: Systemic chronic inflammation (SCI) is implicated in the aetiology of life-limiting diseases in later life, such as cancer, T2 diabetes and mental health disorders. However, global estimates of adolescent inflammation, indexed by biomarkers such as C-reactive protein (CRP), are unknown. We conducted the first study to establish the overall level of CRP in the general population of adolescents worldwide, determine trends in average CRP from 2011 to 2021 and identify subgroups with heightened levels of inflammation.

Methods: A systematic review and meta-analysis was conducted using Ovid MEDLINE, Embase (Elsevier), Cochrane Library (Wiley), and PsychINFO (EBS-COhost) databases. We included observational studies published between 2011-2021 with CRP data from adolescents in the general population. CRP concentrations were assessed by a random effects meta-analysis of log-transformed mean CRP levels. PROSPERO:CRD42021276398.

Results: Ninety-one studies (N=37,347) were included in the meta-analysis. The pooled mean CRP was 1.69mg/L (95%CI 1.43;1.98), with an I^2 of 99.8% between studies, indicating globally elevated levels of inflammation (≥1mg/L CRP) among adolescents. Importantly, we found consistently elevated inflammation among adolescents over the past 10 years. There was a significant mean difference (P<.001) between overweight/obese (2.63mg/L, 95%CI 1.42-1.98) and healthy-weight adolescents (0.79mg/L, 95%CI 0.47-1.32) and between predominantly-male studies (2.59mg/L, 95%CI 2.03-3.29) and predominantly-female studies (1.49mg/L, 95%CI 2.03-3.29, P=.002). Nearly all studies had low-moderate risk of bias.

Conclusion: Rates of inflammation are raised among adolescents, these heightened rates of SCI have existed for a least a decade, rendering this a major public health issue. We identify sub-groups with a heightened risk of raised inflammatory biomarkers, such as those who are overweight. Our findings highlight the need for tailored prevention programs and enhanced monitoring among adolescents at higher risk. By providing the first global reference level of mean CRP for adolescents our findings significantly advance our understanding of adolescent biological health, providing the impetus for future research.

2.1 Introduction

Inflammation is a process by which the immune system attacks invading bacteria or viruses. Systemic chronic inflammation (SCI) occurs when low-grade inflammation persists for a prolonged period, due to inflammatory processes being regularly triggered by environmental and behavioural stressors. C-reactive protein (CRP) is an acute-phase protein and a marker of inflammation produced in the liver as part of the innate immune system. CRP can become pathologic and can cause tissue damage, ultimately triggering further inflammatory processes.[348] SCI results in substances such as CRP being present in circulating blood, thus coming into constant contact with vital organs which can cause damaging effects.[348] In the long-term, SCI increases the risk of many chronic diseases, the most prevalent being cancers,[54] cardiovascular disease (CVD),[349] type 2 diabetes,[55] depression,[350] and Alzheimer's.[351] CVD is the leading cause of death in adults, accounting for 32% of all global deaths.[352] The prevalence of chronic diseases has increased over the last 10 years[353, 354] imposing physical, mental, social, and economic impacts worldwide.

Despite the well-established consequences of SCI in adults, little research has been conducted regarding the levels of inflammation in the adolescent population. Adolescence is a critical period where increased independence can influence health behaviour choices,[355] alongside the potential emergence of some inflammatory diseases (e.g., inflammatory bowel disease (IBD) and asthma) which can have detrimental physical and/or psychological impacts. Twenty percent of IBD diagnoses occur during adolescence[356] and can cause sufferers to miss school regularly,[357] experience poor physical, social, and psychological well-being.[358-360] Similarly, asthma is one of the most prevalent chronic conditions in adolescents.[4] Many disorders, such as IBD and asthma have shown a rise in incidence in young people in recent years.[4, 361, 362] In addition to the emergence of inflammatory diseases during adolescence, there is evidence to suggest that changes to lifestyle behaviours over the last decade may also contribute to increased problematic levels of inflammation among adolescents. Sedentary behaviour has increased substantially,[363] driven by increased electronic device use;[364] coinciding with a reduction in exercise with 16% of Australian 15-17year old's being sufficiently active in 2011-12 to 11% in 2017-18[365]. This is problematic as exercising initially triggers an inflammatory response followed by an induction of anti-inflammatory substances,[366] as a result, regular exercise downregulates systematic inflammation via homeostatic adaptation.[367] Likewise, there has

been a substantial increase in fast food availability and popularity in recent years, along with advances in accessibility due to the rise in food delivery services. The NHANES survey in the USA found that 12–19-year-olds in 2009-2010 consumed an average of 13.1% of their daily calorie intake from fast foods, increasing to an average of 18% in 2017-2018.[368] Ultra-processed food (UPF) sales also substantially increased in higher socio-economic status (SES) countries such as Australia, the USA, and the UK.[369]

Additionally, 61% of Australian adolescents are not meeting the guidelines for sleep.[370] Sleep alterations act as a moderator for inflammatory biomarkers, and acute sleep deprivation increases pro-inflammatory cytokines including CRP.[371] In the USA, 27.5% of adolescents were using e-cigarettes in 2019,[372] which can directly impact the gut barrier inducing an inflammatory response.[373] These health behaviours frequently co-occur, and one common consequence of multiple poor health behaviours is obesity, being a significant issue worldwide and seeing increasing prevalence over the past 10 years.[374, 375] Obesity is strongly associated with higher inflammation, specifically as inflammatory cytokines are saturated in fat cells and are directly involved in fat metabolism,[376] all of which could provide an explanation for the increases in disease prevalence.

Critically, specific groups of adolescents could be at higher risk than others. It is well established, for example, that adolescents living in areas of higher disadvantage or from minority groups are more likely to be overweight or obese[375, 377, 378] alongside the potential for a higher incidence of social stressors[379], trauma[380] and heavy alcohol consumption[381] and tobacco use.[370] Psychosocial stressors are known to stimulate pro-inflammatory cytokines[382] and early-life trauma can cause poor immune functioning throughout life. Within the Dunedin longitudinal birth cohort, those who experienced early life trauma were twice as likely to suffer from SCI in their adult life.[383] Adult females often have slightly higher inflammatory levels than males due to variance in sex-specific reproductive anatomy and hormones and their impact on inflammation.[384] Finally, diets in highly developed countries, such as the USA, UK, and Australia are generally higher in red and processed meats, refined carbohydrates, and UPFs, which increase susceptibility to inflammation[385, 386] compared to more anti-inflammatory traditional dietary patterns, such as the Mediterranean diet characterised by high intakes of vegetables, fruits, legumes, whole grains, and fish being associated with reduced CRP.[387, 388] Given that membership of these at-risk groups often does not change throughout the life course,

and that poor lifestyle choices in adolescence tend to follow a trajectory into adulthood,[389] there are both short and long-term health implications for vulnerable sub-groups.

Currently, we do not know the global mean estimate of SCI in adolescent populations worldwide, nor do we know about sub-groups at increased risk. Moreover, it is important to gain insight into any changes in inflammatory levels over the past 10 years, to lay foundations for future research to explore if specific health behaviour changes that have occurred during this time translate to increases in inflammation. This can assist in identifying future health burdens, and inform targeted prevention programmes for those at risk, government policies, and health care messaging. To our knowledge, there has been no review of the extent of SCI in adolescents. This systematic review and meta-analysis aimed to establish the overall mean level of inflammation in the general population of adolescents worldwide (represented by CRP levels), determine any changes in the mean level of CRP over the past 10 years, and identify sub-groups of the adolescent population experiencing higher or lower levels of SCI.

2.2 Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[390] This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (protocol number CRD42021276398). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
We used CRP as the marker of inflammation; CRP is commonly used as a key measure of inflammation in research as it is the most sensitive acute phase protein response marker available to date. This marker can be measured as either CRP or high-sensitivity CRP (hsCRP), the latter producing more accurate results due to increased detection sensitivity.[391, 392] Low-grade inflammation in adolescents has been classified using a CRP level of ≥1.0mg/L – 10mg/L, [393-395]

2.2.0 Search strategy

The search strategy was developed in consultation with a research librarian, and search terms were guided by the population, interventions, comparators, and outcomes (PICO) approach.[396] A literature search was conducted in September 2021 on four electronic databases; Ovid MEDLINE, Embase (Elsevier), Cochrane Library (Wiley), and PsychINFO

(EBS-COhost). The author (BO) worked with librarians to identify search terms and their synonyms using Medical Subject Headings (MeSH). The words used in the search strategy include terms relating to C-reactive protein, adolescents, and observational studies. The search strategy used for Ovid MEDLINE is supplied in the supplementary material (Appendix 1.1) and minor adaptations were made for other electronic databases.

2.2.1 Inclusion and exclusion criteria

This review considered studies conducted worldwide, in adolescents aged 10-19 (World Health Organisation's definition of adolescence)[397] from the general population. Cohorts qualified as being from the general population when they were not specifically recruited from a clinical population, but instead were recruited from a typical sample of the chosen population. Only studies that reported the mean and standard deviation (SD) or median and interquartile range (IQR) of the CRP or hsCRP (via any immunoassay measurement) of the cohort were included. Authors of studies that measured CRP but did not report these metrics were emailed to retrieve mean CRP levels and were given at least a month to respond. If there was no response during this time these studies were excluded for lack of data. Any studies that had collected data from 2011 onwards were included. Studies that started collecting data before 2011 and finished in 2011 or onwards were excluded on the basis that data collection began before the cut-off. Studies written in any language were included however studies were excluded if they were not able to be translated into English or were systematic reviews or grey literature.

2.2.2 Data extraction

Title and abstract screening were conducted by one reviewer (BO), and full-text articles were screened by one reviewer (BO), with 10% double screened (EH, KM). Disagreements were resolved by discussion. The extraction was conducted by one of three reviewers (BO, EH, IL) with 80% checked for accuracy by an alternative reviewer (BO, IL). The items extracted from each article included a year of publication, year of data collection, design of the study, country, city, sample size, age range, mean age, and variability measurement, % male, mean weight, height, BMI and waist circumference, country SES, further locality socio-demographic information, puberty scale, mean or median CRP and variability measurement, and whether hsCRP or CRP was measured. Fifty studies provided an exact year of data collection, or a range of years (in which case the midrange year was selected). In the remaining 41 studies, a year of data collection was estimated by taking 2 years off of the year of publication.

Where studies reported primary variables, CRP and age, as a median and IQR, these were transformed into a mean and SD using Luo et al's (2018)[398] calculations. Studies were categorised as either majority healthy weight (≥60%), majority overweight/obese (≥60%) or mixed-weights for anything in between, similarly majority male (≥60%), majority female (≥60%) or mixed-sex based on cohorts reported. Country SES levels were assigned to each study using World Bank data[399]. As regions have specific dietary trends, regional variables were given based on the country the study was conducted. The European region was split into 'European Mediterranean' if studies were conducted in countries that typically consume a Mediterranean diet due to its established anti-inflammatory properties (Croatia, Cyprus, Greece, Italy, Morocco, Portugal and Spain)[400], and the remaining being assigned 'European' region.
Where multiple studies used data from the same large epidemiologic datasets, data was extracted from the study with the largest cohort size. If two or more studies reported the same sample size, the study most recently published was chosen.

2.2.3 Measure of research quality

The Joanna Briggs Institute of Prevalence Critical Appraisal Tool (JBI)[401, 402] tool was used to assess the risk of bias in studies included in the review. One item, 'Was the sample size adequate?', was removed from the JBI, as it isn't possible to determine an appropriate sample size given there is a lack of knowledge of the expected global mean of SCI in the adolescent population. The risk of bias was conducted by one of three reviewers (BO, EH, IL) with 80% checked for accuracy by an alternative reviewer (BO, IL). The results from the review were given a score of either 1 for 'yes' or 0 for 'maybe' and 'no', and a total score out of eight was calculated for each study.

2.3.4 Statistical analysis

R software version 3.5.0 was used to run the analysis, using the 'meta' package. To find the extent of SCI, measured by CRP levels in the general population of adolescents, a random effects model of log-transformed mean CRP levels was estimated (Figure 6). We chose to use a random-effects model as the included studies recruited cohorts from the general population only. Assuming that these were random samples of the larger population will enable findings to be generalised beyond included studies. We looked at the extent of heterogeneity measured using the I^2 statistic, which describes the percentage of variability among effect estimates beyond that expected by chance. An I^2 value of ≥75% indicates high levels of heterogeneity.[403] Sub-group analysis was prospectively registered and conducted by sex, weight, country SES level, and

region. A further sub-sample analysis was conducted between studies collecting CRP and hsCRP to investigate potential heterogeneity.

Meta-regressions were used to evaluate any changes in CRP over time and any changes in CRP in relation to age. Furthermore, we conducted a meta-regression examining the association between CRP levels and weight controlling for sex. Finally, a sensitivity analysis was conducted to generate the pooled standardised mean difference between male and female CRP levels, within only the 17 studies that supplied separate male and female CRP data.

2.3 Results

The PRISMA flow chart (Figure 5) displays the study selection flow. After removing duplicates, 4577 studies remained. 114 studies screened were identified as reporting CRP in the general population of adolescents. Thirty studies used data from seven of the same large epidemiology datasets, from which one study from each dataset was chosen using methods previously outlined.

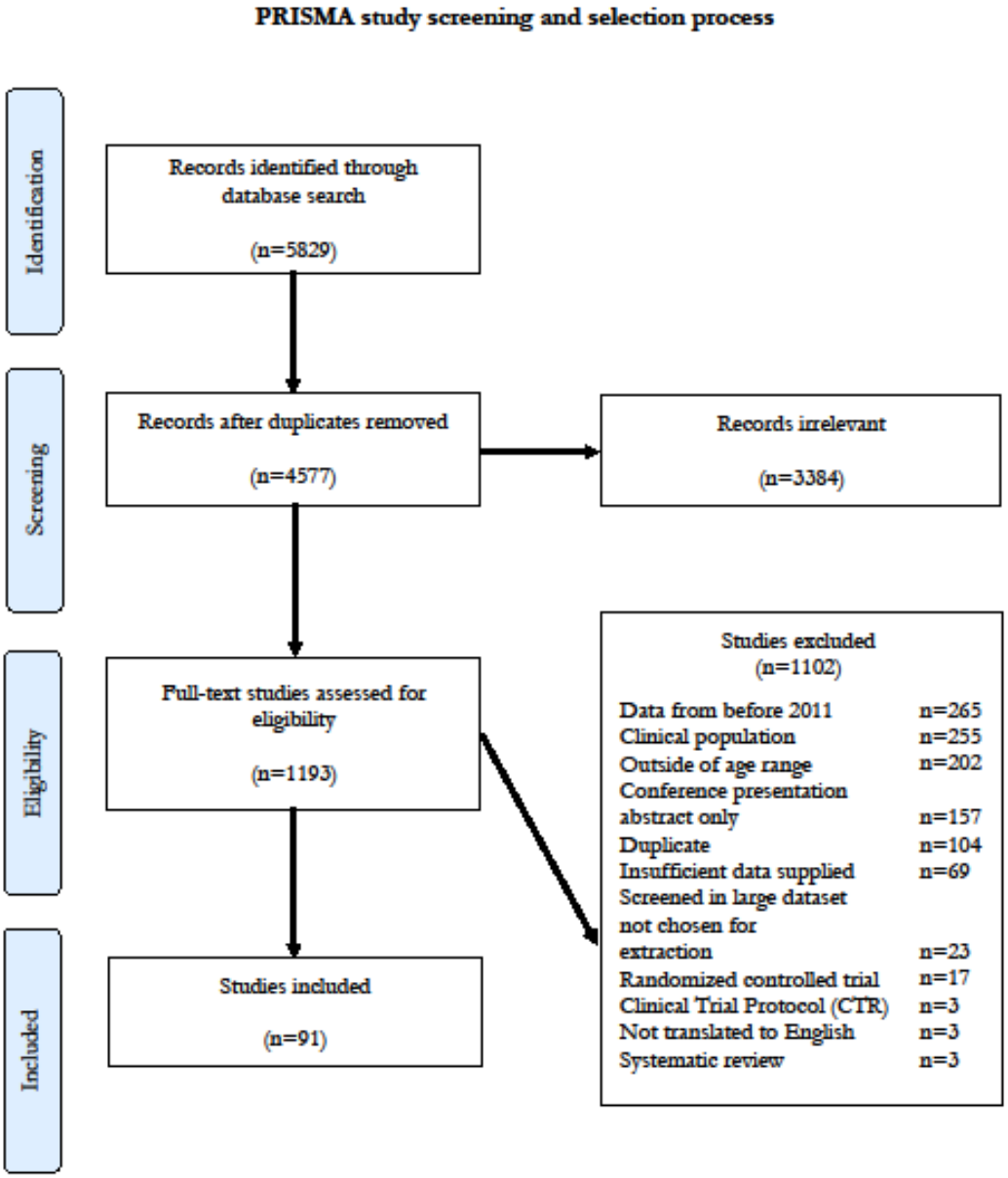


Figure 5 - PRISMA flowchart of study screening and selection process.

Table 4 presents the main results from the included studies. Thirty-two different countries were included in this review, from 5 continents. The included studies collected data from 2011-2019 and included lower-middle-income, higher-middle-income, and high-income countries, as shown in Table 5.

Table 4 - Summary of characteristics for each included study.

	Sample Size & Study Design	**Sample Characteristics**	**Socio-demographics**	**Sub-groups within the overall sample**	**Average CRP (mg/L) & measurement of variation**	**Measurement of CRP**	**JBI ROB Score**
Abeyratne et al. 2020[404]	n= 384 Case-control study Data collected 2017-2019	Sri-Lanka 13.1 ± 1.9 years old 50% Male	Lower middle-income country Colombo district of Sri-Lanka	Healthy weight n=263 Obese n=121	Total mean CRP: 1.62±0.83* Mean CRP healthy weight: 1.28±0.69 Mean CRP obese: 2.36±0.63	hsCRP	6
Ağırbaşlı et al. 2016[405]	n=168 Cross-sectional study Estimated data collection 2015†	Turkey 12.55 ± 3.39 years old 54% male	Upper middle-income country Urban – low to middle SES	Male n=91 Female n=77	Total mean CRP: 0.49 ± 0.42 Median CRP male: 0.36 (IQR 0.9) Median CRP female: 0.45 (IQR 0.72)	hsCRP	5
Agostinete et al. 2017[406]	n= 53 Case-control study Estimated data collection 2015†	Brazil 14.34 ± 1.92 years old 100% Male	Upper middle-income country São Paulo	Athletes n=33 Non-athletes n= 20	Total mean CRP: 3.42 ± 2.3 Mean CRP non-athletes: 1.2 ± 1.0 Mean CRP athletes: 4.66 ± 1.99*	hsCRP	4
Agostinis-Sobrinho et al. 2018[407]	n= 529 Longitudinal study Data collected 2011	Portugal 14.26 ± 1.69‡ years old 49.53% Male	High-income country North Portugal	Low inflammatory score n=352 High inflammatory score n=177	Total mean CRP: 0.94 ± 1.87* Mean CRP low inflammatory score: 0.29±0.43* Mean CRP high inflammatory score: 2.23±2.77*	CRP	7
Ahankari et al. 2021 [408]	n= 401 Cross-sectional study Data collected 2018	India 14.02 ± 2.27 years old 0% Male	Lower middle-income country Rural, disadvantaged central India	No subgroups	Total median CRP: 1.26 (IQR 0.47-2.16)	CRP	6
Alicke et al. 2017 [409]	n= 188 Cross-sectional study Data collected 2015	Ghana 15.02 ± 0.82‡ years old 50% Male	Lower middle-income country Ashanti-Akim North District	Male n=94 Female n=94	Total median CRP: 0.63 (IQR 0.10-2.11) Subgroups NR	CRP	4
Alqaderi et al. 2019 [410]	n=333 Cohort study Data collected 2019	Kuwait 17 years old 49.7% Male	High-income country *No further demographic information*	Normal fasting glucose level =305 Intermediate hyperglycaemia=28	Total mean CRP: 2.79 ± 3.23 Subgroups NR	hsCRP	4
Angin et al. 2014 [411]	n= 66 Cross-sectional study Estimated data collection 2012†	Turkey 13.3 ± 1.8 years old 54.50% Male	Upper middle-income country *No further demographic information*	Healthy weight n=19 Obese n=47	Total mean CRP: 2.41 ± 1.15 Mean CRP healthy weight CRP: 0.9 ± 0.4 Mean CRP obese CRP: 3.03 ± 0.69*	CRP	3
Aris et al. 2020 [412]	n=743 Cohort study Data collected 2012-2016	USA 13.1 ± 0.9 years old 49% Male	High-income country Eastern Massachusetts	No subgroups	Total mean CRP: 0.09 ±1 .16	CRP	3
Assunção et al. 2018 [413]	n= 90 Cross-sectional study Data collected 2015	Brazil 11.89 ± 3.04‡ years old 44.1% Male	Upper middle-income country Salvador, Bahia	Obese no-Non-alcoholic fatty liver diseases (NAFLD)n=34 Obese NAFLD n=56	Total mean CRP: 5.28 ± 6.48 Median CRP no-NAFLD: 3.88 (IQR 1.88-13.67) Median CRP NAFLD: 4.05 (IQR 1.97-7.28)	hsCRP	4

Bacha et al. 2019 [414]	n= 79 Cross-sectional study Estimated data collection 2015†	USA 15.49 ± 0.66‡ years old 43% Male	High-income country Texas	Vitamin D tertile low n=22 Vit D tertile medium n=24 Vit D tertile high n=25	Total mean CRP: 2.18 ‡ 0.92* Subgroups NR	hsCRP	6
Bahrami et al. 2019 [415]	n=940 Cross-sectional study Data collected 2015	Iran 14.56yrs ± 1.52 years old 0% Male	Lower middle-income country North-western Iran – cities of Mashhad and Sabzevar	No subgroups	Total median CRP: 0.97 (IQR 0.50-1.85)	hsCRP	4
Baldwin et al. 2018 [416]	n=1732 Cross-sectional study Data collected 2012-2014	Great Britain 18.4 ± 0.36 years old 49% Male	High Income England & Wales	Non-victimised children n=1273 One type of victimisation n=348 Poly-victimisation n=111	Total mean CRP: 4.67 ± 1.23 Subgroups NR	CRP	8
Boyraz et al. 2013 [417]	n= 201 Case-control study Data collected 2011-2012	Turkey 13.43 ± 4.31‡ years old 52.2% Male	Upper middle-income country Istanbul	Lean n= 63 Mild-moderate obese n=95 Severe obese n=43	Total mean CRP: 2.02 ± 1.06 Mean CRP healthy weight: 1.7 ± 0.8 Mean CRP mild-moderate & severely obese 2.18 ± 1.14	hsCRP	5
Buchan et al. 2013 [418]	n= 192 Cross-sectional study Estimated data collection 2011†	Scotland 14.93 ± 2.65‡ years old 61.5% Male	High-income country West of Scotland, South Lanarkshire public school	Boys n=118 Girls n=74	Total mean CRP: 1.88 ± 2.22* Mean CRP male: 1.71 ± 2.25 Mean CRP female: 1.95 ± 2.19	CRP	5
Buchan et al. 2014 [419]	n=209 Cross-sectional study Estimated data collection 2012†	Scotland 16.73 ± 0.61‡ years old 66.5% Male	High-income country West of Scotland, South Lanarkshire public school	Boys n=139 Girls n=70	Total mean CRP: 2.45 ± 1.99* Mean CRP male: 2.48±1.93 Mean CRP female: 2.4±2.12	CRP	5
Cayres et al., 2015 [420]	n=120 Longitudinal study Data collected 2013-2014	Brazil 11.7 ± 0.81 years old 51.67% Male	Upper middle-income country Presidente Prudente city (western Sao Paulo State)	Never skips breakfast n= 63 Skips breakfast at least once a week n= 57	Total mean CRP: 1.63 ± 3.59* Mean CRP never skips breakfast: 1.62 ± 3.98* Mean CRP skips breakfast at least once a week: 1.65 ± 3.16*	hsCRP	5
Celik et al. 2015 [421]	n=82 Case-control study Estimated data collection 2013†	Turkey 14.19 ± 1.53 years old 56% Male	Upper middle-income country *No further demographic information*	Control group n= 46 Risky group (fathers with history of coronary artery disease) n=36	Total mean CRP: 0.64 ± 0.84* Median CRP control group 0.46 (IQR 0.24-1.62) Median CRP risky group 0.36 (IQR 0.23-0.75)	hsCRP	4
Chakraborty et al 2020 [422]	n=4438 Cross-sectional study Data collected 2012-2014	India 13.46 ± 2.12‡ years old 42.15% Male	Lower middle-income country New Delhi. Private & government schools	Government school n=795 Private school n=3643	Total mean CRP: 0.65 ± 0.83* Median CRP Government school: 0.3 (IQR 0.1-0.8) Median CRP Private school: 0.5 (IQR 0.2-1.4)	CRP	5
Codoner-Franch et al. 2014 [423]	n=110 Cross-sectional study Data collected 2012-2013	Spain 10.83 ± 3.78‡ years old 57.3% Male	High-income country	Healthy weight n=40 Obese n=70	Total mean CRP: 1.86 ± 2.37* Median CRP healthy weight: 0.4 (IQR 0.2-0.7)	hsCRP	4

			No further demographic information		Median CRP obese: 2.8 (IQR 0.9-4.4)		
Cohen et al. 2014 [424]	n=669 Cross-sectional study Data collected 2011	Colombia 11.52 ± 1.13 years old 47.5% Male	Upper middle-income country Bucaramanga	Male n=351 Female n=318	Total mean CRP: 0.89 ± 1.62 Mean CRP male: 0.89 ± 1.71 Mean CRP female: 0.88 ± 1.52	CRP	4
Corica et al. 2019 [425]	n=77 Cross-sectional study Data collected 2017	Italy 10.52 ± 8.02‡ years old 41.10% Male	High-income country Sicily	Healthy weight n=36 Overweight/obese n=41	Total mean CRP: 0.52 ± 0.94 Median CRP healthy weight: 0.1 (IQR 0.1-0.9) Median CRP overweight/obese: 0.2 (IQR 0.1-1.6)	CRP	4
Coutinho et al. 2015 [426]	n=53 Cross-sectional study Data collected 2013	Brazil 14.66 ± 1.1 years old 0% Male	High-income country Curitiba/Parana public schools	No subgroups	Total median CRP: 1.4 (IQR 0.4-5.7)	CRP	5
Dayal et al. 2014 [427]	n=200 Case-control study Estimated data collection 2012†	India 11.6 ± 1.7‡ years old 58% Male	Lower middle-income country Northern India	Healthy weight n=100 Overweight n=100	Total mean CRP: 3.03 ± 1.93* Mean CRP healthy weight: 2.15 ± 1.05 Mean CRP overweight: 3.92 ± 2.2	hsCRP	4
de Dios et al. 2021 [428]	n=723 Cross-sectional study Estimated data collection 2019†	Spain 14.4 ± 1.11‡ years old 46.7% Male	High-income country *No further demographic information*	Male n=338 Female n=385	Total mean CRP: 0.39 ± 0.47* Median CRP male: 0.32 (IQR 0.12-0.88) Median CRP female: 0.28 (IQR 0.10-0.62)	hsCRP	5
Della Corte et al. 2017 [429]	n=243 Cohort study Data collected 2014-2015	Italy 12.57 ± 2.77‡ years old 69.1% Male	High-income country *No further demographic information*	Obese without fatty liver disease n=166 Obese with fatty liver disease n=77	Total mean CRP: 4.0 ± 5.6* Mean CRP without fatty liver disease: 3.6 ± 4.6* Mean CRP fatty liver disease: 4.2 ± 6*	CRP	1
Del Ry et al. 2016 [430]	n=82 Cross-sectional study Estimated data collection 2014†	Italy 12.58 ± 1.82‡ years old 53.7% Male	High-income country *No further demographic information*	Healthy weight n=27 Overweight and obese n=55	Total mean CRP: 1.99 ± 2.1* Mean CRP healthy weight: 0.15 ± 0.22* Mean CRP overweight/obese: 2.9 ± 2.1*	CRP	4
Dursun et al. 2019 [431]	n=267 Case-control study Estimated data collection 2017†	Turkey 13.12 ± 2.13‡ years old 61.08% Male	Upper middle-income country *No further demographic information*	Healthy weight n=49 Obese n=218	Total mean CRP: 2.66 ± 4.6* Mean CRP healthy weight: 1.02 ± 0.46 Mean CRP obese: 3.03 ± 5.02*	hsCRP	5
Esteban-Cornejo et al. 2016 [432]	n=494 Cross-sectional study Data collected 2011-2012	Spain 10.59 ± 3.36 years old 51.82% Male	High-income country Cadiz and Madrid	Boys n=256 Girls n=238	Total mean CRP: 1.26 ± 3.25* Mean CRP male: 1.25 ± 3.14 Mean CRP female: 1.28 ± 3.37	CRP	6
Fedewa et al. 2014 [433]	n=177 Cross-sectional study Data collected 2013	USA 18.1± 0.33 years old 33.3% Male	High-income country University of Georgia	Male n=59 Female n=118	Total mean CRP: 1.3 ± 2.0 Mean CRP male: 1.4 ± 2.4 Mean CRP female: 1.3 ± 1.8	CRP	5
Foster et al. 2020 [434]	n=100 Retrospective chart review	USA 13.9 ± 2 years old	High-income country	Normal uric acid (NUA) n= 61	Total mean CRP: 2.8 ± 2.2 Mean CRP NUA: 2.6 ± 2.1 Mean CRP HUA: 3.0 ± 2.3	hsCRP	6

	Data collected 2016-2018	43% Male	Memphis, Tennessee	High uric acid (HUA) n=39			
Franssen et al. 2019 [435]	n=58 Cross-sectional study Estimated data collection 2017†	Belgium 13.7 ± 1.33‡ years old 53.4% Male	High-income country Hasselt, Belgium (Jessa hospital and Hasselt University)	Lean n=29 Obese n=29	Total mean CRP: 2.25 ± 5.25* Mean CRP lean: 0.3 ± 0.8 Mean CRP obese: 4.2 ± 6.9	CRP	6
Franssen et al. 2021 [436]	n=69 Cross-sectional study Estimated data collection 2019†	Belgium 14.1 ± 1.3 years old 52.2% Male	High-income country Hasselt, Belgium (Jessa Hospital)	Obese without chronotropic incompetence (CI) n=37 Obese with CI n=32	Total mean CRP: 3.45 ± 3.01* Mean CRP obese non-CI: 2.2 ± 2.2 Mean CRP obese CI: 4.9 ± 3.2	CRP	6
Gállego-Suárez et al. 2020 [437]	n=282 Cross-sectional study Estimated data collection 2018†	USA 12.8 ± 2.5 years old 42.2% Male	High-income country Michigan (University of Michigan sites, clinical sites, local schools)	Overweight/obese males n=99 Overweight/obese females n=136	Total mean CRP: 3.08 ± 4.29* Mean CRP male: 2.01 ± 2.53* Mean CRP female: 3.86 ± 5.09*	CRP	5
Garcia-Hermoso et al. 2017 [438]	n=935 Cross-sectional study Data collected 2013-2016	Colombia 13 ± 2.29‡ years old 45.2% male	Upper middle-income country City of Bogota	Boys n=423 Girls n=512	Total mean CRP: 1.15 ± 2.33 Mean CRP boys: 1.27 ± 2.46 Mean CRP girls: 1.05 ± 2.22	hsCRP	6
Giannini et al. 2017 [439]	n=873 Cross-sectional study Data collected 2013-2014	Brazil Age NR 40% Male	Upper middle-income country Porto Alegre (South of Brazil)	Healthy weight n=547 Overweight/obese n=326	Total mean CRP: 0.48 ± 0.81* Median CRP healthy weight: 0.23 (IQR 0.12-0.58) Median CRP overweight/obese: 1.66 (IQR 0.50-3.48)	CRP	4
González-Jiménez et al. 2017 [440]	n=1001 Cross-sectional study Data collected 2013-2014	Spain 13.2 ± 1.2 years old 47.9% Male	High-income country Granada and Almeria (South-east Spain)	Healthy weight n=851 Overweight/obese n=150	Total mean CRP: 1.13 ± 1.11* Mean CRP healthy weight: 1.12 ± 1.1 Mean CRP overweight/obese: 1.24 ± 1.2*	CRP	6
Goyal et al. 2018 [441]	n=160 Cross-sectional study Data collected 2016-2017	India 12.19 ± 2.71‡ years old 53.1% Male	Lower middle-income country Jagraon City, Punjab	Obese without NAFLD n=54 Obese with NAFLD n=106	Total mean CRP: 1.64 ± 0.8* Median without NAFLD CRP: 0.88 (IQR 0.78-1.00) Median NAFLD CRP: 2.1 (IQR 1.54-2.50)	hsCRP	3
Ha et al. 2013 [442]	n=95 Case-control study Estimated data collection 2011†	USA 17.43 ± 1.79‡ years old 38.90% Male	High-income country New York (NYU Medical Centre)	Lean n=32 Obese n=63	Total mean CRP: 2.39 ± 2.46* Mean CRP lean: 0.8 ± 1.7 Mean CRP obese: 3.2 ± 2.4	CRP	6
S. Higgins et al. 2021 [443]	n=379 Cross-sectional study Estimated data collection 2019†	USA 18.33 ± 0.48‡ years old 32.7% Male	High-income country South-east US university campus	Male n=124 Female n=255	Total mean CRP: 1.6 ± 2.96* Mean CRP male: 1.34 ± 2.38 Mean CRP female: 1.73 ± 3.21	CRP	6
V. Higgins et al. 2020 [444]	n=1332 Cross-sectional study Data collected 2017	Canada 13.06± 3.71 years old 49.54% Male	High-income country Greater Toronto and Hamilton	Healthy weight n=910 Overweight/obese n=422	Total mean CRP: 0.49 ± 1.4* Mean CRP healthy weight: 0.3 ± 0.8 Mean CRP overweight/obese: 0.9 ± 2.2	hsCRP	5

Hinriksdótti r et al. 2015 [445]	n=245 Cross-sectional study Estimated data collection 2013†	Iceland 18 ± 0.3‡ years old 52.7% Male	High-income country Reykjavik	Boys n=129 Girls n=116	Total mean CRP: 1.2 ± 1.5 Mean CRP male: 1.4 ± 1.7 Mean CRP female: 1 ± 1.2	CRP	7
Hu et al. 2015 [446]	n=134 Cross-sectional study Data collected 2012	South Korea 13.9 ± 0.61‡ years old 58.2% Male	High-income country Seoul and Kyunggi province	Healthy weight n=67 Obese n=67	Total mean CRP: 2.1 ± 2.9* Mean CRP healthy weight: 0.9 ± 1.3 Mean CRP obese: 3.3 ± 3.6	hsCRP	4
Irawan et al. 2020 [447]	n=59 Cross-sectional study Data collected 2018	Indonesia Age NR 54.2% Male	Lower middle-income country Surabaya	Obese without dyslipidaemia n=21 Obese with dyslipidaemia n=38	Total median CRP: 2.3 (IQR 0.28-2.94) Subgroups NR	hsCRP	4
Katz et al. 2016 [448]	n=61 Cross-sectional study Estimated data collection 2014†	USA 14.37 ± 2.0‡ years old 44.3% Male	High-income country Philadelphia	Obese male n=27 Obese female n=34	Total mean CRP: 4.13 ± 4.47* Median CRP male: 3.26 (IQR 0.29-20.9) Median CRP female: 2.92 (IQR 0.14-16.1)	hsCRP	5
Kaunang et al. 2020 [449]	n=80 Cohort study Data collected 2013-2014	Indonesia Age NR 36.5% Male	Lower middle-income country Manado	Healthy weight n=40 Obese n=40	Total mean CRP: 2.12 ± 3.27 Mean CRP healthy weight: 0.64 ± 1.09 Mean CRP obese: 3.6 ± 4.01	hsCRP	5
Kautz et al. 2020 [450]	n=129 Cross-sectional study Data collected 2012	USA 16.1 ± 1.3 years old 50.7% Male	High-Income country *No further demographic information*	No subgroups	Total mean CRP: 1.71 ± 0.59	CRP	6
Kilic et al. 2016 [451]	n=74 Case-control study Data collected 2014-2015	Turkey 11.05 ± 2.21‡ years old 54.05% Male	Upper middle-income country BLIND University Paediatric Clinic	Healthy weight n=37 Obese n=37	Total mean CRP: 0.73 ± 1.57* Mean CRP healthy weight: 0.38 ± 0.68 Mean CRP obese: 1.08 ± 2.07	CRP	5
Klisic et al. 2020 [452]	n=99 Cohort study Estimated data collection 2018†	Montenegro 18 ± 1.53‡ years old 0% Male	Upper middle-income country Podgorica	First triglyceride to HDL cholesterol ratio tertile n=33 Second/third TGL/HDL-c tertile n=66	Total mean CRP: 0.79 ± 0.9* Mean CRP first TG/HDL-c tertile: 0.43 ± 0.27* Median CRP second & third TG/HDL-c tertile: 0.97 ± 1.05*	hsCRP	3
Koren et al. 2015 [453]	n=31 Cross-sectional study Estimated data collection 2013†	USA 14.7 ± 1.8 61% Male	High-income country Philadelphia (Mostly African American/Hispanic)	No subgroups	Total median CRP: 1.59 (IQR 0.74-6.93)	hsCRP	5
Lewitt et al. 2020 [454]	n=224 Cross-sectional study Estimated data collection 2018†	Wales (UK) 13.5 ± 0.31‡ years old 42.41% Male	High-income country Carmarthenshire, Wales	Boys n=95 Girls n=129	Total mean CRP: 0.34 ± 2.26* Mean CRP male: 0.43 ± 2.38 Mean CRP female: 0.29 ± 2.19	hsCRP	6
Lischka et al. 2021 [455]	n=109 Cross-sectional study Estimated data collection 2019†	Austria 13.1 ± 2.7 years old 33.4% Male	High-income country Vienna (Medical University of Vienna)	Overweight/obese (whole cohort)	Total mean CRP: 0.6 ± 0.5	CRP	3

Mahesty et al. 2020 [456]	n=32 Cross-sectional study Estimated data collection 2018†	Indonesia Age NR 75% Male	Lower middle-income country Semarang	Overweight/obese males n=24 Overweight/obese females n=8	Total mean CRP: 2.6 ± 3.49 Subgroups NR	hsCRP	3
Makni et al. 2013 [457]	n=151 Case-control study Estimated data collection 2011†	Tunisia 13.69 ± 0.9 years old 52.63% Male	Lower middle-income country *No further demographic information*	Healthy weight n=37 Obese/obese with metabolic syndrome n=114	Total mean CRP: 4.62 ± 1.26* Mean CRP healthy weight: 3.1 ± 0.9 Mean CRP obese & obese-MS: 5.12 ± 0.92*	CRP	6
Marzuillo et al. 2018 [458]	n=48 Cross-sectional study Data collection 2012-2017	Italy 11.2±2.78 52.1% Male	High Income *No further demographic information*	Obese with deletion/deletion (del/del) genotype n=15 Obese with deletion/insertion genotype (del/ins) & insertion/insertion (ins/ins) genotype n=33	Total mean CRP: 4.1 ± 3.33* Mean CRP Del/del genotype: 1.0 ± 1.0 Mean CRP Del/ins genotype & Ins/ins genotype: 5.51 ± 3.05*	CRP	3
Masquio et al. 2014 [459]	n=108 Cross-sectional study Estimated data collection 2012†	Brazil 16.76 ± 1.69 years old 37.96% Male	Upper middle-income country São Paulo	Saturated fat intake low (tertile 1) n=36 Saturated fat intake moderate/high (tertile 2/3) n=72	Total mean CRP: 0.23 ± 0.2* Mean CRP tertile 1: 0.23 ± 0.23* Mean CRP tertile 2/3: 0.23 ± 0.19*	CRP	6
McQuillan et al. 2021 [460]	n=50 Longitudinal study Data collected 2016-2018	USA 15.78 ± 1.9 years old 76% Male	High-income country Midwest US	Male/transgender male n=38 Female/transgender female n=12	Total mean CRP: 1.08 ± 1.67 Mean CRP male/transgender male: 1.16 ± 1.71 Mean CRP female/transgender female: 0.84 ± 1.61	CRP	7
Menezes et al. 2018 [461]	n=3523 Cohort study Data collected 2011-2015	Brazil 18 ± 0.13‡ years old 47.2% Male	Upper middle-income country Pelotas	Male n=1663 Female n=1860	Total mean CRP: 2.39 ± 4.01* Mean CRP male: 1.5 ± 3.0 Mean CRP female: 3.2 ± 4.6	CRP	6
Miranda et al. 2020 [462]	n=405 Cross-sectional study Data collected 2014-2015	Brazil 15.92 ± 1.27 years old 0% Male	Upper middle-income country Viçosa, Minas Gerais	Eutrophic & low body fat % (EUT & aBF%) n=179 Eutrophic & high body fat %/overweight-obese & high body fat % (EUT & hBF%/OW-OB & hBF%) n=226	Total mean CRP: 0.84 ± 1.1* Mean CRP EUT & aBF%: 0.54 ± 0.59* Mean CRP EUT & hBF%/OW-OB & hBF%: 1.09 ± 1.34*	hsCRP	7
Nascimento et al. 2016 [463]	n=284 Cohort study Estimated data collection 2014†	Portugal 13.5 ± 2.31‡ years old 52.82% Male	High-income country Porto/Oporto (northwest Portugal)	Overweight/obese male n=131 Overweight/obese female n=117	Total median CRP: 1.79 (IQR 0.76-4.04) Median CRP male: 2.02 (IQR 0.92-4.06) Median CRP female: 1.61 (IQR 0.67-3.93)	CRP	4
Navarro et al. 2016 [464]	n=748 Cross-sectional study Estimated data collection 2014†	Spain 14.6 ± 0.8 years old 46.76% Male	High-income country *No further demographic information*	Healthy weight n=531 Overweight/obese n=217	Total mean CRP: 0.74 ± 1.2* Mean CRP healthy weight: 0.54 ± 0.85* Mean CRP overweight/obese: 1.34 ± 1.76*	hsCRP	4

Nguyen-Rodriquez at al. 2020 [465]	n=1287 Cohort study Data collected 2012-2014	USA 12.14 ± 3.6‡ years old 50.7% Male	High-income country Chicago, Illinois; Miami, Florida; Bronx, New York; San Diego, California	No subgroups	Total mean CRP: 0.95 ± 1.92*	hsCRP	4
Nirmalkar et al. 2018 [466]	n=61 Cross-sectional study Estimated data collection 2016†	Mexico 13.34 ± 0.41‡ years old 50.80% Male	Upper middle-income country Toluca	Healthy weight n= 27 Obese n=34	Total mean CRP: 2.76 ± 0.89* Mean CRP healthy weight: 2.27 ± 0.76 Mean CRP obese: 3.15 ± 0.8	CRP	6
O'Connor et al. 2020 [467]	n=329 Cross-sectional study Data collected 2014-2015	USA 11 ± 0.59 years old 55.5% Male	High-income country Six rural counties in Eastern North Carolina (NC) and Central Pennsylvania (PA)	No subgroups	Total mean CRP: 1.25 (± NR)	CRP	7
Pacifico et al. 2014 [468]	n=548 Cross-sectional study Estimated data collection 2012†	Italy 10.86 ± 3.18‡ years old 51.46% Male	High-income country Rome	Triglyceride (TG)/high-density lipoprotein-cholesterol (HDL-C) tertile 1 <1.10 n=176 TG/HDL-C tertile 2/3 >1.10 n=372	Total mean CRP: 1.43 ± 1.82* Mean CRP TG/HDL-C tertile 1: 1.08 ± 1.14* Mean CRP TG/HDL-C tertile 2/3: 1.6 ± 2.04*	hsCRP	5
Parish et al. 2016 [469]	n=37 Cross-sectional study Data collected 2011-2014	USA 15 ± 1.06‡ years old Sex NR	High-income country Louisiana	Healthy weight n=26 Obese n=11	Total mean CRP: 1.34 ± 1.56* Mean CRP healthy weight: 0.78 ± 1.29* Mean CRP obese: 2.67 ± 1.36*	CRP	6
Perona et al. 2017 [470]	n=1001 Cross-sectional study Estimated data collection 2015†	Spain 13.2 ± 1.2 years old 46.75% Male	High-income country Granada and Almeria (South-east Spain)	Boys n=468 Girls n=533	Total mean CRP: 1.13 ± 1.12* Mean CRP boys: 1.16 ± 1.17 Mean CRP girls: 1.12 ± 1.08	CRP	7
Pires et al. 2014 [471]	n=161 Cross-sectional study Data collected 2012-2013	Portugal 11.92 ± 0.61‡ years old 55.90% Male	High-income country *No further demographic information*	Healthy weight n=41 Obese n=120	Total mean CRP: 2.18 ± 1.04* Mean CRP healthy weight: 0.5 ± 0.13* Mean CRP obese: 2.75 ± 0.42*	hsCRP	3
Poursafa et al. 2014 [472]	n=89 Case-control study Data collected 2012	Iran 14.64 ± 1.21 years old 51% Male	Lower middle-income country Isfahan county	Moderate water hardness n=44 High water hardness n=45	Total mean CRP: 3.49 ± 0.28 Mean CRP moderate water hardness: 4.63 ± 0.71 Mean CRP high water hardness: 2.14 ± 0.17	hsCRP	6
Radhakishun et al. 2014 [473]	n=25 Cross-sectional study Data collected 2012	Netherlands Age NR Sex NR	High-income country Amsterdam	Overweight/obese (whole cohort)	Total median CRP: 3.36 (IQR 0.24-6.23)	hsCRP	3
Rank et al. 2013 [474]	n=463 Cross-sectional study Estimated data collection 2011†	Germany 13.9 ± 2.3 years old 43.4% Male	High-income country *No further demographic information*	Moderately obese n=197 Severely obese n=266	Total mean CRP: 3.83 ± 6.46* Mean CRP moderately obese: 2.12 ± 6.13* Mean CRP severely obese: 5.1 ± 6.43*	hsCRP	5

Ruminska et al. 2016 [475]	n=180 Case-control study Estimated data collection 2014†	Poland 11.63 ± 2.99‡ years old 58.33% Male	High-income country Warsaw, Poland (Medical University of Warsaw in Poland)	Non-obese n=58 Obese n=122	Total mean CRP: 4.77 ± 2.36* Mean CRP non-obese: 4.5 ± 3 Mean CRP obese: 4.9 ± 2	CRP	4
Schaalan et al. 2016 [476]	n=90 Case-control study Estimated data collection 2014†	Egypt 14.52 ± 1.38‡ years old 50% Male	Lower middle-income country Cairo, Egypt (Endemic Disease Hospital at Cairo University)	Healthy weight n=30 Obese n=60	Total mean CRP: 1.52 ± 1.4* Mean CRP healthy weight: 0.3 ± 0.09 Mean CRP obese: 2.13 ± 1.36	hsCRP	6
Seremet Kurklu et al. 2020 [477]	n=343 Cross-sectional study Estimated data collection 2018†	Turkey 13.47 ± 2.04‡ years old 37% Male	Upper middle-income country *No further demographic information*	Dietary inflammatory index (DII) quartile 1 & 2 (1.04-3.80) n=171 DII quartile 2 & 3 (3.81-5.11) n=172	Total mean CRP: 1.75 ± 1.65* Mean CRP DII Q1 & 2: 1.6 ± 1.59* Mean CRP DII Q3 & 4: 1.9 ± 1.69*	CRP	4
Shah et al. 2013 [478]	n=21 Case-control study Estimated data collection 2011†	USA 17.73 ± 2.63‡ years old 48.50% Male	High-income country Boston, Massachusetts	Obese n=10 Obesity & type 2 diabetes n=11	Total mean CRP: 5.48 ± 5.15* Median CRP obesity: 1.7 (IQR 1.1-6.0) Median CRP obesity & T2 diabetes: 8.25 (IQR 4.47-10.5)	hsCRP	6
Silva et al. 2013 [479]	n=150 Cross-sectional study Estimated data collection 2011†	Brazil 12.95 ± 1.34‡ years old 40% Male	Upper middle-income country Piracicaba and Sao Paulo	Healthy weight n=75 Overweight/obese n=75	Total mean CRP: 7.43 ± 1.48* Mean CRP healthy weight: 6.63 ± 1.38 Mean CRP overweight & obese: 8.06 ± 1.22	CRP	6
Simunovic et al. 2019 [480]	n=131 Cross-sectional study Data collected 2017-2018	Croatia 14.07 ± 2.27‡ years old 53.4% Male	High-income country Split	Healthy weight n=39 Obese n=92	Total mean CRP: 2.09 ± 2.16* Mean CRP healthy weight: 0.75 ± 1.63 Mean CRP obese: 2.67 ± 2.11*	hsCRP	5
Sledzinska et al. 2017 [481]	n=101 Cross-sectional study Data collected 2011-2013	Poland 11 ± 0.49‡ years old 52.5% Male	High-income country Gdansk	Healthy body weight n=43 Excess body weight n=58	Total mean CRP: 0.89 ± 0.43* Mean CRP healthy weight: 0.4 ± 0.05 Mean CRP overweight: 1.26 ± 0.12	CRP	5
Soltero et al. 2021 [482]	n=271 Cross-sectional study Estimated data collection 2019†	USA 12.84 ± 2.7‡ years old 48.70% Male	High-income country Greater Minneapolis and St. Paul metropolitan areas	Healthy weight n=114 Obese/severely obese n=157	Total mean CRP: 5.4 ± 8.4* Mean CRP healthy weight: 1.54 ± 3.3 Mean CRP obese/severely obese: 8.21 ± 9.78*	CRP	5
Stanley et al. 2013 [483]	n=30 Case-control study Estimated data collection 2011†	USA 14.95 ± 1.97‡ years old 0% Male	High-income country Massachusetts	Healthy weight n=15 Obese n=15	Total mean CRP: 2.61 ± 5.94* Median CRP healthy weight: 0.3 (IQR 0.2-0.8) Median CRP obese: 3.6 (IQR 0.4-10.1)	hsCRP	5
Stroescu et al. 2016 [484]	n=122 Cross-sectional study Data collected 2013-2014	Romania 14.91 ± 2.52‡ years old 39.4% Male	High-income country Timişoara (Western Romania)	Obese adolescents born average for gestational age (AGA) n=96	Total mean CRP: 7.42 ± 3.14* Mean CRP AGA: 7.0 ± 3.2* Mean CRP SGA: 9.0 ± 2.4*	hsCRP	3

				Obese adolescents born small for gestational age (SGA) n=26			
Swartz et al. 2021 [485]	n=70 Cross-sectional study Data collected 2019	USA 13.6 ± 1.04 years old 51.4% Male	High-income country Davis, California	No subgroups	Total mean CRP: 1.6 ± 4.12	CRP	6
Taranu et al. 2020 [486]	n=22 Longitudinal study Data collected 2017-2019	Romania 11.65 ± 6.14 years old 22.7% Male	High-income country Cluj-Napoca (northwestern Romania)	Overweight/obese (whole cohort)	Total median CRP: 3.9 (IQR 2.0-8.8)	CRP	3
Todendi et al. 2015 [487]	n=470 Cross-sectional study Estimated data collection 2013†	Brazil 13.13 ± 2.99 years old 46% Male	Upper middle-income country Santa Cruz do Sul (Rio Grande do Sul)	No subgroups	Total mean CRP: 1.39 ± 0.69	CRP	4
Tsiroukidou et al. 2021 [488]	n=84 Case-control study Estimated data collection 2019†	Greece 11.46 ± 2.02‡ years old 50% Male	High-income country Thessaloniki, Greece	Healthy weight n=21 Overweight/obese n=63	Total mean CRP: 4.03 ± 7.63* Mean CRP healthy weight: 1.3 ± 0.9* Mean CRP overweight/obese: 4.94 ± 8.63*	hsCRP	5
Urban et al. 2019 [489]	n=212 Cross-sectional study Data collection 2016-2017	Brazil 14.85 ± 2.06‡ years old 69.81% Male	Upper middle-income country Presidente Prudente, São Paulo State	Healthy birth weight n=230 Altered birth weight n= 35	Total mean CRP: 2.13 ± 2.75* Mean CRP healthy birth weight: 2.04 ± 2.81 Mean CRP altered birth weight: 2.95 ± 2.29	CRP	5
Ustyol et al. 2017 [490]	n=140 Case-control study Data collected 2015-2016	Turkey 12.55 ± 0.42‡ years old 49.3% Male	Upper middle-income country Istanbul	Lean n=40 Obese n=100	Total mean CRP: 2.71 ± 1.21* Mean CRP lean: 1.02 ± 0.2 Mean CRP obese & obese NAFLD: 3.39 ± 0.66*	hsCRP	4
Yang et al. 2019 [491]	n=181 Cross-sectional study Estimated data collection 2017†	Taiwan 13.66 ± 2.52 years old 66.6% Male	Upper middle-income country *No further demographic information*	Healthy weight n=102; Obese/severely obese n=79	Total mean CRP: 2.01 ± 2.71 Mean CRP healthy weight: 0.69 ± 0.96 Mean CRP obese/severely obese: 3.05 ± 3.14*	hsCRP	3
Yilmaz et al. 2019 [492]	n=95 Cross-sectional study Data collected 2017	Turkey Age NR 44.2% Male	Upper middle-income country Diyarbakir Province	Healthy weight n=66 Overweight n=29	Total mean CRP: 0.75 ± 2.36* Mean CRP healthy weight: 0.6 ± 1.2 Mean CRP overweight: 1.1 ± 3.9	hsCRP	5
Zhao et al. 2019 [493]	n=1766 Cross-sectional study Data collected 2017	China 11.3 ± 1.12 years old 49.32% Male	Upper middle-income country 3 urban districts and 4 suburban districts in Beijing	Without metabolic syndrome (non-MetS) n=1707 With metabolic syndrome (MetS) n=59	Total mean CRP: 1.0 ± 0.16* Mean CRP non-MetS: 0.97 ± 0.06 Mean CRP MetS: 1.78 ± 0.34	CRP	5
Zhu et al. 2021 [494]	n=3241 Cross-sectional study Data collected 2016-2017	China Age NR 50.83% Male	Upper middle-income country Jiangsu Province (2 large urban sites, 8 small-medium urban sites, 2 rural sites)	Serum zinc levels lowest 2 quartiles (Zn Q1&2) n=1682 Serum zine levels highest 2 quartiles (Zn Q3&4) n=1559	Total mean CRP: 0.42 ± 0.4* Median CRP Zn Q1+2: 0.3 (IQR 0.2-0.8) Median CRP Zn Q3+4: 0.35 (IQR 0.2-0.8)	hsCRP	7

**CRP is calculated*
†Estimated data collection
‡ Calculated age
Abbreviations
CRP = C-reactive protein
hsCRP = High sensitivity C-reactive protein
NAFLD = Non-alcoholic fatty liver disease
NR = not reported

Table 5 - Socio-demographic characteristics and geographic locations of the studies.

Socio-demographic characteristics and geographic locations of the studies (N=91)	
Variable	No. of studies
Geographic location	
Europe	31*
Asia	24
North America	20
South America	14
Africa	2
Year of known data collection†	
2011-2013	23
2014-2016	14
2017-2019	13
Country socio-economic level	
High income	50
Upper-middle income	28
Lower-middle income	13
CRP or hsCRP measurement	
CRP	47
hsCRP	44
Sex‡	
Mixed-sex	62
Female	17
Male	12

**of which 16 consume the Mediterranean diet*

†date given by the author. Remaining studies were screened in assuming data collected was 2 years before publication date

‡mixed-sex = 40-59% male or female, Male or female = ≥60% of either

2.3.0 Mean CRP

Ninety-one studies were included in the meta-analytic sample. The total sample included 37,347 individuals aged 11-19 with a mean age of 13.8 years (SD=1.88). The results of the meta-analysis are shown in Figure 6, showing a mean CRP of 1.69mg/L (95% CI=1.80:2.42) in the general population of adolescents.

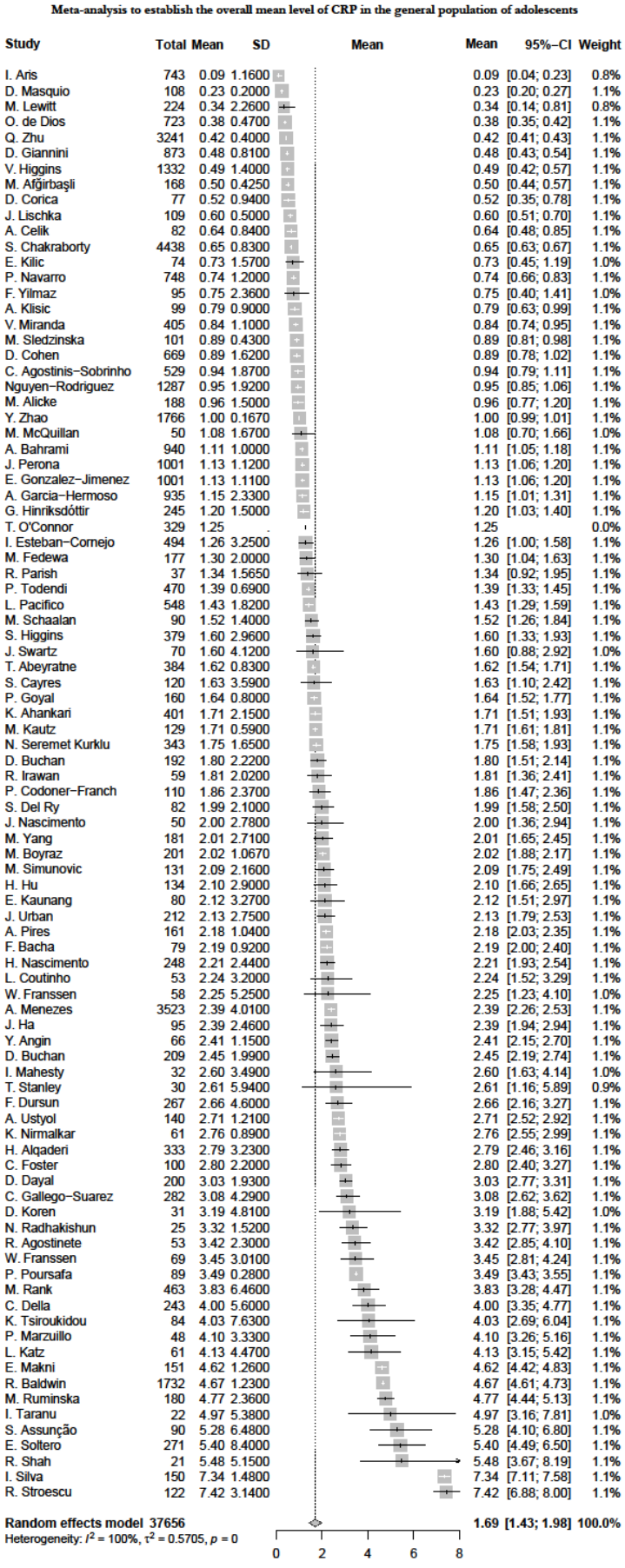


Figure 6 - Meta-analysis to establish the overall mean level of CRP in the general population of adolescents.

2.3.1 Meta-regression for CRP changes over time

Ninety-one studies were included in the meta-regression analysing to explore any changes in CRP over time. Results showed that CRP levels remained stable over the past 10 years across the 32 different countries (Estimate -0.07; 95%CI -0.19:0.05; T value -1.14; P=0.25) (Appendix 1.2).

2.3.2 Sub-sample analysis

The region where the largest number of studies (33%) were conducted was Europe, 35% of the studies collected data between 2011-2013, and just over half of the studies were conducted in a high socio-economic country (50/91), whilst 66% had a mixed-sex sample. Two studies in this review were from the African region, which was removed from the regional analysis as this number was insufficient to generate a reliable estimate. The subgroup analyses for mean differences in mean CRP for region (P=0.27) and country SES (P=0.48) showed no significant difference between groups (Appendix 1.3 & 1.4). When comparing predominantly male (≥60%) with predominantly female (≥60%) cohorts (Figure 7) the former had significantly higher CRP, with a mean difference of 1.1mg/L (P=0.002). There was a significant difference in the subgroup analysis based on weight (Figure 8), with a higher CRP in ≥60% overweight/obese cohorts with a mean difference in mean CRP levels of 2.14mg/L (P=0.0001) compared to ≥60% healthy weight cohorts.

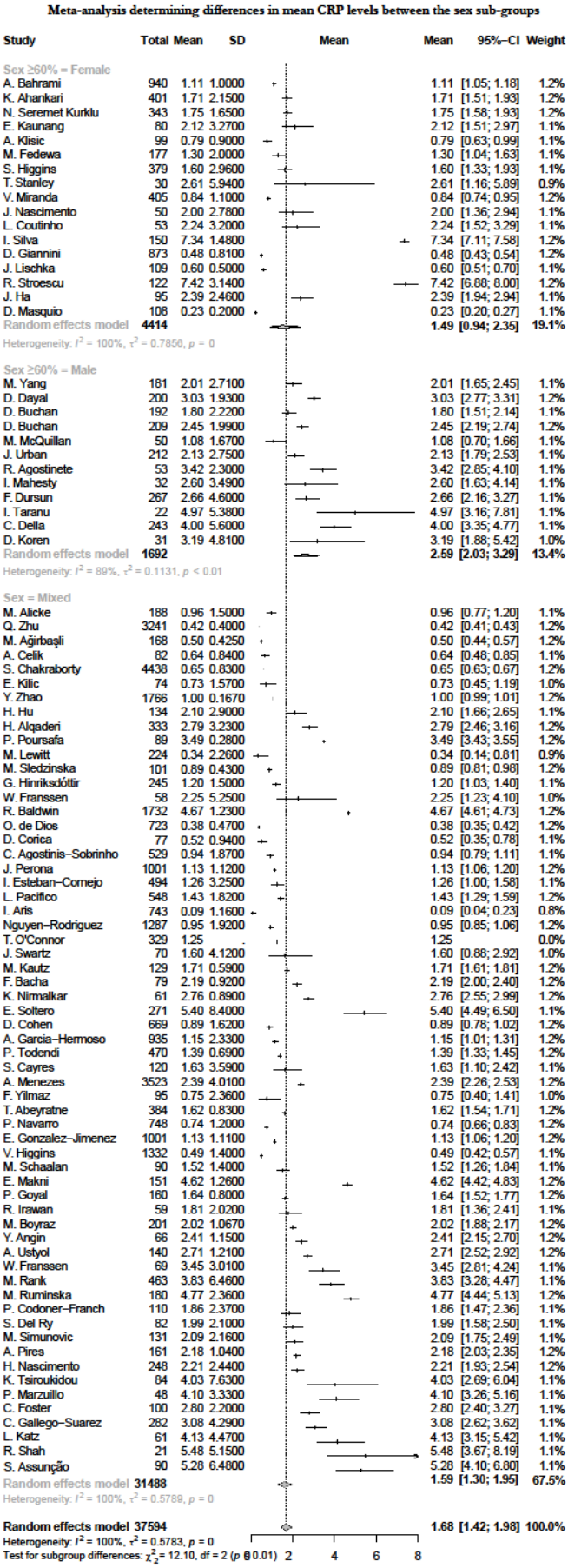


Figure 7 – Meta-analysis determining differences in mean CRP levels between the sex sub-groups.

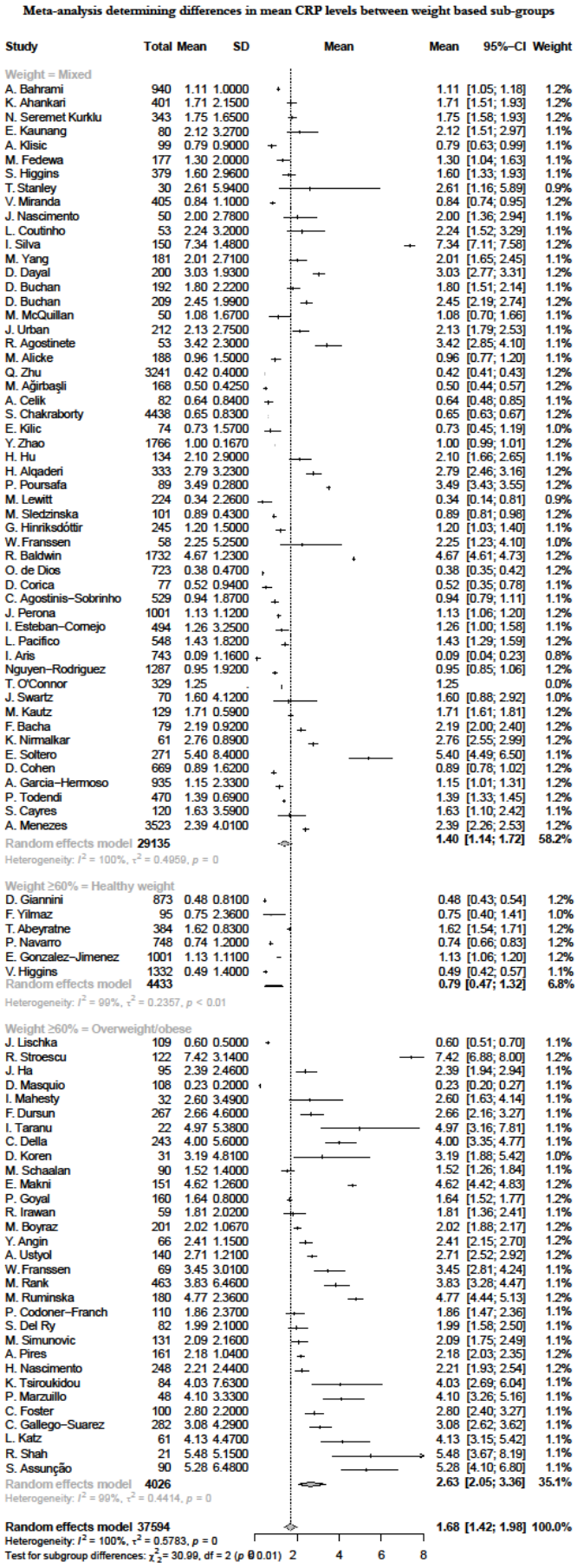


Figure 8 - Meta-analysis determining differences in mean CRP levels between the weight-based sub-groups.

2.3.3 Sensitivity analysis to explore heterogeneity

CRP was collected in 47/91 studies (mean CRP 1.62mg/L) and hsCRP in 44/91 (mean hsCRP 1.75mg/L), and there was no evidence of a significant difference (P=0.64) between mean CRPs collected as CRP or hsCRP (Appendix 1.5). A second sensitivity analysis was conducted to determine if there were any differences when considering the studies supplying an exact year of data collection (n=50) compared to our estimated year of data collection (n=41), the results of this analysis found no evidence of a significant difference (P=0.76, CI -0.19:0.14). The meta-regression to assess any changes in mean CRP at different ages showed no evidence of a significant finding (estimate 0.42; 95%CI -0.77:1.63; T value 0.70; P=0.48). Similarly, the meta-regression examining the association between CRP levels and weight controlling for sex showed no significant findings (estimate 0.28; 95%CI 0.05:0.50; T value 2.49; P=0.50). Finally, evidence from the 17 studies supplying exact CRP for male and female cohorts within their study found no significant difference in mean CRP (SMD=-0.05, 95%CI -0.15;0.06) (Appendix 1.6).

2.3.4 Risk of bias appraisal

The JBI risk of bias results (Appendix 1.7) found that nearly all studies scored moderate to high (≥3 out of 8) for quality control within studies, indicating a low to moderate risk of bias. The only study that scored below this was by Della Corte et al[429] scoring one out of eight.

2.4 Discussion

This comprehensive systematic review is the first to find that the mean level of CRP in the general population of adolescents worldwide was 1.69mg/l, which is above the 1mg/L threshold indicating adolescents are experiencing low-grade inflammation, which in the long term is associated with increased risk of chronic disease.

Although systemic inflammation has emerged as an important predictor of health outcomes, the only previous study to our knowledge that has attempted to gather the average level of CRP in young people was conducted in a child population (2.0-8.9-years-old), within a European-only cohort by Schlenz et [495] where the median CRP levels reported ranged from 0.2-0.3mg/L. Notably, this study removed any participants who were overweight or obese. Given that 340 million children and adolescents were overweight or obese in 2016 and obesity is linked to inflammation, this exclusion profoundly limits the generalisability of these findings to the wider population. However, Schlenz's findings align closely with the mean CRP we report for our

healthy weight sub-group (0.79mg/L CRP), our findings of a slightly higher CRP may be explained by including adolescent cohorts where participants would have increased inflammatory-inducing hormones.[496] Moreover, our study included cohorts from more varied geographic regions and thus reflects a more accurate population estimate of CRP.

We found no evidence that levels of inflammation had changed significantly between 2011-2019. To our knowledge, no previous research has examined changes in CRP over time, despite the importance of identifying trends in inflammation levels as environmental factors and health behaviours change. By virtue of the publication time post-data collection, the most recent year of data collection included in our analysis was 2019. Although there have been increases in poor lifestyle behaviours associated with inflammation over these nine years, it may be that these changes were not large enough to have an impact on population inflammation levels, however due to the large volume of publications meeting our search criteria, extending our search beyond a decade was not feasible. Another explanation could be the general improvement of the world economy between 2011-2019; the majority of countries worldwide either saw no changes or a decline in the proportion of their population living below the poverty line.[497] While neither body size nor the intake of western UPF has declined, these may be mitigated by reductions in other economically driven risk factors for inflammation, such as smoking[498] and psychosocial stressors.

Our results showed substantially higher levels of CRP in studies with overweight or obese compared to healthy-weight adolescents. As previously discussed, there are multiple mechanistic contributors to why overweight individuals may experience higher inflammation[376] and these findings highlight that the effects of excess weight on biomarkers are evident even in adolescence.

Significantly higher levels of CRP were also found in studies that were predominantly comprised of males compared to predominately female cohorts, despite adult females generally having higher CRP levels due to hormonal differences.[384] One explanation as to why we observed contrasting findings is the disproportionate inclusion of samples in the predominantly female versus male samples: of the 18 predominantly female studies included in our meta-analysis, only 4 of these (22.2%) included a ≥60% overweight or obese cohort, whereas 5/12 (41.6%) of the predominantly male studies included a ≥60% overweight or obese cohort. We ran a secondary sensitivity analysis only on studies that provided a precise mean CRP for males and females

within their specific cohort, to determine if these differences remained when looking at the relationship between CRP and sex generating an exact pooled standardised mean difference (Appendix 1.6). Seventeen studies supplied sufficient information and our results found no significant standardised mean difference in CRP between male and female cohorts. Specifically, Menezes et al. (2018)[461] had the largest cohort (males n=1663; females n=1860) among the 17 studies included in this sensitivity analysis and found female CRP to be an average of 3.20mg/L (SD 4.6) and male CRP to be an average of 1.50mg/L (SD 3.0). Klein and Flanagan (2016)[496] suggest that inflammation in males is expected to be higher pre-puberty and in females post-puberty due to hormonal changes that impact an inflammatory response, therefore, whilst some studies included in our review align with the adult literature, our lack of significant difference between sex in the subset of studies could suggest that varied hormonal development among adolescents could result in a less definitive observed difference during this period of life.

A relationship between low SES and higher levels of CRP is commonly found in the literature with social stressors,[499] poverty,[500] poor nutrition[501] and higher exposure to trauma[502] believed to be some of the contributing factors. However, our subsample analysis found no significant differences between the mean CRP of the country-level SES groups. A selection of included studies supplied further socio-demographic information specific to their study cohort, notably, there was variability in CRP across two disadvantaged samples from low-middle income countries[408, 409] (median CRP 1.26mg/L and mean CRP 0.96mg/L), and similarly across two affluent cities in high-income countries[425, 503] (mean CRP 0.35mg/L and 1.27mg/L). When comparing these studies, it is evident that there is much variance in mean CRP levels even among cohorts from specific low- and high-income areas. These findings could suggest that whilst low SES communities can experience some inflammatory-inducing lifestyles, those in high SES communities are not exempt which could be a consequence of exposure to higher accessibility to UPFs or fast foods, and a higher disposable income to purchase them, and the potential to be more sedentary with increased access to devices and reduced requirements for manual chores.

The connection between diet and CRP is regularly explored, with the understanding that 'western' American or British diets, can have inflammatory inducing properties, and the traditional Mediterranean or Japanese diets, have more anti-inflammatory properties. Whilst the lowest CRP levels were in the European-Mediterranean and Asian regions, there were no significant differences in mean CRP found between the different regions. The findings here

could suggest that region-based grouping may be too broad when referring to diets and that country-level dietary intake varies within regions substantially.

A significant strength of this review is its' large scale (n=37,347) and span across multiple countries (n=32) and continents (n=5), making the findings, for the most part, generalisable. This is a comprehensive, pre-registered systematic review, and a meta-analysis that included robust statistical analysis to deliver important health information that has not been done before. A limitation of this review was the high heterogeneity between studies (I^2 of 99.8%), which was, for the most part, not attenuated by further sensitivity or subgroup analysis. Our findings were consistent with another large meta-analysis[504], explored by Peter Imrey (2022)[505] who explains that the large scale of these meta-analyses and the use of continuous variables can inflate the heterogeneity, which is evident when our I^2 statistic decreased partially during our sub-group analysis of just 17 studies within our review (Appendix 1.6). Moreover, the range in pooled mean CRP was quite substantial (0.09-7.42mg/L) and we were unable to gather data on all potentially relevant moderators, for example, our usage of a 'regionality' variable lacks consideration of geographical variance within the regions. Another limitation of our review was the use of country-level SES information, due to insufficient SES information supplied for individual cohorts within studies leading, potentially, to the inaccurate classification of SES for individual cohorts. The absence of studies from a low-income country prevented assessing differences across all country-level SES groups. Finally, insufficient studies were obtained from the African and Oceania regions, thus we were unable to make conclusions in these regions.

2.5 Conclusion

To conclude, this study has highlighted that adolescents are experiencing low-grade inflammation, particularly those who have higher BMI scores. This represents an immediate and long-term threat to health. Across the past 10 years, inflammatory levels have not significantly altered in adolescents, the behavioural and environmental shifts that have occurred during this time could have been mitigated by other worldwide improvements, future research could review more historic data (pre-2011) to gain clearer understanding. Adolescents who are overweight and obese are experiencing significant detrimental immunological impacts, with a higher level of inflammation than their healthy-weight counterparts. Adolescent obesity is an increasingly prevalent issue worldwide and requires immediate action to help prevent long-lasting health issues. Country-level SES may be too broad to depict any relationship in specific SES

differences, alternatively variances in inflammatory stressors between the SES groups could balance inflammatory levels. To fully understand the extent of inflammatory implications of living in different socio-economic statuses, further research is required on cohort-specific SES and its relationship with inflammation levels in adolescents. Previously research has suggested that dietary patterns correlate with inflammation, however, we observed no relationship between regional dietary differences and average CRP levels. To address these issues, future work on country-specific dietary patterns within a region should be considered for a better understanding of dietary inflammatory impacts, allowing recognition of countries that are at higher risk. It is fundamental to consider results in public health practices and policy, particularly as CRP is a modifiable health factor and indicative of future health burdens, as such utilising these findings when focusing public health efforts and tailoring targeted interventions to those at heightened risk could assist in reducing the trajectory of chronic disease incidence.

Chapter 3: Prevalence of noncommunicable diseases and developmental conditions in 5014 Australian adolescents, and their correlations with diet, other lifestyle behaviours, and mental health

Preface

Chapter 2 identified that the general population of adolescents worldwide, on average have inflammatory levels approaching low-grade inflammation, and those who are overweight or obese experiencing low-grade inflammation. Despite this, there is a lack of understanding of the prevalence of common and emerging non-communicable diseases and developmental conditions in adolescents, factors that are a cause or effect of heightened inflammation. Concurrently chapter 1 detailed potential pro-inflammatory risk factors such as the Big 6 health behaviours (poor nutritional intake, physical inactivity, increased screen time, unhealthy sleep, alcohol and tobacco intake), mental health and low SES and their limited exploration in adolescent populations. It is therefore important to explore associations between these factors and common and emerging conditions in adolescents to aid future prevention and treatments attempts. This chapter addresses these gaps and represents the first study worldwide to examine the associations between whole lifestyles (the Big 6 multiple health behaviours, mental health, and socio-demographics) and 11 different non-communicable diseases and developmental conditions in adolescents. This chapter uses the largest cohort of Australian adolescents to assess if associations between common and emerging conditions and health behaviours or mental health differ depending on sex and SES via the use interaction terms within individual regression models.

3.0 Introduction to the Health4Life trial

The Health4Life trial is a large cluster RCT conducted in Australian adolescents, across three states from 2019-2021. As one of the world's largest studies simultaneously examining health behaviours, mental health and noncommunicable disease and developmental condition prevalence in adolescents and to our knowledge, is the first in Australia conducted to date, the Health4Life trial provides a unique opportunity to examine their associations. Integrally multiple health behaviour change (MHBC) interventions allow for concurrent targeting of risk behaviours

that offer a solution for improving adolescent health and preventing future disease. I played significant roles in the development of the Health4Life intervention components, development of measures, recruitment and retention of participating schools and participants, data collection and scientific dissemination. Importantly, in the context of this thesis I led the inclusion of measures to assess non-communicable disease and developmental conditions. The first time such measures have been included in a multisite, multistate Australian trial of this size.

3.0.1 Health4Life sampling framework

Participants in year 7 (ages approximately 11-13 years old) were recruited for Heal4Life if they were fluent in English and provided active consent, along with having parental consent to participate. Due to differences in the number of available schools for recruitment across Australian states, 50% of the sample were recruited from New South Wales (NSW) (25% from Greater Sydney and 25% from other regions), 25% from Western Australia (WA) and 25% from Queensland (QLD). Recruitment was based on stratification by state/region and school gender mix (coeducational, predominantly male >60%, or predominantly female >60%), to ensure a near-even gender split in the total sample.

3.0.2 Health4Life school recruitment

Of the 72 schools recruited, 37 were from NSW, 16 from WA and 16 from QLD. The recruitment flow diagram in Figure 9 provides further details. The locations of the four separate recruitment sites consisted of two in NSW: 'Greater Sydney' Greater Capital City Statistical Area[506]) and Other NSW e.g. Hunter and Illawarra regions, WA: 600km radius from Perth and QLD: 100km radius from Brisbane.

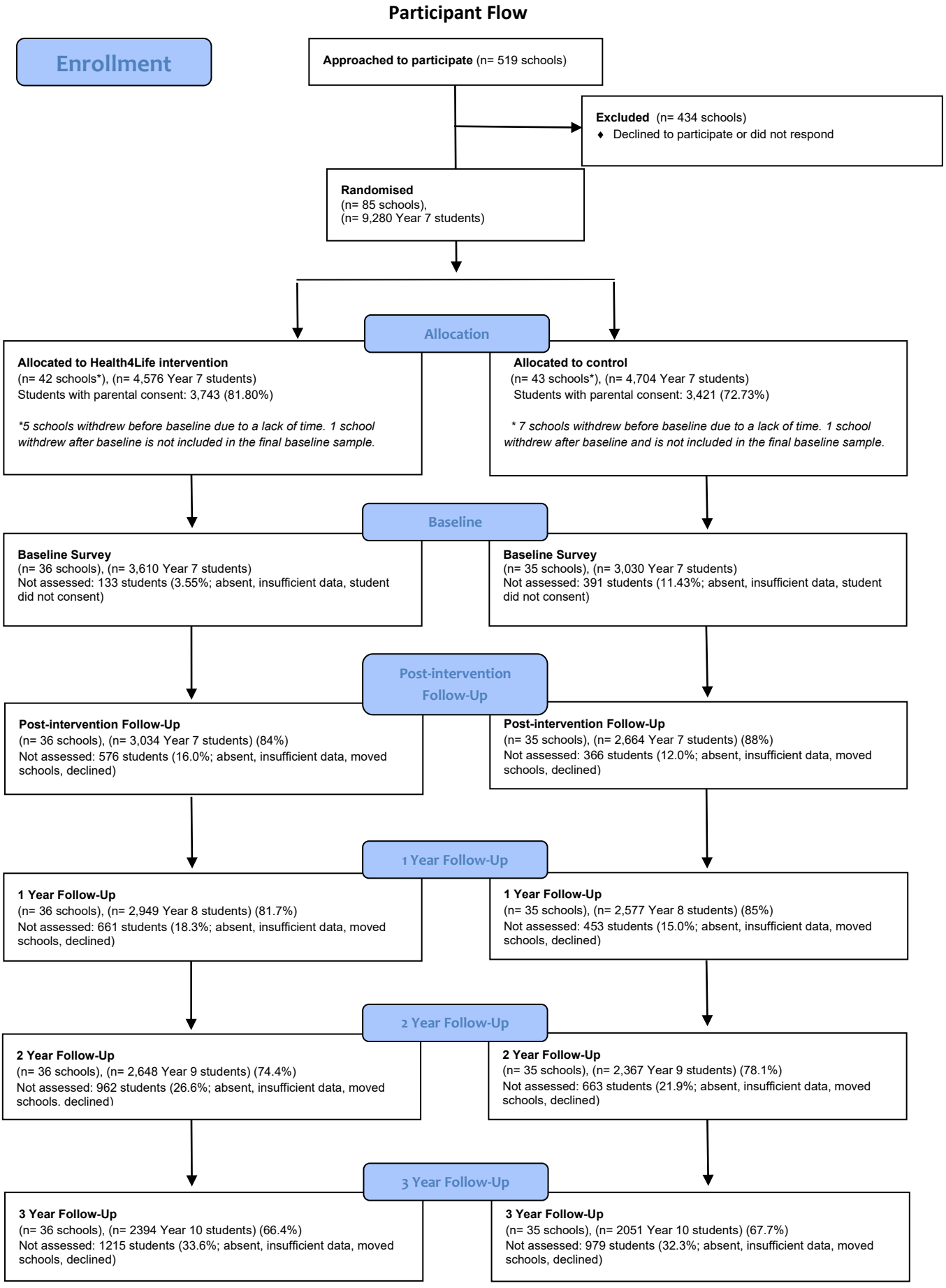

Participant Flow
Enrollment
Approached to participate (n= 519 schools)
Excluded (n= 434 schools)
♦ Declined to participate or did not respond
Randomised
(n= 85 schools),
(n= 9,280 Year 7 students)
Allocation
Allocated to Health4Life intervention
(n= 42 schools*), (n= 4,576 Year 7 students)
Students with parental consent: 3,743 (81.80%)
*5 schools withdrew before baseline due to a lack of time. 1 school withdrew after baseline is not included in the final baseline sample.
Allocated to control
(n= 43 schools*), (n= 4,704 Year 7 students)
Students with parental consent: 3,421 (72.73%)
* 7 schools withdrew before baseline due to a lack of time. 1 school withdrew after baseline and is not included in the final baseline sample.
Baseline
Baseline Survey
(n= 36 schools), (n= 3,610 Year 7 students)
Not assessed: 133 students (3.55%; absent, insufficient data, student did not consent)
Baseline Survey
(n= 35 schools), (n= 3,030 Year 7 students)
Not assessed: 391 students (11.43%; absent, insufficient data, student did not consent)
Post-intervention Follow-Up
Post-intervention Follow-Up
(n= 36 schools), (n= 3,034 Year 7 students) (84%)
Not assessed: 576 students (16.0%; absent, insufficient data, moved schools, declined)
Post-intervention Follow-Up
(n= 35 schools), (n= 2,664 Year 7 students) (88%)
Not assessed: 366 students (12.0%; absent, insufficient data, moved schools, declined)
1 Year Follow-Up
1 Year Follow-Up
(n= 36 schools), (n= 2,949 Year 8 students) (81.7%)
Not assessed: 661 students (18.3%; absent, insufficient data, moved schools, declined)
1 Year Follow-Up
(n= 35 schools), (n= 2,577 Year 8 students) (85%)
Not assessed: 453 students (15.0%; absent, insufficient data, moved schools, declined)
2 Year Follow-Up
2 Year Follow-Up
(n= 36 schools), (n= 2,648 Year 9 students) (74.4%)
Not assessed: 962 students (26.6%; absent, insufficient data, moved schools. declined)
2 Year Follow-Up
(n= 35 schools), (n= 2,367 Year 9 students) (78.1%)
Not assessed: 663 students (21.9%; absent, insufficient data, moved schools, declined)
3 Year Follow-Up
3 Year Follow-Up
(n= 36 schools), (n= 2394 Year 10 students) (66.4%)
Not assessed: 1215 students (33.6%; absent, insufficient data, moved schools, declined)
3 Year Follow-Up
(n= 35 schools), (n= 2051 Year 10 students) (67.7%)
Not assessed: 979 students (32.3%; absent, insufficient data, moved schools, declined)

Figure 9 - Health4Life trial participant flow diagram.

3.0.3 Health4Life data collection

Baseline and post intervention follow up timepoints occurred in 2019 (minimum 6-week gap between baseline and post intervention), 1-year follow up in 2020, 2-year follow up in 2021 and 3-year follow up in 2023. Figure 9 describes participant retention rates at each timepoint. Notably, the COVID-19 pandemic was present during the 12 and 24 month follow up (ages 13 and 14 years old). Self-report data variables collected during the Health4Life trial included demographic variables (age, gender and SES), dietary intake (references images of standard sizes were provided to participants to aid accurate reporting), moderate-to-vigorous physical activity, sleep, sedentary recreation screen time, alcohol and tobacco intake and mental health measures. Further details of measurements can be found later in this chapter (3.3.1 measures).

This chapter is currently under review:

Osman, B., Sunderland, M., Devine, E., Thornton, L., Jacka, F., Teesson, M., Prevalence of non-communicable diseases and developmental conditions in 5014 Australian adolescents, and their correlations with diet, other lifestyle behaviours, and mental health. *Australian and New Zealand Journal of Public Health (*Under review)

(Supplementary materials are available in Appendix 2)

3.1 Abstract

Objective: Amongst Australian youth there is currently a lack of understanding of the prevalence of noncommunicable diseases and developmental conditions and links with modifiable lifestyle behaviours, mental health, and other socio-demographics. This paper aims to address this gap.

Methods: 5014 Australian adolescents (Mage=14.7, SD=0.80) completed a self-report survey assessing noncommunicable diseases/developmental conditions, sex, SES, lifestyle behaviours and mental health. Multivariable logistic regressions were used to estimate the associations between these variables. The moderating effects of sex and SES was investigated by including interaction terms in each regression model.

Results: 45.6% (99%CI) adolescents reported ≥1 noncommunicable disease/developmental condition. Being female, consuming more sugar-sweetened beverages, ultra-processed foods, or alcohol, participating in more screen time, having depression, anxiety or psychological distress were each associated with higher rates of having at least one disease/condition ($p<0.01$). Sex and SES significantly moderated the associations between some lifestyle behaviours and eight diseases/conditions examined.

Conclusion: Australian adolescents experience considerable rates of noncommunicable diseases and developmental conditions, highlighting the significance of this public health issue.

Implications for public health: Links with lifestyle behaviours and mental health highlight their potential importance in public health to assist with prevention and treatment of these common and emerging noncommunicable diseases and developmental conditions in adolescents.

3.2 Objective

There is increasing recognition that a large proportion of Australian adolescents are living with noncommunicable diseases and developmental conditions[1]. Noncommunicable diseases such as diabetes or chronic respiratory disease are among the leading causes of death worldwide; these can be debilitating, being a significant burden physically and economically[507]. Public health

campaigns and research has predominantly focused on addressing noncommunicable diseases in adults, when prevalence is highest and they have caused oxidative stress for elongated periods of time, resulting in further cell damage, disability or even mortality[508]. Such conditions often co-occur with mental health problems as well as unhealthy lifestyle behaviours, which in turn are understood to increase the risk for common mental health problems as well as diseases or developmental conditions[508]. Developmental conditions are a group of disorders that can affect a person's learning, language, physical and behavioural development. Adolescence is a period where onset of many noncommunicable diseases and developmental conditions can occur. Significant physical and psychological adaptations, and poor lifestyle behaviour habits are commonly adopted during this time, making this a key period for prevention and intervention efforts. Yet, to our knowledge, there is no research assessing the associations between multiple lifestyle behaviours, mental health and socio-demographics with noncommunicable diseases or developmental condition prevalence in an Australian adolescent cohort.

Common and emerging noncommunicable diseases or developmental conditions are of primary interest. The most common noncommunicable diseases in adolescents are Atopic conditions such as asthma, eczema, food allergies and hay fever. Prevalence of these conditions has been rising worldwide since the 1980s[2] with particularly high prevalence in westernized countries.[3] Rates of common developmental conditions such as attention-deficit/hyperactivity disorder (ADHD) or autism have also been increasing. The onset of Irritable Bowel Syndrome (IBS) is most common during adolescence[10, 11] impacting the physical, educational, and social lives of sufferers[20]. These conditions, alongside further emerging noncommunicable diseases such as type 1 (T1D) and type 2 diabetes (T2D), significantly impact quality of life and can predispose an individual to further burden of disease or disability.

Lifestyle behaviours such as dietary intake, exercise, tobacco smoking and alcohol intake are linked to chronic disease incidence in adults[508], and emerging associations include poor mental health, sleep, and sedentary recreational screen time[508, 509]. Furthermore, some socio-demographics are understood to predispose an individual to specific conditions, for example those from lower socio-economic status (SES) have a higher risk of asthma[510], ADHD[511] and T2D[512], likely determined by a variety of environmental and behavioural exposures. Males are predisposed to higher rates of autism[513] or ADHD[1], whilst females to higher rates of IBS[514] and hay fever[515], predominantly due to genetic factors such as differing hormones. Additionally, IBS and asthma severity have been known to increase with poor mental health or

lifestyle behaviours [10, 516, 517] making them ideal candidates for targeted public health strategies.

There is a lack of evidence assessing associations between multiple-lifestyle behaviours, mental health, and socio-demographics with these common and emerging diseases/conditions in adolescents. Most worldwide research only evaluates one-to-two health or mental health behaviours with a singular noncommunicable disease or developmental condition, generally in small cohorts. Clarifying prevalence and furthering our knowledge of associations with these common and emerging conditions, at an age where there is an opportunity to intervene, may equip us with the information to inform future public health attempts and research on causality, as well as treatment strategies to mitigate some of the negative outcomes or even prevent their onset.

This study aims to address the gaps in research by using a large sample of Australian adolescents to: 1) Determine overall and specific prevalence of a wide range of common and emerging noncommunicable diseases and developmental conditions (i.e., IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D, T1D, ADD/ADHD and autism/Aspergers); 2) Determine overall and specific prevalence of these conditions separately for males and females and different SES; 3) Analyse associations between lifestyle behaviours (dietary intake, physical activity, sleep, screen time, tobacco and alcohol use) and mental health (psychological distress, depression and anxiety) with noncommunicable diseases, developmental conditions and related severity when controlling for sex and SES; and 4) assess whether these associations differ depending on sex and SES.

3.3 Methods

3.3.0 Participants

Participants were adolescents taking part in the Health4Life cluster RCT among 71 schools, across three Australian states (New South Wales, Queensland, and Western Australia)[370, 518]. As a part of this trial, baseline data was collected from 6639 consenting participants between June and December of 2019. Ethical approval for the study was provided by the Human Research Ethics Committees of the University of Sydney (2018/882), Curtin University (HRE2019-0083), the University of Queensland (2019000037), and relevant school sector ethics committees. This trial followed the Consolidated Standards of Reporting Trials (CONSORT)

guidelines and was prospectively registered (ACTRN12619000431123). Data for this study came from a follow up assessment via an online self-report survey, which was completed in 2021 by 5014 participants.

3.3.1 Measures

Measures validated for use among adolescents were used where possible. Full details of all measures and their cited origins are available in the supplementary material (Appendix 2.1), briefly summarized below.

Sociodemographics:

Participants were asked to report their sex assigned at birth; SES was assessed using the Family Affluence Scale (FAS-III)[519].

Lifestyle behaviours:

Four areas of dietary intake were assessed including ultra-processed food ('UPF' portions) per day-week, fruit (portions) per day, vegetable (portions) per day and sugar-sweetened beverages ('SSB' cups) per day-week. A single item assessed both Alcohol use *'Have you had a full standard alcoholic drink in the past 6 months?'* (*'No'/'Yes'*) and tobacco use '*In the past 6 months, have you tried cigarette smoking, even one or two puffs?'* (*'No'/'Yes'*). Screen time was assessed by time (hours/minutes) spent engaging in sedentary recreational screen time per day over an average week. Sleep durations were measured by average sleep per night (hours/minutes) over an average week. Physical activity (PA) assessed moderate-to-vigorous physical activity (MVPA) time per days/week.

Mental health:

Psychological distress was assessed using questions derived from the strengths and difficulties questionnaire (SDQ)[520], a score of ≤17 indicates having psychological distress. From responses to the patient health questionnaire (PHQ)[521], categorical (mild, moderate, moderately severe or severe) depression scores were calculated. From responses to the patient-reported outcomes measurement information system for anxiety (PROMIS-A)[522], categorical (mild, moderate or severe) anxiety scores were calculated.

Noncommunicable diseases and developmental conditions:

Noncommunicable disease and developmental condition diagnoses asked participants to report on the presence/absence of a variety of conditions. The most common and emerging diseases/conditions in adolescents of interest for this study were IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D, T1D, ADD/ADHD, and autism/Aspergers. A binary

'≥1 common/emerging condition' variable was calculated if one or more disease/condition was reported. Participants with IBS or asthma responded to additional severity questions, including: the IBS severity scale (IBS-SSS)[516] from which we calculated a binary score *('none/mild'* and *'moderate'/severe')*. The asthma severity scale[523] assessed the frequency of asthma attacks in the past 12 months and the persistence of symptoms between attacks in the past 12 months' producing binary scores (*'less than 1 per month'/'1 per month'* and *'1 per week'/'1 per day'; 'none'/'wheezing'* and *'wheezing and shortness of breath'/'activities limited by shortness of breath')*. The final asthma severity questions asked, 'have you had any hospitalization for asthma in the past 12 months' (*'No'/'Yes'*).

3.3.2 Statistical analysis

A data analysis plan was pre-registered prior to beginning analysis[524] and followed without deviation throughout the analysis. R packages were used to conduct all data cleaning and statistical analysis (*'lmtest'[525]* and *'interactions'[526])*. The sample characteristics were examined using descriptive statistics, prevalence estimates and standard errors were estimated using a cluster-robust sandwich estimate to account for clustering of students in each school. Prevalence for ≥1 common/emerging condition, each of the noncommunicable diseases or developmental conditions, and IBS and asthma severity were also estimated separately by sex and SES. Significant differences between sex and SES groups were determined using logistic regression. Separate multivariable logistic regressions were then used to individually estimate the associations between UPF, SSB, fruit, vegetables, exercise, sleep, screen time, alcohol and tobacco use, psychological distress, depression, anxiety with noncommunicable diseases or developmental conditions or IBS and asthma severity, controlling for sex at birth and SES. Associations were considered significant at a $p<0.01$ and odds ratios with 99% confidence intervals (99%CI) were estimated.

Additional moderation analyses on each of the multivariable logistic regressions were conducted by including interaction terms between each of the lifestyle behaviours or mental health covariates with sex and SES, separately. Statistically significant interaction terms were identified ($p<0.01$) and the associations were graphed separately for each level of the moderator. Further robustness analysis was run to generate E-values based on significant associations, these define the minimum strength of an association on the odds ratios that an unmeasured confounder would need to have with the outcome and the predictor to fully explain away a specific predictor-outcome association.

3.3.3 Missing data analysis

A binary variable was created representing those present at baseline-only versus those who completed one or more follow-up surveys. T-tests were used to investigate differences between missing lifestyle behaviours and mental health conditions on baseline continuous variables. Binary and multinomial logistic regressions were used for dichotomous and categorical variables, respectively. Listwise deletion was used when dealing with missing data.

3.4 Results

A total of 5014 participants completed the self-report cross-sectional survey (Mage=14.68 SDage=0.82), there was an even split of sex and most participants were from upper SES and major cities (Table 6 for more information). Included in the main analysis was 4651 participants who reported on at least one noncommunicable disease or developmental condition or 'no diseases or conditions'.

3.4.0 Descriptives

The rates of individual lifestyle behaviours and mental health measures are presented in Table 6, and their differences between those with ≥1 common/emerging disease/condition and those without. Overall, 45.6% (Appendix 2.2) of adolescents reported having at least one of the ten noncommunicable diseases or developmental conditions of interest. The specific prevalence of each condition is presented in Appendix 2.2, of the noncommunicable diseases hay fever (23.2%) and asthma (15.1%) were the most prevalent and T2D (1.0%) was the least prevalent. ADHD/ADD (9.4%) was the most prevalent developmental condition. The severity of conditions is reported in Appendix 2.2. Of note 52% of those with IBS were experiencing moderate/severe IBS severity. Of those with asthma 51% had shortness of breath or activities limited by shortness of breath between asthma attacks, and 13% were hospitalised by asthma in the last 12 months.

Rates varied between sex, with 53.5% of females reporting having ≥1 common/emerging disease/condition compared to 45.5% males (p<0.001) (Table 6). Specifically, females had higher odds of having eczema (OR=1.96, 99%CI 1.51-2.54), food allergies (OR=1.50, 99%CI 1.15-1.97), hay fever (OR=1.36, 99%CI 1.08-1.72), and more persistent asthma symptoms (OR=2.04, 99%CI 1.23-3.38), compared to males; whilst males had higher odds of having ADHD/ADD

(OR=0.73, 99%CI 0.55-0.98), autism/Aspergers (OR=0.73, 99%CI 0.55-0.98), T1D (OR=0.25, 99%CI 0.10-0.59) and T2D (OR=0.12, 99%CI 0.03-0.48) compared to females (Table 7).

Table 6 - Descriptive statistics of participants split by those having at least one common and emerging noncommunicable disease or developmental condition and those without.

Descriptive Statistics

Variable	**All participants**, N = 5,014[1]	**No common/ emerging condition**, N = 2,008[1]	**≥1 common/emerging condition,** N = 1,683[1]	**p-value**[2]
Sex assigned at birth				<0.001
Male	2,481 (49.5%)	1,048 (52.2%)	765 (45.5%)	
Female	2,465 (49.2%)	939 (46.8%)	898 (53.5%)	
Prefer not to say	62 (1.2%)	21 (1.0%)	17 (1.0%)	
Unknown	6	0	3	
Age (years)	14.68 (0.82)	14.68 (0.67)	14.68 (0.94)	0.846
Unknown	7	0	4	
Socio-economic status[3]				0.822
Lower 20%	671 (14.6%)	279 (14.9%)	222 (14.3%)	
Middle 40%	1,711 (37.2%)	699 (37.4%)	581 (37.3%)	
Upper 40%	2,223 (48.3%)	889 (47.6%)	754 (48.4%)	
Unknown	409	141	126	
Regionality				0.141
Major city	4,547 (90.7%)	1,838 (91.5%)	1,516 (90.1%)	
Inner/Outer regional	467 (9.3%)	170 (8.5%)	167 (9.9%)	
UPF intake	6.12 (4.44)	5.73 (3.71)	6.47 (5.02)	<0.001
Unknown	688	140	125	
Servings of fruit per day	2.15 (1.01)	2.20 (0.95)	2.13 (1.04)	0.143
Unknown	393	51	32	
Servings of vegetables per day	2.78 (1.20)	2.77 (1.14)	2.76 (1.18)	0.908
Unknown	268	1	2	
Cups of SSB per week	1.05 (1.32)	0.98 (1.18)	1.06 (1.37)	0.044
Unknown	259	2	2	
Number of days per week engaging in PA[4]	4.00 (2.11)	4.08 (2.08)	3.98 (2.10)	0.146
Unknown	294	5	8	
Screen time per day (hrs.)	6.79 (5.40)	6.30 (4.49)	6.97 (5.92)	<0.001
Unknown	281	24	35	
Sleep per night (hrs.)	8.56 (1.30)	8.56 (1.21)	8.56 (1.30)	0.982
Unknown	394	97	103	
Alcoholic drink in the last 6mnths				<0.001
No	3,952 (84.0%)	1,736 (86.6%)	1,380 (82.1%)	
Yes	750 (16.0%)	269 (13.4%)	300 (17.9%)	
Unknown	312	3	3	
Cigarette in the last 6mnths				0.298

Variable	All participants, N = 5,014[1]	No common/ emerging condition, N = 2,008[1]	≥1 common/emerging condition, N = 1,683[1]	p-value[2]
No	4,763 (98.7%)	1,927 (99.1%)	1,608 (98.7%)	
Yes	61 (1.3%)	17 (0.9%)	21 (1.3%)	
Unknown	190	64	54	
Psychological distress				<0.001
No	3,605 (77.5%)	1,691 (84.3%)	1,247 (74.2%)	
Yes	1,047 (22.5%)	314 (15.7%)	434 (25.8%)	
Unknown	362	3	2	
Depression severity				<0.001
None/minimal	2,234 (48.4%)	1,101 (55.2%)	768 (46.1%)	
Mild depression	1,115 (24.1%)	495 (24.8%)	387 (23.2%)	
Moderate depression	641(13.9%)	233 (11.7%)	235 (14.1%)	
Moderately severe depression	346 (7.5%)	103 (5.2%)	144 (8.6%)	
Severe depression	282 (6.1%)	62 (3.1%)	131 (7.9%)	
Unknown	396	14	18	
Anxiety severity				<0.001
None/slight	3,068 (66.6%)	1,476 (74.3%)	1,055 (63.7%)	
Mild	483 (10.5%)	189 (9.5%)	181(10.9%)	
Moderate	748 (16.2%)	255 (12.8%)	283 (17.1%)	
Severe anxiety	306 (6.6%)	67 (3.4%)	137 (8.3%)	
Unknown	409	21	27	

[1]n (%); Mean (SD)

[2] Pearson's Chi-squared test; Welch Two Sample t-test examining differences between those with ≥1 common/emerging condition and those without.

[3] Relative socio-economic status within this cohort

[4]Moderate to vigorous physical activity for at least 60 minutes a day

3.4.1 Binary logistic regressions

3.4.1.0 Noncommunicable diseases and developmental conditions

In the binary logistic regression models (Table 7) having ≥1 common/emerging condition was associated with consuming more SSB (OR=1.08, 99%CI 1.01-1.15), UPF (OR=1.03, 99%CI 1.01-1.06) or alcohol (OR=1.39, 99%CI 1.08-1.79), participating in more screen time (OR=1.02, 99%CI 1.00-1.04), having severe rates of depression (OR=2.98, 99%CI 1.96-4.53), severe anxiety (OR=2.69, 99%CI 1.85-3.91) or reporting psychological distress (OR=1.85, 99%CI 1.46-2.34). Nonsignificant binary logistic regression models can be found in table Appendix 2.3.

IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D, T1D, ADHD/ADD and autism/Aspergers were each individually associated with increased UPF intake, having drank alcohol or smoked tobacco, or having psychological distress, more severe anxiety and

depression. The strongest associations found that the odds of T2D were higher in those who smoked tobacco (OR=29.58, 99%CI 12.18-71.83), drank alcohol (OR=13.18, 99%CI 5.52-31.4) or with severe anxiety (OR=45.04, 99%CI 1.40-144.29) and that the odds of chronic fatigue were higher in those with severe depression (OR=18.30, 99%CI 6.83-49.01). All diseases/conditions apart from hay fever were also significantly associated with higher screen time. T2D, Chronic fatigue and autism were each significantly associated with almost all of the lifestyle behaviours or mental health conditions.

3.4.1.1 Noncommunicable disease severity

Of the adolescents with IBS, those who drank alcohol (OR=6.44, 99%CI 1.68-24.56) or smoked tobacco (OR=12.03, 99%CI 2.29-63.11) had increased odds of having more severe IBS symptoms than those who did not (Appendix 2.6).

Of the adolescents with asthma, between the severity measures of higher frequency of asthma attacks, more persistent asthma symptoms in the past 12 months and having been hospitalized for asthma in the past 12 months, there were associations with all lifestyle behaviours and mental health measures other than PA. The odds of more frequent asthma attacks were higher in those who had smoked (OR=5.53, 99%CI 2.25-13.59), odds of more persistent asthma symptoms were higher in those who had severe depression (OR=2.98, 99%CI 1.39-6.36) and odds of being hospitalized for asthma in the past 12 months were higher in those who had smoked (OR=6.48, 99%CI 2.43-17.29), have severe depression (OR=13.78, 99%CI 4.79-39.67) or anxiety (OR=8.61, 99%CI 3.11-23.77) (Appendix 2.6).

3.4.1.2 Sex and SES moderations of noncommunicable diseases and developmental conditions

Looking at the sex moderation analysis, associations between having ≥1 common/emerging condition, IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D with some lifestyle behaviours or mental health measures were significantly moderated by sex (Appendix 2.4, Figure 10 & Appendix 2.9). The strongest associations found that of all the adolescents who drank alcohol (OR=0.17, 99%CI 0.05-0.63) or had severe anxiety (OR=0.15, 99%CI 0.02-0.93), males had higher odds of having chronic fatigue in comparison to females (Appendix 2.4, Figure 10). Secondly, of all of those with severe anxiety (OR=0.12, 99%CI 0.03-0.50) or severe depression (OR=0.21, 99%CI 0.04-0.97) males had increased odds of having IBS in comparison to females (Appendix 2.4, Figure 10).

Looking at the SES moderation analysis, SES only moderated associations between chronic fatigue, food allergies, T2D, autism/Aspergers and some of the lifestyle behaviours and mental health measures (Appendix 2.5). The strongest associations found that of all those adolescents with mild anxiety, those from low SES had higher rates of T2D compared to those from high SES (OR= 0.54, 99%CI 0.28-1.03) (Appendix 2.5). Secondly, of all those adolescents consuming less vegetables or participating in less PA, those from high SES had higher rates of autism/Aspergers than those from low SES (vegetable OR=0.93, 99%CI 0.88-0.97; PA OR=0.93, 99%CI 0.88-0.97) (Appendix 2.5).

3.4.1.3 Sex and SES moderations of noncommunicable disease severity

Looking at the sex moderation analysis, associations between IBS and asthma severity and SSB intake, depression and anxiety were significantly moderated by sex (Appendix 2.7). The strongest associations found that of all the adolescents who consumed more SSB, males had higher odds of more severe IBS in comparison to females (OR=0.51, 99%CI 0.27-0.93) (Appendix 2.7). Secondly, of all of those who had severe depression, males had higher odds of frequent asthma attacks in comparison to females (OR=0.09, 99%CI 0.00-0.92), and of those who had severe anxiety, males had increased odds of being hospitalised by asthma in the past 12 months in comparison to females (OR=0.03, 99%CI 0.00-0.25) (Appendix 2.7). There were no significantly SES moderations with severity of IBS and asthma

Table 7 - Binary logistic regressions to estimate the associations between lifestyle behaviours/mental health and individual common and emerging diseases/conditions, whilst controlling for sex at birth and SES, including E-values for significant associations only.

Variables	≥1 common/ emerging condition		Irritable Bowel Syndrome		Asthma		Eczema		Type 2 Diabetes		Chronic Fatigue		Hay fever		Food Allergies		ADD/ADHD		Autism/ Aspergers		Type 1 Diabetes	
	OR[1]	**99%CI[2]**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**
Sex – Female[3]	1.31 **	1.08-1.58	0.70	0.45-1.09	0.90	0.75-1.09	1.96 **	1.51-2.54	0.12 **	0.03-0.48	0.88	1.54	1.36 **	1.08-1.72	1.50 **	1.15-1.97	0.73 *	0.55-0.98	0.73 *	0.55-0.98	0.25 **	0.10-0.59
E-value	**1.95**						**2.15**		**16.15**				**1.61**		**2.37**		**2.08**		**2.08**		**7.46**	
UPFs	1.03 **	1.01-1.06	1.14 **	1.10-1.18	1.04 **	1.02-1.06	1.04 **	1.01-1.07	1.19 **	1.13-1.25	1.15 **	1.10-1.20	1.02 *	1.00-1.69	1.03 *	1.00-1.07	1.06 **	1.03-1.09	1.10 **	1.06-1.14	1.18 **	1.12-1.23
E-value	**1.21**		**1.54**		**1.24**		**1.16**		**1.67**		**1.57**		**1.11**		**1.21**		**1.31**		**1.43**		**1.64**	
SSB	1.08 *	1.01-1.15	1.45 **	1.17-1.81	1.13 **	1.04-1.23	1.02	0.90-1.16	1.68 **	1.35-2.08	1.48 **	1.24-1.76	1.03	0.94-1.13	1.08	0.96-1.22	1.18 **	1.08-1.29	1.28 **	1.10-1.50	1.52 **	1.26-1.84
E-value	**1.37**		**2.26**		**1.51**				**2.75**		**2.32**						**1.64**		**1.88**		**2.41**	
Alcoholic drink <6mnths - Yes[4]	1.39 **	1.08-1.79	6.91 **	4.28-11.16	1.45 **	1.12-1.87	1.49 *	1.04-2.14	13.18**	5.52-31.4	4.73 **	2.62-8.56	1.36 *	1.04-1.77	1.43 *	1.01-2.03	2.63 **	1.94-3.55	2.74 **	1.81-4.16	6.09 **	3.26-11.37
E-value	**2.13**		**13.3**		**2.26**		**1.74**		**25.85**		**8.93**		**1.61**		**2.21**		**4.7**		**4.92**		**11.66**	
Tobacco <6mnths – Yes[5]	1.35	0.58-3.12	13.55**	7.55-24.30	2.64 **	1.85-3.75	1.86 *	1.13-3.07	29.58**	12.18-71.83	8.94 **	4.47-17.88	1.88 **	1.39-2.54	1.74 *	1.07-2.83	5.49 **	3.71-8.14	4.98 **	2.80-8.86	16.42**	7.09-38.02
E-value			**26.59**		**4.72**		**2.07**		**58.66**		**17.37**		**2.08**		**2.87**		**10.45**		**9.43**		**32.33**	
Screen time	1.02 **	1.00-1.04	1.14 **	1.11-1.18	1.03 **	1.01-1.05	1.03 *	1.00-1.06	1.13 **	1.08-1.18	1.10 **	1.06-1.14	1.00	0.99-1.02	1.03 **	1.00-1.06	1.06 **	1.04-1.08	1.07 **	1.05-1.11	1.11 **	1.06-1.15
E-value	**1.16**		**1.54**		**1.21**		**1.14**		**1.51**		**1.43**				**1.21**		**1.31**		**1.34**		**1.46**	
Sleep	1.00	0.92-1.09	0.77 *	0.61-0.96	0.95	0.86-1.05	0.98	0.86-1.12	0.64 **	0.46-0.89	0.68 **	0.54-0.85	0.96	0.89-1.04	0.99	0.88-1.12	0.90	0.79-1.02	0.91	0.74-1.12	0.73	0.53-1.01
E-value			**1.92**						**2.5**		**2.3**											
Physical activity	0.98	0.95-1.02	0.85	0.72-1.00	1.01	0.95-1.07	0.96	0.91-1.01	0.82	0.66-1.01	0.83 *	0.71-0.97	1.02	0.98-1.05	0.99	0.93-1.06	0.93	0.87-1.01	0.82 **	0.72-0.92	0.88	0.73-1.05
E-value											**1.7**								**1.74**			

Psychological distress – Yes[6]	1.85**	1.46-2.34	3.94**	2.25-6.89	1.70**	1.34-2.16	1.29*	1.00-1.66	10.87**	5.13-23.01	7.82**	4.43-13.78	1.47**	1.17-1.84	1.72**	1.33-2.24	3.46**	2.68-4.46	4.33**	2.68-6.97	7.86**	3.95-15.61
E-value	**3.1**		**7.34**		**2.79**		**1.53**		**21.23**		**15.12**		**1.72**		**2.83**		**6.38**		**8.13**		**15.2**	
Depression – Mild[7]	1.08	0.86-1.35	1.03	0.44-2.39	1.18	0.88-1.59	1.08	0.81-1.43	0.86	0.17-4.21	1.70	0.66-4.34	1.19	0.94-1.49	0.99	0.71-1.38	1.70**	1.18-2.44	1.51	0.78-2.94	0.60	0.14-2.45
E-value																	**2.79**					
Depression - Moderate[7]	1.37*	1.06-1.79	2.05	0.87-4.85	1.33	0.97-1.83	0.88	0.58-1.20	3.04	0.75-12.33	3.92**	1.59-9.62	1.34**	1.03-1.76	1.29	0.84-1.99	2.15**	1.42-3.26	1.83	0.87-3.82	2.47	0.92-6.59
E-value	**2.08**										**7.3**		**1.58**				**3.72**					
Depression - Moderately severe[7]	1.87**	1.31-2.66	2.87	0.94-8.72	1.82**	1.27-2.60	1.17	0.77-1.77	5.66*	1.38-23.07	7.80**	3.06-19.85	1.31	0.92-1.86	1.53	0.98-2.40	4.54**	2.89-7.13	4.86**	2.58-9.16	2.63	0.79-8.75
E-value	**3.15**		**5.19**		**3.04**		**1.38**		**10.8**		**15.08**		**1.55**		**2.43**		**8.55**		**9.19**		**4.7**	
Depression - Severe[7]	2.98**	1.96-4.53	11.13**	5.19-23.83	2.65**	1.75-4.02	1.87*	1.08-3.23	24.4	8.03-74.59	18.30**	6.83-49.01	1.81**	1.25-2.63	1.86*	1.02-3.38	6.41**	3.86-10.64	5.76**	2.87-11.56	13.80**	5.51-34.58
E-value	**5.41**		**21.75**		**4.74**		**2.08**				**36.09**		**2.03**		**3.12**		**12.3**		**11**		**27.09**	
Anxiety – Mild[8]	1.31	0.92-1.88	2.16	0.78-5.99	1.40*	1.01-1.91	1.24	0.78-1.97	3.76	5.99-23.69	3.39	0.92-12.47	1.35*	1.02-1.78	1.33	0.84-2.09	1.51	0.90-2.53	2.59**	1.35-4.96	2.21	0.48-9.99
E-value					**2.15**								**1.6**						**4.62**			
Anxiety - Moderate[8]	1.47**	1.11-1.94	3.54**	1.85-6.78	1.33*	1.02-1.73	0.84	0.60-1.19	7.69**	2.40-24.62	5.00**	2.06-12.17	1.22	0.98-1.52	1.70**	1.23-2.35	2.83**	2.06-3.89	3.59**	1.91-6.75	4.45**	1.65-11.99
E-value	**2.3**		**6.54**		**1.99**				**14.86**		**9.47**				**2.79**		**5.11**		**6.64**		**8.37**	
Anxiety - Severe[8]	2.69**	1.85-3.91	15.68**	7.95-30.92	2.39**	1.48-3.86	2.14**	1.36-3.39	45.04**	1.40-144.29	24.85**	9.48-65.16	1.65**	1.13-2.43	2.23**	1.47-3.38	5.30**	3.50-8.03	7.66**	4.17-14.06	18.72**	6.82-51.32
E-value	**4.82**		**30.85**		**4.21**		**2.29**		**89.58**		**49.19**		**1.89**		**3.89**		**10.07**		**14.8**		**36.93**	

[1] Odds ratios
[2] 99% Confidence intervals
[3] These results are compared to males
[4] These results are compared to those who have not drank alcohol in the past 6 months
[5] These results are compared to those who have not smoked tobacco in the past 6 months
[6] These results are compared to those who do not have psychological distress
[7] These results are compared to those with no depression
[8] These results are compared to those with no anxiety
* P<0.01
** P<0.001

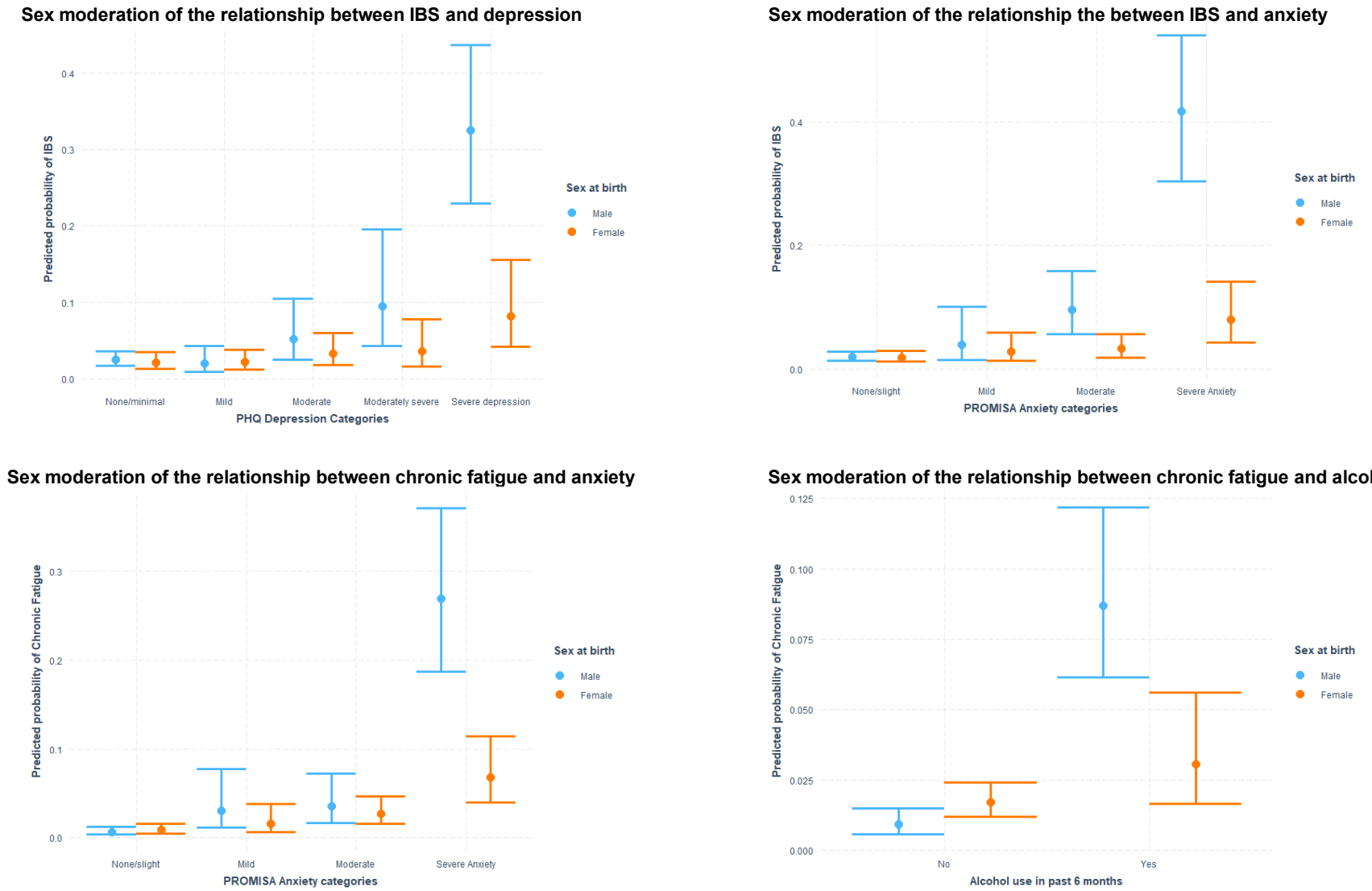


Figure 10 - Sex moderation analysis of binary logistic regressions interaction graphs of the strongest significant associations.

3.5 Discussion

This study aimed to determine the prevalence of and associations between noncommunicable diseases and developmental conditions and related severity with lifestyle behaviours and mental health in a large cohort of adolescents, it also aimed to assess whether these associations differed depending on sex and SES. In the current study, almost half of the adolescents reported having at least one noncommunicable disease or developmental condition, highlighting the significance of this public health issue amongst adolescents. Asthma, hay fever, eczema, food allergies and ADHD were the most prevalent diseases/conditions. According to the Australian National Health Survey 2020-2021[527], 11.7% of 15-17 year olds had asthma, the slightly higher rate in this sample (15.1%) may be due to the high proportion living in a metropolitan area, which is known to correlate with a higher risk of asthma compared to those living in a regional area[510]. The prevalence of hay fever (23.3%), food allergies (10.1%) and ADD/ADHD (9.4%) aligned with the rates found in recent Australian literature[21, 527, 528], however our sample reported a lower prevalence of eczema (10.6%)[529]. Of concern adolescents that have IBS and asthma were reporting severe symptomology, this proves problematic during adolescence as it can result in reduced physical activities and impacts to mental health [10, 20, 517] which can further induce a continuous cycle of inflammation. The common atopic diseases, such as hay fever, eczema, food allergies and persistent asthma symptoms were more prevalent in females. In line with the literature males had higher rates of the developmental conditions ADHD[1] and autism/Aspergers[513] and reported higher rates of T1D [530] and T2D.

Poor lifestyle behaviours of tobacco, alcohol, or high UPF intake and poor mental health measures of psychological distress, moderately-severe depression and severe anxiety, were significantly associated with every noncommunicable disease or developmental condition measured. The strong associations found between tobacco and alcohol and these noncommunicable diseases and developmental conditions could be in part explained by both behaviours being less normative in Australian adolescents, therefore it is increasingly seen as an indicator of severity of physical and mental health across the board much like other externalizing conditions[531]. UPF intake in adolescents has been increasing and its association with poor health outcomes is supported by a growing body of evidence, highlighting its detrimental effect on cardiometabolic and inflammatory markers contributing to chronic disease prevalence[136]. There is an independent bi-directional relationship between UPF and mental health conditions[137], making it understandable for these two variables to be significantly associated

with noncommunicable diseases/developmental conditions in tandem. Poor mental health can inhibit an inflammatory response[532] and dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) altering hormonal balance[533]. This can contribute to the onset of disease and vice versa which could help justify this strongest associations found between psychological distress, moderate-to-severe anxiety, and depression with each one of the noncommunicable diseases and developmental conditions measured. Finally, participating in more screen time was associated with all diseases/conditions apart from hay fever. Screen time usage is currently at an all-time high in adolescents, known to coincide with adverse health outcomes such as weight status, depression, poor physical activity and social support[534]. Overall findings illustrate those adolescents with noncommunicable diseases or developmental conditions are generally in worse physical and mental health than their peers, outlining their vulnerability and the demand for targeted interventions. Multiple health behaviour change public health efforts and programs should consider specifically emphasizing tobacco, alcohol and UPF avoidance and improving mental health to best assist with prevention and treatment of these common and emerging diseases/conditions.

Examination of the associations with noncommunicable disease severity allows for a greater understanding of this bilateral relationship, giving the potential to inform alleviation or minimization of symptoms. The associations between asthma severity and almost all lifestyle behaviours and mental health measures (Appendix 2.6) contributes important insights from Australian data. Linkages between poor mental health, lifestyle behaviours and asthma severity have previously been established in the UK, Taiwan, Canada, Sweden and USA[517]. Risk taking behaviours such as alcohol or tobacco use have been associated with worse asthma outcomes such as poorer health, medication adherence or symptom control [535], whilst a proinflammatory diet (high in UPFs, SSB, low in fruit and vegetables) have been linked to worsened asthma prevalence and symptomology[535, 536]. Simultaneously some studies suggest having a chronic condition at a young age could be the driver for more risky lifestyle behaviours or poorer mental health[517], whilst there are mixed findings that some types of medication to treat asthma such as corticosteroids, may itself be the reason for worsened mental health. Overall whilst there are clear associations, the direction of relationships are speculatory and further longitudinal research is required to examine causal relationships.

Critically we found that males disproportionately had more associations with noncommunicable diseases or developmental conditions than females when their lifestyle behaviours or mental

health were worse. Males reporting poor mental health were found to have the strongest relationships with the most noncommunicable diseases (Appendix 2.4, Figure 10 & Appendix 2.9) (≥1 common/emerging condition, IBS, asthma and asthma severity, eczema, chronic fatigue, hay fever, food allergies). One explanation for this could be due to research showing that males generally have lower rates of mental health issues than females, possibly caused by underreporting due to cultural stigma or failure to seek help[537], therefore males reporting poor mental health could potentially represent a greater marker of severity. Other poor lifestyle behaviours such as drinking alcohol or tobacco use were also strongly associated with higher prevalence of noncommunicable diseases compared to females. The increase in testosterone males experience during adolescence could inhibit more impulsive or sensation seeking behaviour[538], or increased susceptibility to adhere to peer pressure[539]. These findings highlight that males are at higher risk of partaking in the onset of alcohol or tobacco use, whether it is a cause or effect of a noncommunicable disease, making these behaviours important to target in public health messaging and future prevention programs.

Although there is evidence of SES disparities in health, there were minimal significant interactions in this sample, which could be in part explained by our cohort being generally from higher SES. Many associations were centred around dietary intake, as both high UPF and low SES are both independent risk factors for chronic fatigue[540, 541] it is unsurprising that our findings of adolescents eating higher UPF were more likely to report chronic fatigue if they were from low SES compared to their high SES counterparts. However, of interest was the higher rates of food allergies and autism/Aspergers in those from high SES when vegetable intake and PA was lower when compared to those from low SES. When assessing relationships with autism/Aspergers consideration needs to be given to SES. Individuals from lower SES cohorts may be underdiagnosing autism/Aspergers due to lack of resources or awareness. This has been reported elsewhere as a contributing to factor for increased diagnoses in higher SES [542, 543].

3.5.0 Limitations

This research was broadly exploratory and designed for hypothesis generation, having some limitations. Firstly, many statistical tests were undertaken and despite using more conservative p-values and conducting further robustness analysis on significant results via E-values, there could still be an increased risk for false positives in findings. Secondly, there is a potential bias that can occur when using self-report data. However, prevalence of poor lifestyle behaviours, mental health, noncommunicable diseases and developmental conditions in this study were similar to, or

higher than, recent Australian government data adding confidence to the findings. The second limitation of this study is the cross-sectional study design, which limits our ability to establish causal relationships. Finally, whilst our sample spanned across three Australian states, most of the participants were from urban areas and generally from higher SES backgrounds meaning the sample was not nationally representative.

3.6 Conclusion

In a large cohort of Australian adolescents nearly half reported have one or more noncommunicable disease or developmental condition which can impact current physical and mental health, and potentially contribute to future disease or disability. Whilst this cross-sectional analysis cannot depict the causal effect of lifestyle behaviours, mental health, and socio-demographics on condition prevalence these associations highlight the important inter-relationship signifying the need for a whole lifestyle approach to help with future public health prevention and treatment attempts. Finally, understanding if these associations are moderated by sex is vital to better understand differences between males and females' experiences and ultimately help to better guide future public health efforts. Further research is needed using longitudinal data to obtain an improved understanding of causal relationships and further inform future public health messaging.

Chapter 4: Exploring the association between adolescent-perceived parental monitoring on dietary intake

Preface

Chapter 1 provided a synopsis of the available data on the contemporary prevalence of poor dietary intake in adolescents. It is well established that poor dietary intake is a leading contributor to adolescent obesity, and chapter 2 discovers that generally adolescents who are overweight or obese are experiencing chronic inflammation. Furthermore, chapter 3 establishes that poor dietary intake is associated with higher rates of non-communicable diseases and developmental conditions in Australian adolescents, particularly UPF being associated with all common and emerging conditions measured. Subsequently it is important to explore contributing factors that are associated with adolescent dietary intake, to help guide future prevention attempts and public health messaging. A prominent and potentially important factor is type of parenting style. One parenting style that has undergone initial exploration in its relationship with adolescent dietary intake is parental monitoring. Previous literature suggests that greater levels of parental monitoring is associated with favourable adolescent dietary intake, highlighting its potential as a target to improve widespread poor dietary intake in adolescents, reduce obesity rates and subsequently lower levels of chronic inflammation. Adolescent-perceived parental monitoring, however, has not before been explored, an important construct as it represents an adolescent's actual experience of how they are parented. This chapter addresses this important gap by exploring the associations between adolescent-perceived parental monitoring and dietary intake from four key food groups, in a large sample of Australian adolescents.

This chapter has been published:

1. Osman, B., Champion, K.E., Thornton, L., Burrows, T., Smout, S., Hunter, E., Sunderland, M., Teesson, M., Newton, N. C., & Gardner, L. A. (2024). Exploring the association between adolescent-perceived parental monitoring on dietary intake. *Maternal & Child Nutrition*, 20, e13650. https://doi.org/10.1111/mcn.13650

4.0 Abstract

Introduction

Parenting practices such as parental monitoring are known to positively impact dietary behaviours in offspring. However, links between *adolescent-perceived* parental monitoring and dietary outcomes have rarely been examined and never in an Australian context. This study investigated whether adolescent-perceived parental monitoring is associated with more fruit, and vegetable, and less sugar-sweetened beverages (SSB) and junk food consumption in Australian adolescents.

Methods and Measures

Cross-sectional data were collected as part of baseline measurement for a RCT in 71 Australian schools in 2019. Self-reported fruit, vegetable, SSB and junk food intake, perceived parental monitoring and sociodemographic factors were assessed. Each dietary variable was converted to 'not at risk/at risk' based on dietary guidelines, binary logistic regressions examined associations between dietary intake variables and perceived parental monitoring whilst controlling for gender and SES. ANZCTR clinical trials registered (ACTRN12619000431123).

Results

The sample comprised 6053 adolescents (M_{age}=12.7, SD=0.5; 50.6% male-identifying). The mean parental monitoring score was 20.1/24 (SD=4.76) for males and 21.9/24 (SD=3.37) for females. Compared to adolescents who perceived lower levels of parental monitoring, adolescents reporting higher parental monitoring had higher odds of insufficient fruit (OR=1.03; 95%CI=1.02-1.05) and excessive SSB (OR=1.07; 95%CI=1.06-1.09) intake, but lower odds of excessive junk food (OR=0.96; 95%CI=0.95-0.98) and insufficient vegetable (OR=0.97, 95%CI=0.96-0.99) intake.

Conclusion

Adolescent dietary intake is associated with higher perceived parental monitoring; however, these associations for fruit and SSB differ to junk food and vegetable intake. This study may have implications for prevention interventions for parents, identifying how this modifiable parenting factor is related to adolescent diet has highlighted how complex the psychological and environmental factors contributing to dietary intake are.

4.1 Introduction

Adolescence is a critical period characterised by increases in autonomy, shifting influences on dietary intake and greater consumption of junk foods and beverages[355]. The occurrence of puberty during adolescence signifies a vital period of development, where balanced nutritional intake is of high importance to support neurological and physiological growth[544]. This rapid growth period requires considerable nutrient demand as it is a time when 45% of skeletal growth takes place[545] and up to 37% of total bone mass may be accumulated[546]. However, adolescents are a nutritionally vulnerable group. Data show that 95% of 12-17 year-olds in Australia[547] and 92% of 11-18 year olds in the United Kingdom[548] do not meet the recommended daily guidelines for fruit and vegetable intake, while 9-13 year-olds in America have a mean Healthy Eating Index dietary score of 46.85 (SD 24.93), significantly below the score of 100 indicating meeting dietary guidelines[549] and similar patterns have been reported in Canada[550] and Europe[551]. This age group also consume the most added sugars[552], with 10% of this population consuming 1 cup of sugar-sweetened beverages (SSB) per day[553]. Poor dietary intake and nutritional patterns established in adolescence tend to track into adulthood and are associated with an increased risk of later chronic diseases, such as cardiovascular disease and some cancers[554].

To ensure adolescents lay strong nutritional foundations early in life to prevent diet related disease in later life, an improved understanding of the modifiable parenting factors influencing adolescent dietary intake is needed. According to a comprehensive model proposed by Vaughn et al[228], there are three main types of food parenting practices: coercive control (e.g. restriction, pressure to eat), structure (e.g. monitoring, modelling) and autonomy support (e.g. encouragement, education). Research indicates that parental control (placing limits and restrictions on behaviours and insistence on compliance)[238] is associated with restrained and emotional eating in offspring[555-557] and increased intake of SSB and less nutrient-dense foods[558]. Research indicates that parental autonomy support (providing options and meaningful justification during decision-making, alongside being empathetic to the youths position[559]), results in an adolescent being more likely to internalize and demonstrate greater self-determination resulting in improved health behaviours such as dietary intake[560]. In terms of structural parenting practices there is good evidence that parental monitoring plays a key role in children's dietary behaviours when a child is young[234], however less is known about the influence of parental monitoring during the transitional adolescent period. Parental monitoring

refers to a parent's awareness of their child's whereabouts and knowledge of their activities and friendships[229, 561], along with the child's contribution and voluntary descriptions of their free-time activities. Open channels of communication and awareness of, but not control over, adolescents' whereabouts are key characteristics of parental monitoring. Parental monitoring has been associated with a significantly higher quality diet, as well as acting as a protective factor for positive adolescent eating patterns[235, 236, 286, 562, 563]. Conducted among 4088 American adolescents one of the only studies reporting adolescent-perceived parental monitoring and dietary intake in general population adolescents[564, 565]found high perceived-parental monitoring was associated with a healthy dietary intake whilst low perceived-parental monitoring was associated with unhealthy dietary intake.

Gender is known to be associated with eating behaviours and dietary quality. Female adolescents are more likely to engage in restrictive eating behaviours, while male adolescents are more likely to consume SSB and junk food, and less likely to consume the recommended servings of fruit and vegetables[566]. There is emerging evidence that gender is also associated with differing parenting approaches, with female adolescents reporting higher levels of parent dependability and trust in parents than males[567]. Simultaneously, the food environment can be shaped by socio-economic status (SES). Research consistently shows low-SES is linked to lower fruit and vegetable consumption, coupled with increased saturated fat and refined sugar intake[568]. While factors including lack of education, food insecurity and economic hardship play a role [569], differences in parental practices among lower SES populations may also impact adolescent dietary intake[570]. For examples, home environments where there is increased economic stress and work-related pressures[571] may limit a parent's ability to effectively monitor their child's behaviours[572].

Whilst some research documents how parent-reported parenting practices can impact dietary intake during adolescence, studies examining the impact of *adolescent-perceived* parental monitoring on diet are scarce. Literature suggests that parents and adolescents commonly perceive parenting behaviours different[573], therefore adolescent-perceived parental monitoring has the opportunity to accurately reflect the adolescents' actual experience of their parents behaviours. Kim (2019)[565] found higher adolescent-perceived parental monitoring was associated with healthier dietary intakes among US adolescents. However, to date, no study has examined these links in an Australian sample. Further, there has been no research controlling for key demographic factors linked with parental monitoring, including gender and SES, which is critical

to informing tailored prevention and intervention approaches. Therefore, the present study aims to explore the relationships between adolescent-perceived parental monitoring and dietary intake in a large sample of Australian adolescents (12-14 years old) controlled by gender and SES. We hypothesise that adolescents who perceive high parental monitoring will be more likely to meet dietary guidelines for fruit and vegetable intake and consume less junk food and SSB than those who perceive low parental monitoring.

4.2 Materials and methods

4.2.0 Participants

This study is a secondary analysis of cross-sectional baseline data collected for the Health4Life Study, a large cluster randomised controlled trial (RCT) among 71 schools across three Australian states of New South Wales (NSW; n=37), Western Australia (n=16) and Queensland (n=18). This RCT aimed to improve six health behaviours (dietary intake, exercise, sleep, screen time, tobacco, and alcohol use) in adolescents to prevent future chronic disease, full details of the RCT can be found in the published protocol [574]. In short, the sample consisted of Grade 7 students aged 11-14 years from independent (n=38), government (n=24), and Catholic (n=9) secondary schools. Randomisation to either the intervention or control group was stratified by school location (metropolitan or regional) and school gender composition (coeducation, predominantly male [>60%], or predominantly female [>60%]) and conducted by a biostatistician with no role in school recruitment. Parental consent and student consent were obtained, and 6,639 students participated in an online self-report survey in 2019. A full report on the baseline characteristics of the Health4Life sample has been published previously[575]. Ethical approval was gained from the University ethics committees (University of Sydney 2018/882, Curtin University HRE2019-0083, the University of Queensland 2019000037), NSW Department of Education, and relevant Catholic school committees.

4.2.1 Measures

Demographic information. Students self-reported their gender (male, female, non-binary/gender fluid[576]) and age. SES was assessed using the Family Affluence Scale (FAS)[577] an individual level indicator of family affluence. The summed raw scores were then transformed into normally distributed ridit score that represents relative SES position compared to other individuals in this sample. Ridit transformation was originally developed by Bross[578], our ridit scores range from 0 (most disadvantage) to 1 (most advantaged). Similar to the standard practice used in other

studies[579], our ridit score was then used to convert adolescents into three groups: lowest 20% (low affluence), middle 60% (medium affluence) and highest 20% (high affluence), representing individuals who fall in a lower (ridit < 0.2), middle (ridit ⩾ 0.2 and ⩽ 0.6) or higher range (ridit > 0.6).[580]

Dietary intake. Dietary intake was assessed using standardised questions derived from the NSW Health SPANS survey[547]. Participants were asked about their usual intake of fruit and vegetables ("I don't eat fruit/vegetables", "less than 1 serve per day", "1 serve per day", "2 serves per day", "3 serves per day", "4 serves per day", "4 serves per day", "5 serves per day", "6 serves per day", "more than 6 serves per day") and were provided with visual aids to represent a standard serve. Based on responses, a binary variable (0/1) was used to represent insufficient vs sufficient fruit and vegetable intake based on the Australian national guidelines for their age group (consuming 2 or more serves of fruit a day and 5 or more serves of vegetables a day)[581]. To assess SSB consumption, students reported how many cups they usually consume per week ("never/rarely drink", "1 cup or less a week", "2 to 4 cups a week", 5 to 6 cups a week", "1 cup a day", "1 ½ cups or more a day" to "2 or more cups a day"), with Australian examples and visual aids provided. Based on responses, excessive SSB consumption was classified as drinking >5 cups per week. Frequency of junk food consumption, including one item each on takeaway meals or snacks (from places like McDonalds, KFC, Dominos or local fast food places), snack foods (sweet and savoury biscuits, cakes, donuts or muesli bars), potato crisps (or other salty snacks), hot chips (French fries, wedges or fried potatoes), ice cream or ice blocks and confectionary (lollies, or chocolate) was assessed ("Never/rarely", "1-2 times a week", "3-4 times a week", "5-6 times a week", "once every day", "two or more times a day"). Based on responses, excessive junk food consumption was classified as consuming more than 1 serve of junk food a day. Finally, a binary composite indicator of poor diet, was calculated based on these individual binary dietary variables, to describe participants as 'at risk' or 'not at risk' for poor overall diet for descriptive analysis, representing those who drank more than 5 cups of SSB a week, ate less than 2 serves of fruit and 5 serves of vegetables a day and more than 1 serve of junk food a day.

Adolescent-perceived parental monitoring. A validated 6-item general parental monitoring scale[229] was used to assess adolescent-perceived parental knowledge of a child's whereabouts ("my parents usually know what I am doing after school", 'my parents know who my friends are", "my parents know where I am after school", "if I am going to be home late, I am expected to call my parents to let them know", "I tell my parents who I'm going to be with before I go out", "I talk

to my parents about the plans I have with my friends"). Each item is scored from 0 to 4 ("never", "rarely", "sometimes", "often", "always") and total scores range from 0 (lowest perceived parental monitoring) to 24 (highest perceived parental monitoring).

4.2.2 Statistical Analysis

Descriptive statistics were used to generate the frequency and percentage of the variables of interest in the total sample, grouping these by gender and SES. Due to low numbers of participants falling into the non-binary/gender fluid category these were omitted from the analyses, gender analysis therefore only included 'male'/'female' genders. A series of binary logistic regressions were conducted to examine associations between perceived parental monitoring and each binary dietary outcome: fruit intake (<2 vs 2+ serves per day), vegetable intake (<5 vs 5+ serves per day), SSB intake (>5 vs 0-5 cups per week), and junk food intake (>1 vs 0-1 serve per day) whilst controlling for gender and SES. Prior to fitting the models, assumptions were tested and met. For each regression analysis, the dietary outcome was the dependent variable and parental monitoring was the independent variable. All regressions included a school cluster variable to account for the non-independence of students clustered within schools and odds ratios (OR) and 95% confidence intervals (CI) are reported. Further demographic breakdown of this sample can be found elsewhere[370]. Models used complete case analysis, and as the sample size is very large and missing data was negligible (below 5.4% for all dietary outcomes), no further examination of missing data was conducted as is standard practice [582]. All analyses were conducted in Jamovi 1.6.16.

4.3 Results

4.3.0 Sample Characteristics

The baseline sample comprised a total of 6639 adolescents, of whom 6053 provided valid responses to the perceived parental monitoring questionnaire and were therefore included in analyses. Participants were aged 11-14 years, with a mean age of 12.7 (SD=0.5) and 50.6% identified as male. 15.1% (12.6-17.6%) of the cohort classified as low SES, 36.7% (34.3-39.1%) as medium SES, and 48.2% (44.2-52.1%) as high SES.

Table 8 - Dietary behaviours in the total sample.

Dietary behaviour	n	%	SE
Poor diet* (composite of high SSB, insufficient fruit & veg, and high junk foods) (n=5815)	2920	50.2	1.3
Excessive sugar-sweetened beverage consumption (>5 cups a week) (n=6466)	705	10.9	0.9
Insufficient fruit intake (<2 serves/day) (n=6444)	1492	23.2	1.1
Insufficient vegetable intake (<5 serves/day) (n=6439)	5363	83.3	0.6
Excessive junk food intake (>1 serve/day) (n=5728)	2357	41.1	1.1

**'Poor diet' is a binary variable (yes/no), and is a composite of having poor dietary consumption for each of the 4 dietary behaviours (excessive SSB, insufficient fruit, insufficient veg and excessive junk food).*

As illustrated in Table 8, half of the sample (50.2%) reported poor diet based on the composite indicator, with the vast majority (83.3%) reporting insufficient vegetable intake. Excessive junk food intake (41.1%) and insufficient fruit intake (23.2%) was also common, with approximately one in ten (10.9%) adolescents consuming excessive SSB. Table 9 provides an overview of adolescent-perceived parental monitoring by demographic characteristics. Mean scores for perceived parental monitoring in the total sample were 21.0/24 (SD 4.22) respectively. Female adolescents reported higher levels of perceived parental monitoring compared to males, and adolescents of higher and medium relative SES reported higher levels of parenting monitoring compared to those of lower SES.

Table 9 - Perceived parental monitoring (out of 24 points) by sample characteristics.

		Mean perceived parental monitoring score[235]
Gender+	Male (n=3026)	20.1 (4.76)
	Female (n=3027)	21.9 (3.37)
Relative family affluence	Low	20.3 (5.25)
	Medium	21.1 (4.04)
	High	21.2 (3.92)

4.3.1 Binary logistic regressions for dietary behaviours

A one unit increase in perceived parental monitoring scores was significantly associated with increased odds of insufficient fruit intake (OR=1.03; 95% CI=1.02-1.05, P<.001). Similarly, a one unit increase in perceived parental monitoring scores was associated with increased odds of excessive SSB intake (OR=1.07; 95% CI=1.06-1.09, P<.001). Conversely, a one unit increase in perceived parental monitoring scores was associated with a lower odds of reporting excessive junk food intake (OR=0.96; 95% CI=0.95-0.98, P<.001). Similarly, a one unit increase in perceived parental monitoring scores was associated with lower odds of not meeting the guidelines for vegetable intake (OR=0.97, 95% CI=0.96-0.99, p<.01).

4.4 Discussion

This study examined whether adolescent-perceived parental monitoring was associated with dietary intake among Australian adolescents. As hypothesised, we found that adolescents who perceived *higher* levels of parental monitoring were more likely to not meet guidelines for fruit intake and consumed excessive SSB, whereas those who perceived *lower* levels of parental monitoring were more likely to not meet the guidelines for vegetable intake and consumed excessive junk food. Consistent with prior research[583] we found adolescents reported high levels of perceived parental monitoring, with females perceiving higher levels of parental monitoring compared to males[283], and adolescents of higher relative SES reporting higher levels of perceived parental monitoring compared to those of lower SES.

The finding that higher levels of perceived parental monitoring was associated with high SSB intake and insufficient fruit intake contradicts prior research that has shown that adolescents with higher parent-perceived parental monitoring have more favourable dietary outcomes[235, 236, 286]. One possible explanation is that SSB consumption is an autonomous behaviour that largely occurs outside of the home (e.g. on the way to/from school, during leisure activities with peers) and therefore is less susceptible to the influence of parental monitoring[584]. As directionality of findings cannot be determined in our cross-sectional study, it is also possible that this relationship could be highlighting that parents of adolescents who are drinking more SSB have resulted in using higher parental monitoring in an attempt to reduce this. Contributing to this is the abundance of marketing from SSB companies to tactically target youth, alongside their high addictiveness and palatability, which could override the effects of parental monitoring when an adolescent gains more autonomy over their food choices. These findings also support

results from a recent meta-analysis which found that parent-based interventions were not effective in reducing SSB intake among adolescents; however these interventions did significantly improve fruit, vegetable and junk food intake[585].

The unexpected associations between high perceived-parental monitoring and insufficient fruit and excessive SSB intake could also be due to other factors in an adolescent's environment. Firstly, a parent's own knowledge and beliefs about food, alongside food resources available to them (i.e., cost or food accessibility), will govern what foods are available in the adolescent's home. Additionally, parents act as role models for their adolescents' dietary behaviours, potentially contributing to ongoing cycles of poor dietary intake. As parental monitoring is only one factor contributing to an overall parenting style, it is important to consider how other parenting factors could contribute to poor fruit and SSB intake, including attitudes, beliefs and rules relating to a particular food group (e.g., vegetables), which may not apply to another food group (e.g., SSB).

Our finding that higher perceived parental monitoring was associated with lower odds of excessive junk food and insufficient vegetable intake aligns more closely with the literature[236, 586]. The positive impact of perceived parental monitoring on these behaviours could be explained by some of these foods being predominantly consumed during meals, which a parent remains largely responsible for, particularly when comparing to SSB and fruits which are generally consumed when snacking. In line with this, it could be more difficult for an adolescent to purchase junk foods such as takeaway foods due to accessibility or cost, in comparison to SSB which are more affordable and could be sourced easily in local vending machines or convenience shops where adolescents are not reliant on a parent to drive them or even be aware of their purchasing. A further explanation could be that more traditionally, vegetables and 'healthy meals' have been primarily emphasised and advertised to parents, and the risks of high SSB intake is still relatively under-appreciated, particularly when considering the existential growth in consumption over recent years.

The use of adolescent reported perceptions of their caregivers' parenting practices allows for an accurate representation of how the adolescent themselves feel parented and reduces bias of self-report from the parents' perspective. Future research could look at both parent and adolescent-perceived parenting practices as both views could provide different perspectives. The complexity of how parenting impacts adolescent dietary intake have also previously been explained by Basset

(2008)[587] who witnessed that even when an adolescent is exercising autonomy over their food choice, if a parent is monitoring and controlling the environment by using coaxing and coaching strategies an adolescent can respond by complaining or ignoring advice, whilst taking responsibility and reflected on their behaviors and keeping in mind their parents advice, even if in some cases this does not transcend to immediate action, adolescent food choice is ultimately actively co-constructed by both adolescent and parent, proving adolescents may act in some ways and in others can restore guidance which they may choose to act on at a later date.

4.4.0 Strengths and limitations

The present results should be considered in light of several limitations. Firstly, being a cross-sectional analysis, we are unable to determine the directionality of relationships and establish causality. For example, it is possible that parents who are concerned about their adolescents' eating behaviour may increase their parental monitoring. Additionally, although large and geographically diverse, our sample was not nationally representative, and students were predominantly English-speaking and living in major cities. Nonetheless, the sample comprised of adolescents living across three Australian states and attending a diverse range of secondary schools (independent, government and Catholic). Our dietary outcomes were also collected via adolescent self-report, as objective assessment was not possible due to the scale of the RCT. We did not take into account parents' own dietary behaviours or home food environments, which could have resulted in some confounding factors being missed. Finally, SSB consumption could have been underreported as energy drinks consumption was not part of the current analysis. Similarly, our perceived-parental monitoring measure focuses predominantly on a child's whereabouts and general perceived parental monitoring, as opposed to monitoring of an adolescent's diet specifically, therefore high adolescent-perceived parental monitoring could have been reported when a parent was prioritising other risky behaviours such as alcohol use, for example.

Simultaneously our research has some considerable strengths, including the novel use of adolescent-perceived parental monitoring, which could be considered a more important format than parent-perceived monitoring due to reflecting the actual adolescent experience. In addition, most previous literature has only reviewed these relationships in relation to one food group, whereas our analysis of multiple food groups fills knowledge gaps on how perceived parental monitoring impacts different dietary variables in the one cohort. Our large Australian sample size incorporated gender and SES, where no previous research on perceived-parental monitoring on

dietary intake in adolescents has been conducted. Future research should also monitor parenting practices specific to diet and explore different parenting styles in comparison with parental monitoring, such as initiatives like Triple P (teaching positive parenting practices)[588], other food parenting practices or household food inventories. A recent survey in adults found that out of all health behaviours parents chose dietary habits as the behaviour they would most like to change for themselves and their adolescents[575], therefore combined interventions moving forward should aim to target both the parents and the adolescents to improving adolescent diet and overall food environments in the home.

4.5 Conclusion

Our results contribute knowledge specifically around perceived-parental monitoring's association with adolescent dietary intake, a factor contributing to overall parenting style. However, our findings indicated that perceived-parental monitoring is associated with different dietary variables in different ways. Despite increasing autonomy during adolescence, parents still have an important impact on aspects of their adolescent's dietary behaviours, thus dietary interventions among early adolescents should not overlook the role of parenting practices. Findings may have implications to inform further exploratory analysis which could assist in guiding future prevention interventions for parents and adolescents, identifying how this modifiable parenting factor is related to adolescent diet has highlighted how complex the psychological and environmental factors contributing to dietary intake are. Further research is needed incorporating parents' own diet and different parenting practices[589] from both an adolescent and parents' perspective to help better depict the most recommended style for the optimum diet during adolescence.

Chapter 5: C-reactive protein: associations with dietary intake in adolescents and feasibility of collection via dried blood spot in Australian schools

"Let food be thy medicine and medicine be thy food" Hippocrates– the 'father of medicine' 460BC-377BC.

Preface

The associations between poor dietary intake and common and emerging non-communicable diseases and developmental conditions identified in Chapter 3 aligns with other emerging literature indicating pro and anti-inflammatory dietary potential (described in chapter 1). The surge of intake in calorie dense and nutrient poor foods in adolescents worldwide establishes this health behaviour as a vital consideration for public health improvements and prevention. Previous literature indicates that specific foods, food groups and whole diets may have differing inflammatory and anti-inflammatory properties, however most research has been conducted in adult populations. Simultaneously, there is a gap in the literature describing accessible and non-burdensome ways to collect bio samples in adolescents, particularly in Australia, contributing to the ongoing limited biobehavioural research in this cohort.

This chapter addresses these gaps and represents the first study to assess the feasibility of conducting inflammatory marker retrieval via hsCRP utilising dried blood spots (DBS) in adolescents within a school setting. This chapter also examines important associations between specific dietary variables, percentage of energy from core and non-core foods and global diet scores with hsCRP in Australian adolescents to help guide future longitudinal research.

This chapter is currently under review:

Osman, B., Burrows, T., O'Dean, S., Sunderland, M., Jacka, F., Thornton, L., Teesson, M. C-reactive protein: associations with dietary intake in adolescents and feasibility of collection via dried blood spot in Australian schools. *Public Health Nutrition. (*Under review)

(Supplementary materials are available in Appendix 3)

5.0 Abstract

Objective: Elevated high-sensitivity C-reactive protein (hsCRP) is a precursor to chronic disease and useful marker in prevention research. Poor dietary intake is associated with higher hsCRP, yet minimal research has evaluated these associations in adolescents. This study aimed to examine associations between total diet quality, percentage energy from core and non-core food groups, and hsCRP collected via dried blood spot (DBS), and assess the feasibility of DBS collection within a school setting in a sample of Australian 15–16-year-olds.

Design: Participants completed the Australian Eating Survey assessing diet quality and intakes from core (i.e., fruits, vegetables, wholegrains) and non-core (i.e., ultra-processed foods, sugar-sweetened beverages) food groups. Research staff conducted bioimpedance measurements and hsCRP collection via DBS. Linear regression models and correlations examined associations between dietary intake and hsCRP.
Setting: Australian schools.

Participants: Adolescents (n=20) 65% male, mean age of 15.8 years old (SD 0.40).
Results: HsCRP collection via DBS in a school setting is feasible, cost-effective and nonburdensome, however consideration should be given to time required to obtain relevant approvals and minor difficulties retrieving DBS. Directionality of associations between dietary intake variables and hsCRP generally aligned with adult literature. The strongest correlation was between higher consumption of non-core foods and higher hsCRP (r=0.44).

Conclusions: Biobehavioural research via DBS is minimally invasive and feasible in a school setting, however future research should consider learnings from this study for planning and efficiency. Directionality of associations suggest adolescents are likely not immune to the biological impacts of poor dietary intake. However, larger-scale research and more DBS resources is needed.

5.1 Introduction

Long term low-grade inflammation is becoming well established as a precursor to chronic disease incidence[52], supporting its optimisation in biobehavioural studies across different populations. C-reactive protein (CRP) is an acute phase reactant of the innate immune system

and a marker of inflammation. Ongoing circulating levels of low-grade CRP results in regular contact with vital organs and activation of oxidative stress[51], which is directly linked with future risk of cardiovascular disease (CVD)[52], type 2 diabetes[52], depression[56] and Alzheimer's[57]. Poor lifestyle behaviours and mental health are modifiable triggers of an inflammatory response. Poor dietary intake specifically is a fundamental modifiable risk factor for poor health that impacts the population globally. Healthy diets should be balanced, characterised by high intakes of core foods (i.e., fruits, vegetables, and wholegrains) and low intakes of non-core foods (e.g., ultra-processed foods 'UPFs' and sugar-sweetened beverages 'SSB'), and meeting national guidelines where possible to retrieve sufficient nutrient intake. Excessive consumption of non-core foods such as UPFs[590] are associated with higher CRP, whilst fruit[591], vegetable[590] and fibrous grains[291] are anti-inflammatory. Poor dietary intake and excessive food consumption result in an increased proportion of people with obesity, which is also strongly associated with inflated levels of CRP[592].

Predominantly, previous research has focused on the inflammatory impacts of poor diets in adults, when oxidative stress has occurred for elongated periods of time and chronic diseases have already emerged. Adolescents are a vulnerable group warranting further investigation due to biological and developmental shifts with a high nutritional demand, and evidence suggests that dietary behaviours adopted during this developmental period tend to track into adulthood[518]. Indeed, evidence is beginning to show that adolescents are not exempt from the immunological impacts of poor dietary intake[590]. There are direct associations in adolescents between unfavourable consumption of specific dietary groups such as UPF and SSB[590, 593] with increased CRP. Ultimately similar correlations between UPFs and noncommunicable disease prevalence have been found in both adolescents and adults[137], which could be a result of systemic inflammation caused by UPF consumption. From a public health perspective, adolescents are at a vital age to improve dietary intake to help set healthy foundations and nutritional habits, optimise growth, and prevent low grade inflammation and ultimately the onset of disease. Additionally roughly 80% of all Australian adolescents regularly attend school from years 7-12[594], making schools an invaluable environment for targeted prevention programmes and epidemiological measurements in Australia and worldwide.

High sensitivity C-reactive protein (hsCRP) is the optimum measurement of CRP, enabling a lower detection limit than conventional CRP, which is particularly important when focusing on low-grade inflammation[595]. Adolescents are deemed to have low grade inflammation with

levels of hsCRP ≥2mg/L, (≥3mg/L hsCRP for adults). Traditionally the gold standard approach to collecting hsCRP immunoassays is intravenously[596], however, this approach is invasive, requires many resources including trained medical staff, and is commonly conducted in a medical setting, reducing ecological validity by potentially increasing stress-induced inflammation[597]. Possibly better suited to adolescents are emerging non-invasive and more accessible approaches to collect hsCRP immunoassays, including dried blood spot (DBS), saliva, or urine samples. Whilst saliva and urine samples both have valuable independent uses in research, literature suggests weaknesses in their validity for hsCRP markers. HsCRP fluctuations can occur in saliva samples as a result of poor oral hygiene or diseases[598] or can reflect an acute inflammatory response[599]. Whilst urine samples could be impacted by kidney functionality or metabolically induced hsCRP changes throughout the day[599]. The accuracy of results from both processes can also be significantly impacted by poor storage and processing of immunoassays[598, 599]. DBS is potentially an underused, non-invasive, and efficient way to collect hsCRP in adolescents. Multiple studies have shown hsCRP collected via DBS has high validity and strongly correlates with venous blood samples[600, 601]. DBS collection is simple and does not require medical staff to administer (participants could conduct themselves at home), and DBS samples do not require special storage requirements unlike all other bio sample collection methods. However, to our knowledge feasibility of hsCRP collection via DBS in adolescents within a school setting has never been explored. If feasible, this method could be invaluable in biobehavioural research, enabling ease of repeated measures which is specifically advantageous when assessing longitudinal impacts of dietary variables on adolescents' health or dietary intervention effects. The aims of this study were to examine associations between core foods, non-core foods, Australian recommended food scores and hsCRP and to examine the feasibility of using DBS in an adolescent school-based pilot sample

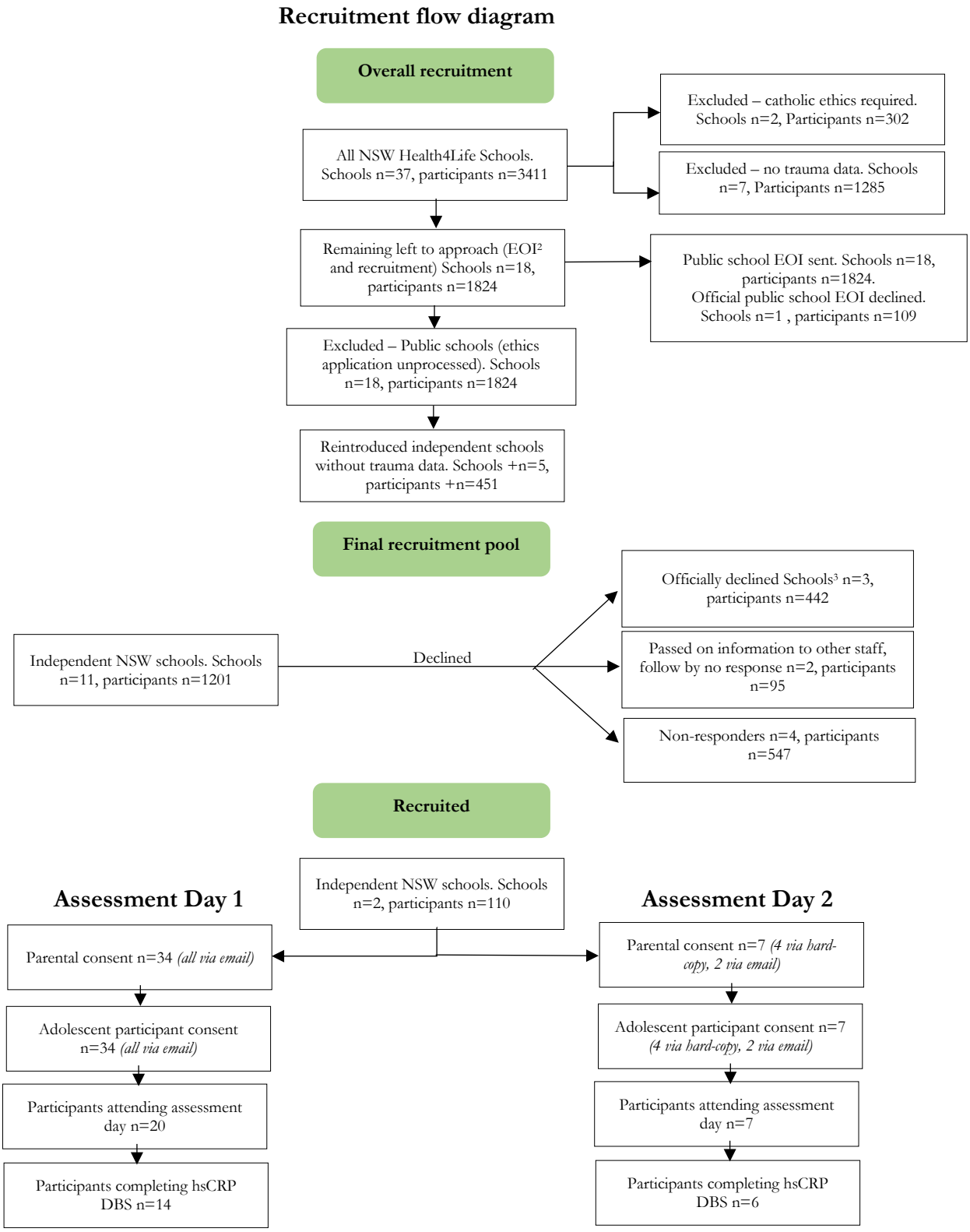
5.2 Methods

5.2.0 Study design and participants

This observational cross-sectional study recruited a pilot sample of participants (15-16years old) that were originally recruited as part of the larger Health4Life trial from 2019-2022[518], spanning across three states in Australia. Independent schools from New South Wales (NSW) were recruited following all previous trial commitments being met in late 2022/early 2023. Of the schools that had principal approval to take part, parents were required to actively consent, followed by active consent from their adolescents.

Assessment days were conducted within an allocated room at the school, over one dedicated lunch time (40-60-minutes) to avoid interrupting classes and at least one teacher was required to be present on the day. Teachers and adolescents were each provided with lunch and adolescents were given a $20 gift card for participating. During assessment days participants were asked to complete an online survey, bioimpedance measurements and DBS samples. Once immunoassays were processed, both adolescents and parents were emailed a brief health report with information about hsCRP and adolescent's hsCRP results. Adolescents were informed before and during the assessment that they were allowed to withdraw from the study without prejudice at any given time if they felt uncomfortable. At least two research staff attended each assessment day and measurements were collected at three different stations.

Protocols and standard operating procedures (SOPs) (Appendix 3.1) followed the National health and medical research councils 'National Statement on Ethical Conduct in Human Research'[602]. Reporting of this study followed the STrengthening the Reporting of OBservational studies in Epidemiology – Nutritional Epidemiology (STROBE-nut) checklist[603] (Appendix 3.2), and the CONSORT extension for pilot and feasibility trials[604] (Appendix 3.3). To facilitate the examination of DBS in a school setting, detailed reporting of the facilitators and barriers along with reflections from the research team were collected throughout the preparation and completion of this study.



[1]*Participant numbers reflect the maximum number of students from baseline data (potential for some lost to follow up);* [2]*Expression of interest;* [3]*Reasons for declining – "too busy", "unable to facilitate this", "school regulations to not allow any BMI measurements".*

Figure 11 - Participants flow diagram.

5.2.1 Measures

5.2.1.0 Dietary intake

The self-report Australian Eating Survey® food frequency questionnaire (AES-FFQ) is a validated food frequency questionnaire (FFQ) for assessing usual food and nutrient intake in children and adolescents over the previous 3-6 months[605, 606]. Participants were reminded that survey responses were anonymous and were encouraged to answer questions as truthfully as possible. The AES-FFQ asks consumption of 120 common foods and drinks with frequency of response options ranging from 'never' to '**≥7 times per day'** alongside 15 demographic and behavioural questions. The AES-FFQ produces data on the food and nutrient consumption of the adolescent's dietary intake tailored to their age, gender, and life stage. Nutrient intake was computed using data in the AUSNUT 2011-2013 database[607], including the percentage of energy (kilojoules) consumed from core foods (foods considered important components of a balanced health diet i.e. whole grains, protein, dairy, fruit, vegetables) and non-core foods (food that are lacking in nutrients and are energy dense i.e. UPFs such as take out, SSB, cakes, biscuits, pastries)[608]. The AES-FFQ also provides the Australian recommended food score (ARFS), using a subset of questions to a global food score. This produces a total score out of 73 as a measure of diet quality, representing overall healthiness and nutritional quality and variety of an individual's eating pattern[609]. The ARFS is based on the frequency of consumption the individual foods groups fruit, vegetables, dairy, meat and grains recommended in the Australian Dietary Guidelines[610], with most foods awarded 1 point for a consumption frequency of ≥once per week. Higher scores reflect greater dietary variety, including fruit (0-12), vegetables (0-20), dairy (0-10), meat (0-7) and grains (0-12), water (0-1) and spreads/sauces (0-2) and a total score is calculated by summing the points for each item ranging from 0-73.

5.2.1.1 Dried Blood Spot for HsCRP

DBS services were outsourced to the pathology company 'NutriPath'. NutriPATH DBS kits comply with The National Pathology Accreditation Advisory Council (NPAAC) and include sterilizing swabs, two lancets, a 12-dot blood collection sheet, and return postage for each participant. All dots on the blood collection sheet are required to be filled with a full blood spot (see SOPS in Appendix 3.1 for more details). DBS kits also enable a user to conduct DBS on themselves at home however, for consistency and accuracy of collection when working with adolescents, research staff administered DBS collections for this trial. All research staff underwent training to administer DBS collection on another person and attended a practice assessment day to ensure collection consistency between staff. Participants verbally confirmed

they were happy to proceed once they reached the DBS station and were verbally checked on throughout the collection process, including being asked for permission if a new finger prick was required. Adolescents were instructed to shake their hands and rub them together to increase blood flow before fingers were pricked. Research staff were instructed to proceed with filling all 12 dots on blood collection sheets unless a participant began to feel uncomfortable or would like to stop for any reason, full details are supplied in the SOPs (Appendix 3.1). Once DBS immunoassays were processed in the lab, hsCRP results were returned in mg/L.

5.2.1.2 Bioimpedance

Anthropometry and bioimpedance was measured by research staff who underwent two New South Wales Health online courses for safely conducting bodily measurements in adolescents to minimise harm. Research staff also completed a training day to ensure all staff were equipped to conduct measurements. SOPs were carefully developed with a multidisciplinary team, using standardised procedures. All measurement results were hidden from the adolescent being measured and others partaking in the study, however all measurements were conducted in a shared room including a teacher with the adolescents fully clothed for the safety of the participant and research staff. Height was gathered first using the same stadiometer for all participants (see SOPs in Appendix 3.1for further details). Height was input into the Tanita MC-780MA Bioelectrical impedance analysis machine, an accurate bioimpedance measurement tool[611]. The bioimpedance machine required participants to be barefoot and retrieved weight (kg), body mass index (BMI) and body fat percentage.

5.2.1.3 Statistical analysis

A data analysis plan was pre-registered[612] and followed accurately, aside from refraining to transform the non-core and core variables into a ratio, instead keeping them in their raw percentage form. Statistical analyses were performed using RStudio 2023.06.1+524. All independent and dependent variables were continuous. BMI was converted to a BMI-Z score using the 'zanthro' function in R, and descriptive analysis was used to determine the distribution of hsCRP via histograms. HsCRP was non-normally distributed with a positive skew (skew 1.88, kurtosis 2.38), therefor log transformed. The log-transformed hsCRP variable had acceptable skew (0.79) and kurtosis (-0.67) therefor deemed normally distributed[613]. Linear regression models (using 'lm' function in R) were used to investigate the associations between core, non-core foods and hsCRP while controlling for sex and total kilojoules consumed. Further linear regression models were used to investigate the associations between overall ARFS score, fruit,

vegetable, dairy, grains, and meat ARFS scores with hsCRP while controlling for sex. A final linear regression model was used including all independent variables to depict the variables with unique associations to HsCRP. Coefficient β effect sizes were classified according to Cohens classification of effect sizes: 0.10-0.29 are small, 0.30-49 are medium and 0.50 or greater are large effect sizes[614]. A correlation matrix was generated between hsCRP and all predictor variables using the 'corr' function in R. Post-hoc sample size calculations were conducted in GPower 3.1. based on observed correlations (95% confidence interval [CI] and P>0.05) and linear multiple regression models (95%CI and P>0.05) in this pilot study to better inform future studies on the required sample size.

5.3 Results

A convenience sample of two independent schools in greater Sydney, NSW was recruited (Figure 11 for further information). Further demographic information of the final sample can be found in Table 10. In total twenty-seven adolescents participated, of which hsCRP for 7 participants wasn't collected, either through personal choice (n=3) or insufficient time to complete (n=4) (Table 13 for further information). The final sample of n=20 had a mean hsCRP of 1.9mg/L, which is approaching the indicator for low-grade inflammation in adolescents of ≥2mg/L. Adolescent dietary scores were generally poor, and percentage of energy from non-core foods was comparable to that of UK adolescents which was 39.5%[608].

Table 10 - Participant descriptive statistics.

	Total n=20 (SD)	**Male n=13 (SD)**	**Female n=7 (SD)**
Age (years)	15.80 (0.40)	15.76 (0.43)	15.66 (0.51)
hsCRP	1.9mg/L (2.98)	0.87mg/L (1.00)	3.8mg/L (4.44)
BMI-z score	0.77 (0.99)	0.56 (0.88)	1.15 (1.15)
Mid puberty	n=5	n=4	n=1
Later pubertal	n=12	n=9	n=3
Post puberty	n=3	n=1	n=2
Average energy consumption	8230 kJ (3711)	9286 kJ (3657)	6267 kJ (3154)
% of non-core food intake	34.6% (11.9)	32.4% (8.4)	38.6% (16.7)
% of core food intake	65.3% (11.9)	67.5% (8.4)	61.3% (16.7)

Mean ARFS score (0-73)	25.4 (8.7)	27.4 (8.3)	21.7 (8.6)
Mean ARFS fruit score (0-12)	3.8 (2.2)	4.0 (2.3)	3.4 (2.1)
Mean ARFS vegetable score (0-20)	8.9 (3.8)	9.2 (3.9)	8.4 (4.0)
Mean ARFS meat score (0-7)	2.7 (1.2)	3.15 (1.2)	2 (0.8)
Mean ARFS grain score (0-12)	4.3 (1.7)	4.84 (1.5)	3.42 (1.8)
Mean ARFS dairy score (0-10)	2.8 (1.8)	3.15 (1.9)	2.28 (1.6)

5.3.0 Associations findings:

Two of the effect sizes from the linear regression models investigating the associations between dietary variables and hsCRP were small, ARFS dairy (β=0.11, 95%CI:-0.22-0.44, P>0.481) and ARFS fruit (β=-0.11, 95%CI:-0.38-0.15, P>0.365). ARFS meat (β=-0.39, 95%CI:-0.89-0.10, P>0.114) demonstrated a moderate effect size (Table 11). Findings from the multivariable model found that meat (β=-0.38, 95%CI:-0.90-0.14, P>0.14), dairy (β=0.36, 95%CI:-0.13-0.86, P>0.14) and grains (β=-0.35, 95%CI:-1.0-0.30, P>0.261) had the most unique associations with hsCRP (Table 12).

Table 11 – Individual linear regression models investigating associations between dietary variables and hsCRP when controlling for sex.

Dietary intake	β	95%CI	P Value
% of core foods	-0.02	(-0.08-0.03)	P>0.382
% of non-core foods	0.02	(-0.03-0.08)	P>0.383
Total ARFS score	-0.02	(-0.09-0.05)	P>0.546
ARFS vegetable score	-0.01	(-0.16-0.15)	P>0.919
ARFS fruit score	-0.11	(-0.38-0.15)	P>0.365
ARFS grains score	-0.06	(-0.44-0.31)	P>0.721
ARFS meat score	-0.39	(-0.89-0.10)	P>0.114
ARFS dairy score	0.11	(-0.22-0.44)	P>0.481

Table 12 – Combined multivariable model investigating unique associations between ARFS dietary subgroups with hsCRP when controlling for sex.

Dietary intake	β	95%CI	P Value
ARFS vegetable score	0.10	(-0.12-0.32)	P>0.334
ARFS fruit score	-0.16	(-0.51-0.18)	P>0.321
ARFS grains score	-0.35	(-1.0-0.30)	P>0.261
ARFS meat score	-0.38	(-0.90-0.14)	P>0.135
ARFS dairy score	0.36	(-0.13-0.86)	P>0.137

5.3.1 Correlation matrix

The correlation matrix (Figure 12) found variables that had the strongest correlations with hsCRP were a higher BMI-z score (r =0.61), higher percentage of non-core food consumption (r =0.44) and lower ARFS meat score (r =-0.43).

Figure 12 - Correlation matrix between hsCRP, dietary intake, BMI-z and sex.

5.3.2 Sample size calculations:

Based on the effect sizes found in this study, the sample sizes required to have sufficient power to detect a significant correlation between hsCRP and non-core foods is n=57, core foods n=57, ARFS score n=182, ARFS vegetables n=1063, ARFS fruit n=90, ARFS meat n=60, ARFS grains n=439, ARFS dairy n=652.

Based on the effect sizes found in the linear regression models, the sample sizes required to have sufficient power to detect significant associations between hsCRP and non-core foods is n=593, core foods n=593, ARFS score n=652, ARFS vegetables n=1859, ARFS fruit n=121, ARFS meat n=36, ARFS grains n=219, and ARFS dairy n=120.

5.3.3 Feasibility:

The results of this study suggest HsCRP collection via dried blood spots is feasible in adolescents within a school setting, where valid DBS data was collected from 74% (20/27) of participants attending an assessment day. Of the participants that did not complete DBS during the assessment day, 3.7% (1/27) were unable due to a medical condition, 7.4% (2/27) reported a fear of DBS and 14.8% (4/27) were incomplete due to research staff running out of time (further information in Table 13). Notably there were barriers and facilitators to the efficacy of this trial. These are laid out in Table 13.

Table 13 – Facilitators and barriers to retrieving FFQ and hsCRP via DBS from adolescents in an Australian school setting.

Preparation phase facilitator	Preparation phase barrier

Rigorous preparation for the trial:
• SOPs co-designed with other researchers, complying with NPAAC.
  ○ Stations for each assessment
  ○ Pre-labelling all documents and materials
• All research staff completing online and face-to-face training, and a practice assessment day.
• Testing online FFQ survey for login, functionality, and data collection.
• Small focus group determining type of lunch items and vouchers adolescents this age would like.
	Australian government-school ethics:
	• Significant delays caused and the main contributor to a small sample size: administrative delays from government school ethics, partly due to ongoing recovery from the impacts of the pandemic/remote learning. Researchers required to proceed with non-government (independent) school recruitment only, as the attempt to begin processing our government school ethics application had not begun until 2 years after our submission (January 2024), at which point the study was complete.

Building a rigorous ethics application: • Following NPAAC guidelines for best standard practices. • Retrieving advice from other researchers who have further experience in bio sample collection. • Using DBS kits already complying with NPAAC guidelines *may* have eased ethics approval (speculatory). • Using a validated FFQ[605] built specifically for adolescents.	*Outsourcing to a DBS supplier:* • High cost. • DBS resources in Australia are currently very limited and hard to source, particularly adolescent approved. • Lack of reliability: initial supplier withdrew as recruitment begun causing delays due to sourcing a new supplier, submitting an ethics amendment, and awaiting approval. Cost was 3x higher for a new supplier reducing maximum recruitment size. • Research staff required more than the 2 lancets that were originally supplied in the DBS kits per adolescent.

Outsourcing to a DBS supplier: • Supplying pre-prepared DBS kits with all necessary equipment. • Kits are simple to use in a school setting, less resources and health and safety equipment required. • Conducted by research staff (medical professional not required). • NPAAC compliance already sought. *Using the AES-FFQ* • Validated and built for/easy to use in an adolescent cohort.	*Utilising an existing RCT* • Had shortly finished a 4-year commitment to participating in the trial. Some teachers/schools felt as though they didn't want to commit further. • Some delayed recruitment attempts due to waiting for schools to finish commitments. • Parents *may* have felt their child had participated enough in the existing trial (speculatory).
Utilising Health4Life schools: • Researchers had teacher contact details and built a repour with them. • Potential for teachers having a vested interest in preventative health. • Potential for parents having a vested interest in preventative health or positive experiences of their child participating in existing trial. • Researchers having ethics approval to link data on adolescent participants.	*School recruitment in general:* • Reliant on a school agreeing (governing what opportunities reach the parents/adolescents). • Engagement in the study from coordinating teachers governs trial efficiency and parent/student engagement (from consent to participation). • Trial coordination is governed by individual schools' access to resources/staffing. • Schools are tentative to agree to 'biomarker' studies due to health and safety concerns (one school declined participation due to an unconditional rule of no BMI retrieval despite safety measures in place). • 3 levels of consent are required – school, parent, and adolescent. Utilises researcher time retrieving each level consent. • Schools were recovering from the pandemic and catching up on missed curriculum items. • Some teachers felt adolescents were better to spend the lunch time focusing on exam preparation stating they are "too busy".
Participation phase facilitator	**Participation phase barrier**
Preparation for the trial: • Assessment days predominantly ran smoothly, and teacher/student feedback was favourable. • The AES-FFQ was faster than anticipated and adolescents reported no difficulty in completing. • Some adolescents expressed excitement about the free nutritious lunch and/or $20 completion vouchers. • Health reports successfully sent to participants and parents once hsCRP immunoassays were processed.	*Preparation for the trial:* First assessment day: • 2 extra adolescents arrived on an assessment day with consent. Neither contact ID labels to de-identify them at each station or their lunches were prepared (delaying the start of the assessments). • School Wi-Fi blocked the survey website, data hot-spotting was required and delayed the start of assessments. • 15 consenting adolescents did not arrive on the day. • Bioimpedance machine didn't display all 10 results for each participant, research staff proceeded with the 3 displayed (weight, BMI, body fat %).
Outsourcing to a DBS supplier: • Completed DBS sheets were labelled with de-identified contact IDs and posted to the supplier for laboratory processing. • De-identified results were securely sent back to the research team, in a cleaned spreadsheet. • Blood spot sheets were all successfully processed in the lab with no retrieval errors. • Saving research staff time by outsourcing these services.	*DBS collection:* • Some adolescents chose not to do DBS during the assessments: ➢ 2-reported fear of DBS ➢ 1-medical condition • During the first assessment day research staff did not have time to complete 4 DBS due to confounding issues raised above. • Difficulty filling all 12 dots on blood collection sheet taking longer than anticipated, requiring blood flow stimulation and multiple fingers punctured (with participants consent). • Upon completion 1 adolescent felt dizzy. Research staff utilised plan in place for adverse events. • Assessment day with more participants could have benefited from more time/research staff for improved efficiency.

5.4 Discussion

The aims of this study were to examine the feasibility of using DBS in an adolescent school-based pilot sample to examine associations between core foods, non-core foods, Australian recommended food scores and hsCRP. Overall, DBS collection in an adolescent school-based setting is feasible and economically viable. Secondly, directionality of associations mostly aligned with that of adult literature that is, non-core foods (UPFs) were positively associated with hsCRP and core foods (fruit, vegetables, grains) negatively associated with hsCRP[591, 615, 616].

Overall, it was highly feasible to collect hsCRP via DBS in adolescents in a school setting. Given the high validity of DBS, its affordability, minimal invasiveness and need for resources, this tool should be considered in future clinical research and biobehavioural studies. Other non-invasive tools for collecting CRP (saliva or hair sample), in contrast can be burdensome for the participant or the researcher to complete or store, alongside the potential for lesser validity in results. Despite growing attention acknowledging the potential in DBS[617], it is largely underrecognized and there is currently a substantial lack of resources in Australia to supply biobehavioural studies with DBS equipment. Due to the lack of access to DBS resources at the researchers' institutions, DBS services were outsourced to one of the few pathology companies in Australia offering this service. Comparatively, DBS is much more well established in the USA and the UK. Importantly bio sample ethics approval in adolescents is understandably strict, DBS tools are less invasive and safer to use therefore could alleviate some ethical difficulties and broaden access to biobehavioural research. Sufficient safety measures and preparation for DBS ethics approval will streamline this process, however consideration for further administration delays from government school ethics should be given when on a timeline. The final key takeaway from DBS feasibility in adolescents is being prepared for the time it may take to fill a large quantity of blood collection spots and incorporating tasks that could help with circulation (e.g., warm room, some physical activity etc). Respectively, the duration of time for DBS would not near that of the preparation and collection time needed for intravenous blood withdrawal. However, the current study would have benefited from more research staff to fit in all DBS collection, bioimpedance measurements and FFQ during a 40–60-minute school lunch break to have avoided missing DBS collection for 4 participants. A recent tool has been created that would assist with this factor, whereby a DBS is attached to the upper arm of the adolescent and

automatically retrieves DBS[618]. Currently this is being used in young Australian athletes for anti-doping purposes but shows great potential for usage in biobehavioural studies.

Greater fruit, vegetable, and grain consumption correlating with lower hsCRP within our cohort aligns with that of adult literature. There is an abundance of contributing anti-inflammatory properties from fruit and vegetables, of note vitamin A (rich in leafy green vegetables, peppers, mango, carrots, pumpkin, sweet potatoes, melons and tomatoes), vitamin C (rich in citrus fruits, strawberries, cruciferous vegetables such as broccoli or cauliflower, tomatoes, peppers and white potatoes) and vitamin E (rich in mangoes, avocadoes, spinach, sunflower seeds, peppers, pumpkin and asparagus) have each been established to significantly reduce inflammation [89, 619]. Along with unrefined/whole grains, fruits and vegetables are rich in antioxidants, folate and flavonoids which each induce the suppression of pro-inflammatory cytokines[590, 620]. A crucial component of whole grains, vegetables and fruits are their fibre content. When digested by the gut microbiota, fibre produces short chain fatty acids (SCFAs) which plays a vital role in gut health, and fibre as a whole fuels gut diversity, both of which contribute key anti-inflammatory properties[291, 615]. Simultaneously, high fibre foods have lower glycaemic index increasing satiety, inhibiting the hunger hormone ghrelin and increasing synthesis and absorption of glucose in the body (through SCFAs)[291]. These healthful attributes of fibre are some of the contributing reasons to its direct correlations with disease prevention or reduction, explored in depth through high quality reviews[616, 621]. This directionality of associations found between higher fruit, vegetable, and grain intake and lower hsCRP in adolescents, along with the supporting literature supports health messaging around the importance of their consumption.

Findings that greater dairy intake correlates with higher hsCRP is not consistent with most existing adult literature. A recent systematic review found that 5/7 studies examining dairy found no associations with CRP or other markers of inflammation[590]. Of the two studies that found associations, one cohort consisted of only asthma sufferers (naturally heightening susceptibility to inflammation), and another found a mixture of pro-and anti-inflammatory associations relating to diary intake, varying between males and females[622]. A second systematic review of 52 clinical trials in mostly adult subjects found overall that dairy intake was anti-inflammatory, aside from those allergic to bovine milk in which case was pro-inflammatory[623]. Further explanation to varying inflammatory associations could be due to the saturated fat content, dietary antigens, additional hormones, and antibiotics occurring in most dairy products, the latter two a result of modern-day farming. There is, however, a strong argument that dairy's health

benefits disproportionately outweigh these factors (if allergies or other medical conditions are not present), such as the abundance of live bacteria diversifying and improving the gut microbiota, calcium, vitamin D, vitamin A and protein content in dairy, each of which contribute anti-inflammatory properties in their own way[415]. As such, it is important to also acknowledge that the types of dairy consumption may play a role in varying findings, i.e. those dairy products high in healthy gut bacteria such as live yogurts have more anti-inflammatory properties compared to those with lesser health properties and higher saturated fat content such as butter. Bone developmental at this age is a primary health concern that can determine lifelong bone density and later life medical conditions such as osteoporosis, therefore calcium and vitamin D rich foods should be encouraged. Future government policies to reduce or eliminate the hormonal and antibiotic usage in farming would alleviate some of the less healthful properties of dairy products.

The positive correlation between greater meat consumption and lower hsCRP in this study for the most part does not align with the literature; however, this could be in part due to the ARFS meat score used. The ARFS meat score incorporates serves of mincemeat, beef, lamb, pork, chicken, fresh fish, canned tuna or salmon and other seafoods. These meat sources each contain distinct variances in macro and micronutrients and are metabolized in the gut in differing ways, the ARFS meat score hinders our ability to depict which meat sources were mostly consumed. Red meats contain and induce production of harmful toxins when consumed, alongside sulphates, haem iron and overarching alterations of the gut microbiota including generation of Trimethylamine-N-oxide (TMAO), each of which contribute to an inflammatory response[152]. Red meats are also higher in saturated fat and sodium than other meat sources and are well recognised to strongly correlate with increased risk of diseases such as cardiovascular disease and colorectal cancer[152]. White meat such as chicken also causes generation of TMAO in the gut microbiota, of which elevated levels have been linked with atherosclerosis, congestive heart failure and cardiovascular mortality[154]. However overall, there is weaker correlations between white meat consumption and inflammation, therefore ultimately disease. This could be in part due to its lesser content of saturated fats and its ability to help maintain gut homeostasis by increasing lactobacillus or A.muciniphila levels[152]. Fish is unique to each of these, being the most healthful option of these meat categories as it is rich in immunoregulatory properties such as omega-3 fatty acids (PUFAs), tryptophan, taurine, vitamin A, and melatonin. The most explored and highlighted beneficiary of fish consumption is PUFAs, being anti-inflammatory and a key component of the immune system[307]. PUFAs have been directly associated with a

reduction in chronic diseases, one such study even finding improved outcomes to critically ill ICU patients when tube-fed continuous infusions of fish oil[624]. An overarching factor to consider when discussing meat consumption is the benefits sought from higher protein intake and higher satiety which could in turn reduce over consumption of other less nutrient dense foods. Other high protein sources such as legumes (beans, lentils, chickpeas), soybeans or tofu, eggs and nuts can help to combat some of the unhealthful properties found in meat whilst supplying protein, satiety, and other nutritious benefits. Overall meat is complex and diverse in relation to its impact on the immune system and inflammatory responses, the associations we found in this study were the strongest of any of our associations which gives a compelling argument for its future need for further research, whilst importantly taking into account specific meat types to explore any variance.

Understanding these inflammatory and anti-inflammatory properties of individual food groups is important when considering our findings of, a higher percentage of core foods being association with lower hsCRP and a higher percentage of non-core foods a higher percentage of hsCRP. Core and non-core food grouping was originally formulated by the Australian guide to healthy eating [625] and has since broadened in usage to other countries such as the UK[608]. Grouping foods in this way can be a useful tool for research, clinical practices or on an individual level for an improved understand of a person's diet as a whole and to simplify balanced diet messaging i.e. "it is recommendation to consume roughly 80% core foods and less than 20% noncore foods". Our association directionality aligning with that hypothesised highlights the potential for this food grouping to be an efficient marker of whole diets in biobehavioural studies, however further research is needed in larger cohorts.

Consistent with most diet quality scores, the total ARFS score reflects the frequency and variety of consumption of core foods, aligning with the national guidelines and is a global food score which can allow for cross country usage and comparison[609]. Notably the ARFS does not take into consideration the consumption of non-core foods (pro-inflammatory foods), yet its higher score was associated with lower hsCRP levels. This indicates that those consuming a healthy varied diet, frequently incorporating foods from core food groups may help to maintain biological health in adolescents. Core foods include fruits, vegetables and whole grains which are naturally higher in fibres providing increased satiety, therefore higher core food consumption generally results in less available energy consumption for non-core foods.

Post-hoc sample size calculations based on the effect sizes observed in our analyses showed larger sample sizes are needed to have sufficient power to detect significant associations between our diet variables and hsCRP. The range of effect sizes found in this study (-0.38 to 0.36) are similar to that found in a study looking cross-sectionally at associations between differing diets' and hsCRP in adult CVD risk populations (of which effect sizes ranged from -0.35 to -0.17) [626]. This studies inclusion of a population at risk of CVD and older adults could explain the slightly lower effect sizes than in our sample. As effect sizes in our study align with other research that has larger sample sizes, it is likely that if there were more power, results could have been statistically significant.

This study is not without limitations. Firstly, our sample size of n=20 is small and non-generalisable, specifically all adolescents were recruited from independent schools which generally indicates a higher familial affluence and higher socio-economic status (SES). This is particularly important as we may have found higher hsCRP levels in lower SES adolescents, as this association is expected in lower SES adult populations[627]. Generally lower SES cohorts may have poorer nutrition and other health behaviours, lower health literacy and increased exposure to stressors, all of which can contribute to inflammation[627]. As a pilot study in a relatively unexplored topic however, our sample size of n=20 contributes important learnings, effect sizes and sample size calculations which should be considered for future research. Furthermore, this study does have some notable strengths, firstly its use of a robust and validated FFQ and its subsequent ARFS score which is representative of a global diet score. The FFQ is not only a well-tested tool but simple and fast for participants to complete with no difficulties experienced, which are important considerations when conducting research with younger people and limited time. Another strength was the incorporation of a DBS kit to retrieve bio samples within adolescents. Notably these kits were originally designed to be conducted at home making them accessible, which is vital when considering inclusivity of rural and remote adolescents that are too often unable to participate in health research.

To conclude our findings, DBS is deemed a favourable, non-invasive format for collecting hsCRP in adolescents, in schools giving opportunity to broaden access to biobehavioural research for both adolescents and to researchers or public health bodies. More DBS resources will need to be available in Australia to ensure this is feasible at scales. Directionality of results are promising, highlighting that adolescents seem to be experiencing the biological impacts of higher or lower hsCRP from the specific foods they are eating, consistent with previous adult

research. There is no better time to be investing into adolescent preventative health, as UPF and SSB intake reaches insurmountable levels, child and adolescent obesity is at an all-time high and non-communicable diseases both in adolescents and adults is on the rise. Further research is needed to examine associations between adolescent dietary intake and hsCRP in a larger population sample, whilst assessing which, if any, foods have a more unique impact on increasing or reducing hsCRP than others.

Chapter 6: General discussion

Preface

Poor modifiable health behaviours, mental ill health, low SES, and sex are associated with increased systemic chronic inflammation, which plays an important role in the aetiology of chronic disease. In adults, some of these chronic diseases such as CVD, T2D and Alzheimer's Disease are among the leadings causes of death worldwide. Meanwhile adolescents are experiencing increased prevalence of atopic conditions, obesity and mental disorders, with peak onset for mental disorders occurring during adolescence and early adulthood[628].
This may be a consequence or exacerbated by poor health behaviours such as poor diet, inadequate exercise, deficient sleep, increased sedentary recreational screen time, alcohol, and tobacco consumption (also known as the Big 6) commonly emerging during adolescence and prevailing into adulthood[629]. Adolescence is also a period of developmental and neurobiological shifts that occur during puberty and result in increased nutritional demand, alongside sensation seeking and impulsive behaviours[630] whilst still being largely influenced by their familial, social and environmental surroundings. Adolescence is therefore a complex and vital time for preventive interventions, to halt the trajectory to lifelong chronic disease. Despite this, there is limited understanding of adolescent inflammation and its associations with poor health behaviours and mental health.

The overarching aim of this thesis was to fill the evidence gaps identified in Chapter 1 (Table 3) by investigating associations between nutritional intake and the remaining Big 6 health behaviours, mental health, socio-demographic variables, and inflammation or disease in adolescents, and to investigate familial factors associated with adolescents' diet. To fill these gaps this thesis aimed to:

- Establish an understanding of the global prevalence of systemic chronic inflammation in the general population of adolescents worldwide, identify sub-groups at higher risk of inflammation, and any changes in levels of inflammation over time.
- Determine the prevalence of non-communicable diseases and developmental conditions in Australian adolescents and their correlations with the Big 6, mental health, SES and sex.
- Investigate associations between adolescent-perceived parental monitoring and intake of ultra-processed food, sugar-sweetened beverage, fruit and vegetable.

- Assess the feasibility of assessing hsCRP via dried blood spot (DBS) in Australian adolescents, and to use this method to examine associations between hsCRP and total diet quality and percentage energy from core and non-core food groups.

This thesis offers a substantive and multifaceted contribution to the literature via its novel exploration of global and Australian data. Sophisticated analyses of risk factor associations and outcome prevalences and associations, as well as demonstrating the feasibility of innovative biobehavioural methods, provide future directions requiring urgent investigation. This final chapter will summarize the overall findings of this thesis (6.1), present its strengths and limitations (6.2), discuss implications of this body of work, and provide recommendations for future directions (6.3).

6.1 Overview of findings

6.1.0 Knowledge gap 1 – Prevalence and present concerns

This thesis has filled a notable gap in the epidemiological understanding of the prevalence of inflammation, diseases and conditions as well as poor health behaviours in adolescents. **Chapter 2** is the first study to retrospectively determine the global estimates of adolescent inflammation worldwide (32 countries), via a large-scale meta-analysis. This study found that the global mean estimate of 1.69mg/L CRP in the general population of adolescents worldwide is approaching the low-grade inflammation threshold of ≥2mg/L. Consistent with these findings, **Chapter 5** presents similar mean inflammation levels in Australian adolescents at 1.9mg/L, however given this was a pilot study consisting of n=20 the results have limited generalisability.
Chapter 3 identified the prevalence of 10 common and emerging non-communicable diseases and developmental conditions in a large national sample of Australian adolescents and found that 45.6% have ≥1 disease or condition. Further exploration of symptom severity of IBS and asthma found that over half of the adolescents with these conditions were experiencing severe symptomology, denoting the scale of the present concern. Furthermore, 51.6% of Australian adolescents reported having mild-severe depressive symptoms and 23.85% had mild-severe anxiety symptoms.

C**hapters 3, 4** and **5** present an understanding of the prevalence of poor modifiable health behaviours. Concerningly **Chapters 3** and **4** found that most adolescents were not meeting the national guidelines for sleep, physical activity, screen time or dietary intake. Further in-depth

investigations into the severity of poor dietary intake in adolescents in **Chapter 4** found that 83.3% of 12.5-year-olds were not meeting the guidelines for vegetable intake and 41.1% were consuming ≥1 UPF per day. In addition, 15.5-year-olds in **Chapter 3** had an average ARFS score of 25.4 out of 73 and 34.6% of energy intake came from non-core foods (the recommended is <20%).

Furthering our knowledge of the current prevalence rates and present concerns in this thesis has provided a critical overview of the currently immunological and behavioural health profiles of adolescents. In summary, a disproportionate number of adolescents are living with raised levels of inflammation, non-communicable diseases or developmental conditions and poor mental health, whilst adhering to unhealthy lifestyles. This highlights the vital demand for an improved understanding of causal relationships to contribute to prevention and reduction in disease burden in the future.

6.1.1 Knowledge gap 2 – Associations with health behaviours and mental health

This thesis has filled a notable gap in the public health understanding of the associations between adolescent lifestyles and inflammation, non-communicable diseases or developmental conditions, and the associations between adolescent-perceived parental monitoring and dietary intake. **Chapter 3** represents the first study to provide a contemporary analysis of the associations between the Big 6 health behaviours and mental health with non-communicable diseases or developmental conditions. Notably UPF, poor mental health, tobacco and alcohol intake had the most associations with diseases and conditions, whilst those with ≥1 disease or condition had 9.1% more depressive symptoms and 10.6% more anxiety symptoms than their counterparts. One important determinant of adolescent health behaviours is the parenting styles an adolescent experiences, which was explored in **Chapter 4**. This chapter demonstrated that higher adolescent-perceived parental monitoring was associated with higher vegetable and lower UPF intake, but higher SSB and lower fruit intake. These findings could indicate parenting has more leverage on foods typically consumed at mealtimes rather than those consumed during snacking, but overall strengthens the argument that factors contributing to adolescent's dietary intake are paramount, yet complex and multi-faceted.

Chapter 5 builds on these findings by conducting a detailed exploration of specific dietary intake associations with inflammation (hsCRP), and found that noncore foods (UPFs) were associated with higher hsCRP and core foods (fruits, vegetables, and grains) were associated with lower

hsCRP. Interestingly, non-normative directions of associations were identified such that higher meat intake was associated with lower hsCRP and higher dairy intake was associated with higher hsCRP, with **Chapter 5** also discussing plausible reasonings for these findings. It is important to note that **Chapter 5** is a pilot study and due to small sample sizes, associations were non-significant and based on directionality only. These findings highlight the need for further research in larger adolescent cohorts to clarify specific dietary intake associations with inflammation.

Chapters 2 and **5** establish vital associations between those who are overweight or obese and inflammation. The most noteworthy finding from **Chapter 2** was that, among 37,347 adolescents worldwide, those who were overweight or obese had an increased difference in mean CRP level of 2.14mg/L (P=0.0001) compared to healthy weight cohorts, providing the first mean CRP reference for inflammatory differences by weight. Results from an Australian cohort in **Chapter 5** aligned with these findings, (Figure 12) where BMI z-scores had the strongest correlation with hsCRP ($r = 0.61$) compared to any other included covariate. Despite the increased rates of adolescent obesity over the past decade, **Chapter 2** did not find any significant changes in inflammatory levels over the past nine years. However, it is possible that 9 years is too short a time period for significant changes in inflammation to have occurred. Further current and historic comparisons merit investigation.

Overall, by filling the notable gap in literature, **Chapters 2, 3** and **5** have identified that health behaviours and mental health are associated with inflammation, diseases, and conditions in adolescents, highlighting the crucial role they may play in the prevention and treatment of disease, whilst also calling to attention the need for important new longitudinal research to explore causal relationships.

6.1.2 Knowledge gap 3 – Associations with socio-demographic factors

This thesis has filled a notable gap in distinguishing the associations between sex, SES and inflammation, non-communicable diseases, or developmental conditions. **Chapter 2** is the first study worldwide to identify no significant differences in inflammatory levels based on sex and country level SES. Crucially, the country level SES findings should be considered in light of its limitations, however the large, geographically vast, and robust analysis of sex differences are an important contribution to the literature. Building on these findings, **Chapter 3'**s comprehensive

exploration of SES associations in an Australian setting found that those from low SES backgrounds had higher rates of chronic fatigue, food allergies, T2D and autism.

Additionally, **Chapter 3's** comprehensive exploration of sex differences discovered that, overall, females have higher rates of diseases and conditions than males, however, susceptibility of different diseases or conditions did depend on the adolescent's sex. Critically, males had disproportionately more associations with noncommunicable diseases or developmental conditions than females when their health behaviours or mental health were worse. Furthermore, **Chapter 4** demonstrated that higher parental monitoring was perceived in females and high SES adolescents compared to their peers, an important consideration as a potential contributing factor to health behaviour and disease relationships**.** Overall, **Chapters 2, 3** and **4** identified novel associations alongside the need for further research on the relationship between SES, sex, parenting and inflammation in adolescents, with a particular need to consider pubertal stage due to potential variations this could cause.

6.1.3 Knowledge gap 4 – Feasibility of adolescent biobehavioural research

This thesis has established the feasibility of collecting inflammatory markers via dried bloods spots in an Australian school setting. **Chapter 5** found that conducting DBS in adolescents within a school setting is indeed feasible, economical, and minimally invasive. This chapter offers insightful learnings of the successes and challenges faced when conducting DBS in a school setting, alongside useful SOPs, and sample size calculations to contribute to the biobehavioural literature. DBS as an option for retrieving hsCRP has high validity and shows promise as a tool to enable increased biobehavioural research within adolescents, a priority highlighted throughout this thesis's body of work.

6.2 Strengths and limitations of the research

A key strength of this thesis is the large sample sizes (n=37,347 and n=5,014) in **Chapters 2**, **3** and **4.** This allows for robust epidemiology contributions to the literature and, for the most part, generalisability globally and nationally. Specifically, **chapter 2** includes data from 32 countries and sizeable inclusions of different sexes and body weights, whilst **chapter 3** and **4** includes a substantial number of gender- and culturally diverse participants enabling group comparisons of these social determinants as well as data from three different states. However, a limitation of working with these sizeable datasets was their cross-sectional design. Cross-sectional data

precludes causal analyses, a component that should be examined further in future research to aid prevention efforts. This thesis lays essential foundations to accommodate future causal and associative analysis by filling an important epidemiological gap in distinguishing current prevalence and associations with inflammation or disease, that were otherwise largely unknown in adolescence. Another limitation of this thesis was the use of self-report data in **Chapters 3, 4** and **5,** which can result in self-report bias or inaccurate reporting. However, this was addressed in this thesis by using validated self-report measures and adolescents were also assured of the confidentiality of their responses to reduce these risks, objective measures were also used where feasible (**Chapter 5**). In support of this the prevalences of poor health behaviours, mental health, noncommunicable diseases and developmental conditions captured in **Chapter 3** were similar to, or even slightly higher than, recent Australian government data, reinforcing confidence in the accuracy of the findings. Finally, the Health4Life dataset used in **Chapters 3, 4** and **5** is not truly population-representative with respect to SES as the sample were typically reporting a higher SES than the general Australian population, therefore SES associations may be less generalisable.

There are significant strengths to using CRP as a biomarker for inflammation, as discussed in **Chapters 2** and **5**. In short, CRP is the most well used cytokine within research and clinical environments as a marker of inflammation. CRPs validity has been thoroughly tested and it is the most comparable inflammatory marker with other literature, of particular importance for **Chapter 2's** meta-analysis. It is essential however, for emerging immunological science to consider that different inflammatory markers are triggered depending on the stage of the immune response cascade being captured. Whilst CRP is an efficient marker of inflammation that can give a valid indication of inflammatory levels, a gold standard method would be to collect a variety of inflammatory markers from each stage of the immune response system. Another important limitation of all inflammatory research, which is most relevant to **Chapter 5** of this thesis due to small sample sizes, is the potential for acute inflammation to be present within any participant experiencing current infection or disease at the time of bio sample collection. Larger samples, such as that in **Chapter 2,** help to alleviate this issue as values for overall means and standard deviations represent more accurate levels.

While there are numerous strengths in the comprehensive meta-analysis conducted in **Chapter 2**, such as its sample size, global span, and robust statistical analysis, there are also some limitations which warrant consideration. Firstly, there was high heterogeneity between studies (I^2 of 99.8%), which was, for the most part, not attenuated by further sensitivity or subgroup

analysis. However, our findings were consistent with another large meta-analysis[504], further discussed by Peter Imrey (2022)[505] who explains that the large scale of these meta-analyses and the use of continuous variables can inflate the heterogeneity, which was evident when our I^2 statistic decreased when we examined a smaller sub-group of just 17 studies. Furthermore, insufficient cohort SES information was available within studies, resulting in the use of country-level SES information. This is a broad measure and could have inaccurately classified the SES of individual cohorts. Additionally, the absence of studies from low-income countries prevented the examination of differences across all country-level SES groups. Finally, only a small number of studies were obtained from the African and Oceania regions, thus we were unable to make conclusions on these regions within the regional analysis. Missing information is somewhat expected within systematic reviews and should be harnessed as an opportunity to acknowledge the gaps in the research, further justifying the necessity for adolescent CRP data from low SES and oceanic countries.

Chapter 4 has some additional methodological limitations. Firstly, there is a chance that SSB was underreported as energy drink consumption was reported separately to the other measures and not included in this current analysis. Secondly, while parental monitoring was chosen for examination due to literature suggesting its impact on adolescent dietary intake and variation between SES and sex, **Chapter 4** did not consider other potential confounding variables such as parents' health literacy, own dietary patterns or home food environments. This was primarily due to scope of the present thesis, and future research should consider adolescent's whole environment and parenting exposure to help determine further important variables contributing to dietary intake. Equally several strengths are evident in this chapter, firstly research on adolescent-perceived parental monitoring is scarce, and to our knowledge, this is the first study examining these associations in an Australian sample. This is crucial due to the cultural and environmental differences across countries. Secondly, no previous analysis has included gender and SES which are two key social determinants of health. Finally, most prior literature has only focused on associations with an individual food group. Our analysis of multiple food groups addresses this significant gap, as considering overall dietary intake is crucial for understanding overall health.

By virtue of **Chapter 5** being a pilot and feasibility study, its primary limitation is having a sample size of n=20. Furthermore, the sample was recruited from non-government schools, introducing the possibility of failing to capture the potentially different inflammatory levels

among lower SES communities. However, despite the smaller sample size, this pilot was still able to significantly progress the literature in a relatively unexplored area, contributing important methodological learnings and effect and sample size calculations which should be considered for future research. Furthermore, this study possesses several strengths, firstly it uses a robust and validated FFQ[631] (AES-FFQ) which also produces a ARFS score which provides a global diet score. The AES-FFQ is not only a well-tested tool but is also simple and fast for participants to complete, and no user difficulties were experienced. Another strength was the incorporation of a DBS kit to retrieve bio samples within adolescents. Not only does the DBS kit provide a valid objective measure of hsCRP, but it was also originally designed to be conducted at home making them accessible, a vital consideration for future inclusivity of rural and remote adolescents that are too often unable to participate in health research due to this factor.

Finally, whilst **Chapter 3** was broadly exploratory and designed for hypothesis generation, robust statistical analysis was conducted including separate logistic regressions, multivariable logistic regressions and moderation analysis whilst controlling for covariates and further sensitivity analyses were run to generate E-values based on significant associations, which provide further evidence for the robustness of these findings.

6.3 Implications of thesis and future directions

Detailed implications drawn from the conclusions of this thesis and suggestions for future directions are provided below for three key stakeholders: policy, public health and prevention, and future directions for researchers.

6.3.0 Policy

6.3.0.1 Legislations

This thesis provides an in-depth account of observed health associations in adolescents, the majority of which were found between poor dietary intake, mental health and inflammation or disease. As discussed in **Chapters 1** and **3** there is an important bidirectional relationship between poor dietary intake and mental health, **Chapters 1** and **5** describe how independent dietary variables relate to inflammation and, **Chapters 1** and **2** subsequent relationships between obesity and inflammation. Given these findings and the rise of poor dietary intake, specifically UPF[142] and resultant obesity[83, 217], in adolescents worldwide, there is a compelling case for

increasing and new legislations on food. Food processing is a lucrative business that has risen rapidly over recent decades[119, 142]. Manufacturers' aims of increasing profitability results in many foods being manipulated and processed to greater degrees without sufficient public or scientific awareness of their contents or damaging effects [112, 118, 122].

Current legislations in Australia could be reinforced to help improve the quality of products, or increase awareness to those purchasing them. Suggested actions include increasing the sugar tax. Whilst some progress has made as the sugar tax has recently increased in the 2023-24 budget[632], the sugar tax is only applicable to SSB but no other foods with high sugar content such as confectionary, cakes and ice creams. Positively the Australian government has suggested this tax gain will be reinvested into preventative health however, the sugar tax on SSB has gone up to $0.40/100g of sugar, meaning the cost of an average 375ml can of soft drink will only increase by 16cents. This small cost increase may not be sufficient to deter consumers, particularly as the healthy alternative of bottled water commonly equates to or costs more than SSB, and SSB are regularly on special offers[632]. Currently (*May 2024*) a 1.25L of Coca-Cola at the leading Australian supermarket is $3.85 and a smaller 1L bottle of Evian water is $3.85. It is projected that a 20% tax increase on SSB would result in 24million years of life gained globally over 50 years[633]. Countries enforcing higher sugar tax on SSB have seen real world improvements in recent years, Mexico raising SSB prices by 11% cut consumption by 37% within two years and caused a 4.7% increase in the chances an individual would stop drinking SSB after three years[634].

Most countries around the world have either completely eliminated industrially produced trans-fats (e.g., Denmark, Lithuania, Thailand, Poland and Saudi Arabia), enforced limitations on the amount of trans fat allowed per food items, or have requirements for clear trans-fat labelling (e.g., America, Egypt, Philippines, Mexico and Canada). Despite this, Australia currently has no legislations on the amount of trans fats that are within foods[635], nor is there a requirement to display the trans-fat content within a packaged food item, unless labelled claims have been made in relation to fats or cholesterol. This is unlike total and saturated fat which is required to be declared on all labelling. Food Standards Australia and New Zealand are not following suit with other countries because an average Australian is expected to consume less than the 1% energy intake from trans-fats recommended by WHO[636] and positively has one of the lowest levels of trans fat exposure in the world. However, considering the magnitude of health implications from

consuming trans-fats (explained in **Chapter 1**) and their lack of otherwise nutritional benefit, at a minimum Australians should be entitled to trans-fat content being labelled in purchasable foods. **Chapter 1** describes how phthalates and BPA contribute to UPFs inflammatory inducing effects[637]. These compounds are present in food packaging and can increase the production of inflammatory cytokines, IL-1, IL-6, TNF-1 and oxidative stress[126-131]. Despite this, in Australia, phthalates are only restricted to being less than 1% of the composition of children's (0-36 month only) eating vessels, toys and utensils[638], and all other remaining plastics and food packaging are devoid of any restrictions. Furthermore, adolescents from Western-Europe with detectable exposure to phthalates (via urinary samples) had significant associations with asthma diagnoses[143]. These detrimental effects are becoming more evident, yet there is still a lack of public awareness and minimal legislations around their usage in Australia with similar trends being experienced worldwide[639].

Additionally new legislations could be enforced to help alleviate some of the detrimental effects of foods. Firstly, improving food labelling could encourage food transparency, reduce confusion and allow the public to have more control over their own health. Suggestions include, products being labelled as an UPF on the package. This could be easily implemented as the current NOVA UPF[112] classification system could be utilised. Similarly, as saturated fat is considered a primary health issue in Australia, a saturated fat content colour coded system on products could be implemented. Finally, updates to current misleading labelling could be enforced. Currently, the food health star rating is built upon comparability to other products within their category, leading to some foods such as 'chewy choc chip' bars (containing sugar, glucose, emulsifiers, vegetable oils, honey, modified starch and humectant), a small (31.3g) ultra-processed bar containing 5% of an adults daily recommended intake of saturated fat and 6% daily recommended intake of sugar, being labelled as a 4/5 health star rating as they are compared to other unhealthy snack products. The NOURISHING framework set out by the World Cancer Research Fund[640, 641] is a promising initiative guiding national efforts to improve 10 key policy areas across three domains: food environment, food systems and behavioural change communication (Table 14). One of the 10 policy areas within the food environment domain is to improve policies on nutrition labelling standards and regulations on implied claims on food. Australian policies such as the health star rating reflect components of this NOURISHING framework, however unfortunately its comprehensive set of policies is not fully implemented Australia-wide.

Bans or tighter restrictions on non-nutritive additives in foods could be hugely beneficial to human health. As described in **Chapters 1** and **5** additives, emulsifiers, antibiotics, and hormones added to UPFs or intensely farmed animal products directly impact the gut, immune response and have the potential to contribute to antibiotic resistance. Alongside antimicrobial resistance another negative health outcome of consuming excess antibiotics are their impact and alterations on the gut microbiome and general immunity. Promisingly, in a 2015 review focusing on antimicrobial resistance, Australia ranked the fifth lowest for antibiotic use in agriculture among the 29 countries examined[642]. Ultimately there are still significant levels of antibiotics in Australian animal products, and many animal products are imported from other countries that could have higher antibiotic content.

Finally, large co-operations economically exploit young people by producing cheap, palatable, and addictive food products, specifically targeting adolescents as a vulnerable population with impulsive behaviours. This thesis has described throughout each chapter that consumption of UPF and SSB during adolescence is at unprecedented levels, and the existing literature shows that exposure to food and drink advertising influences preferences[100] and increases intake[101]. Australian children are thought to be exposed to 35 hours of food advertising a year through what they are watching[643]. Nevertheless, the current system is failing to protect young people from dangerous marketing where limited vague legislations are currently in place, set by the advertising industry themselves. International research has shown these vague and bias legislations have little impact on reducing children's exposure to unhealthy food marketing[644]. Legislations to ban advertising and targeting to children and adolescents could help reduce the exposure to this vulnerable population. Alarmingly, new trends in social media influencers promoting products such as Prime energy drinks are causing a surge in their sells and there are currently no legislations in place in Australia to protect young people from this type of exposure. One study suggests restricting unhealthy food advertising to children is modelled to be one of the most cost effective and feasible obesity-prevention interventions, saving an estimated $38 for every $1 invested[645]. Similarly, the UK has introduced new advertising restrictions to young people and subsequently has seen a positive shift towards healthier foods, whilst positively impacted household food expenditure[646].

6.3.0.2 Accessibility to healthy foods

Policies should be improved to target social determinants of health. **Chapters 1**, **2**, **3** and **4** of this thesis highlight the associations between lower SES adolescents and inflammation or disease

prevalence and lower parental monitoring. Whilst further research is needed on this topic, it is known that those from low SES backgrounds generally have higher exposure to food insecurity, lower health literacy[569], poorer parenting styles[647], less green spaces[648] or access to sport[649]. Economic inequality could be targeted by policies encouraging healthy foods to become more affordable, which could be done by, for example, improving relationships with farmers or offering increased farming subsidies[650] whilst simultaneously taxing large corporations producing UPFs and SSB. Denmark saw a 4% decrease in saturated fat purchases after enforcing a saturated fat tax on food and nutrient intake[651], whilst Hungary found their UPF tax significantly reduced overall consumption of UPF and improved population health[652]. Overall, it is predicted that the most successful outcomes would come from reinvesting taxes from UPFs to subsidise fruit and vegetable costs whereby a 10% UPF tax would reduce UPF consumption by 5-9% and increase fruit consumption by 11% and vegetables by 7% per household[653].

Given most children and adolescents attend school in Australia, the school context offers great opportunities to increase accessibility to healthy foods. Policies to increase investment for disadvantaged schools could improve school canteen offerings, offer more affordable healthy food options and increase access to sports and wellbeing. Similarly, policies could work towards improving built environments in low SES communities. Some suggestions include incentivising healthier affordable food choices (cafes, restaurants, and convenience stores) to those living locally, giving them improved access to foods[654]. Furthermore, more green space should be encouraged in lower SES communities and affordable access to sports clubs or facilities should be made available to encourage participation. A successful example is The Baltimore Green Space Initiative which transformed vacant lots in low SES communities to green spaces, finding a direct association with higher physical activity, reduced stress levels and improved mental health of the local community[655]. Overall, welfare benefits for families could be improved to enable healthy food purchasing and sporting activities, some further ideas of guiding welfare expenditure are discussed later in this chapter.

6.3.0.3 Improve healthy lifestyles through education and incentives

All five previous chapters of this thesis suggest that, on average, adolescents are not eating a sufficiently healthy diet. There are many factors that contribute to adolescent's dietary intake, including their personal choices governed by knowledge, preferences, peers, cost and marketing; home food environments which can be governed by parental health literacy, preference,

accessibility, income or cost and parenting in general, such as parental monitoring. As such policies to improve these varied components could help to improve both knowledge, access and decision making from the parent and adolescent. Adolescent dietary knowledge could first be improved by utilising educations programmes such as Health4Life, proven to improve knowledge on diet and other health behaviours, whilst being an engaging and relevant programme, completed within schools and aligning with the school curriculum[656]. Secondly, schools could be incentivised to take students to education or volunteering sessions at local food bank services such as 'Our Big Kitchen'[657] or OzHarvest's curriculum aligned 'FEAST' program[658]. These programs accommodate bonding activities and teach students about food insecurity as well as how to prepare food, resulting in batches of meals being prepared and given to food insecure public. Teachers themselves could also attend the teacher training 'FEAST' by OzHarvest offers[658], educating teachers on food waste, healthy eating, and easy classroom cooking which sustains on going education for future students. Local governments could supply all schools with equipment such as seeds to plant vegetable patches in schools, encouraging student involvement and education. This gives students an opportunity to learn more about food processes and skills to cultivate their own vegetables and fruits, with the potential for access to some fresh produce, previously proven to be effective in increasing fruit and vegetable intake[659].

Those families receiving welfare should be incentivized to purchase healthier foods. This could be encouraged by supplying food coupons worth more in value for fruit, vegetables, dairy and wholegrains and worth less in value for UPFs, SSB and other non-core foods. There are many opportunities to improve health literacy in lower income families, by offering free or incentivized training or cooking programs. NEST is an evidence-based program[660] offered by OzHarvest, consisting of 2.5 hours each week of interactive activities and practical cooking classes aimed at addressing food insecurity. Parents who attend receive a take home cookbook containing meals that cost $3 or less per serve to make and a completion certificate. Further, course completion could be incentivized by providing more government core-food vouchers. Alongside improving health literacy and cooking skills, parental education itself could be provided on parenting practices that may have favorable adolescent outcomes. Supported by research[585], resources such as leaflets, books or online training programs (such as Health4Life Parents and Teens coming in 2025) could be incentivized for parents to complete. Each of these are ideas to work towards reducing health disparities, aiming to decrease the predisposition of an adolescent having poorer health outcomes based on their SES.

6.3.0.4 More resources for those at increased risk

The magnitude of the Australian adolescent population (45.6%) having ≥1 noncommunicable disease or developmental condition, alongside their frequent associations with poorer health behaviours and mental ill health from **Chapter 3** suggests that policies could be pursued to better support those adolescents at risk. Policy improvements could encourage all medical professionals who diagnose or treat common and emerging conditions in adolescents such as atopic conditions, IBS or ADHD, to recommend lifestyle medicine alongside their usual protocols. Medical professionals could supply adolescents and their caregivers with informative resources to improve the Big 6 and mental wellbeing, and at-risk adolescents could also be enlisted in free health behaviour and mental wellbeing programmes to improve these factors. Policies could also enlist extra school resources for those with a disease or condition, such as having mandated sessions with the school wellbeing resources and free healthy school lunches. Focusing policies on those at higher risk of the bidirectional relationship between poor health behaviours, mental health and disease has the potential to help alleviate symptoms which could in turn reduce the trajectory to worsened disease states or missing school or social activities caused by diseases.

Finally, all 10 key policy areas of the NOURISHING framework should be fully implemented across Australia, with strategic goals in place to achieve in each of these domains in the future.

Table 14 - The World Cancer Research Funds 'NOURISHING' policy framework to promote healthy diets and reduce obesity [640, 641].

Food environment	Food system	Behavioural change
Nutrition label standards and regulations on the use of claims and implied claims on food	**H**arness food supply chain and actions across sectors to ensure coherence with health	**I**nform people about food and nutrition through public awareness
Offer healthy food and set standards in public institutions and other specific settings		**N**utrition advice and counselling in health care settings

Use economic tools to address food affordability and purchase incentives		**G**ive nutrition education and skills
Restrict food advertising and other forms of commercial promotion		
Improve nutritional quality of the whole food supply		
Set incentives and rules to create a healthy retail and food service		

6.3.1 Public health and prevention

6.3.1.0 Recognition of this significant public health issue

A primary aim of this thesis was to explore and identify the immunological health of adolescence, utilising large datasets both worldwide and nationally. **Chapter 2's** finding that the mean CRP levels of the general adolescent population worldwide are approaching the threshold for low-grade inflammation, and **Chapter 3's** finding that almost half of Australian adolescents are experiencing ≥1 noncommunicable disease or developmental condition, highlights that this is a significant public health issue in the adolescent population. There is disproportionate care in the public health sector, whereby the adolescent population are largely overlooked with the bulk of the Australian Government health budget being spent on the age group 70-74[661]. Indeed, those with diseases of course require treatment. However, the increased prevalence of such conditions in younger people should encourage a surge of funding on preventative health which would ultimately help the economy now and in the long term.

Many diseases or conditions that emerge during adolescence are somewhat less debilitating than severe chronic diseases that generally arise in later life, which can result in a lack of consideration for biological health in this population. However, this thesis combined with other research[56, 69, 70, 170, 183, 205] indicates important immunological associations between poor lifestyles and mental health in adolescents. As such increased public health funding and prevention attempts

could have the opportunity to alleviate current negative side effects and improve way of life, alongside reducing the risk of severe chronic diseases in later life.

6.3.1.1 Public health and prevention focused on those at increased risk

Evidence shows that tailoring treatment and prevention to those at risk can significantly improve target outcomes[214, 239, 518], which is of particular interest when target outcomes aim to subsequently result in improvements in lifestyles, disease prevalence, and mental health conditions. **Chapters 2** and **5** indicate direct associations between either being overweight, obese, or having an increased BMI with higher levels of inflammation, the mechanisms underpinning this relationship have been detailed previously in this thesis. Public health attempts to improve lifestyles of adolescents who are overweight or obese should be increased. Currently among the prominent public health initiatives in place in Australia are 'healthy lifestyle programs for schools' or 'active kids' vouchers. However, these programmes could be significantly improved or further enforced. For example, active kids' vouchers consist of two $50 vouchers per year to use towards sport, creative or cultural activities for a child or adolescent, specifically for families receiving family tax benefit. Sport and exercise facilities can be expensive, some families (that are or are not receiving family tax benefits) may not have the financial means to commit their adolescent and the small voucher supplied by active kids may only allow an adolescent to experience an introduction to a sport or class, without long term resolution or improvement in accessibility. Considering the inflammatory relationship with unhealthy weight gain, more markers for inflammation could be used in public health settings to help monitor health trajectories. A valuable tool during prevention or treatment stages are dried blood spots which could allow for a fast, accessible and affordable method for collecting information on health trajectories. **Chapter 3** reports that males with worsened health behaviours or mental health have increased rates of diseases or conditions compared to females, whilst causal assumptions cannot be made these findings provide strong indications that public health campaigns targeting males specifically could aid prevention or treatment.

6.3.1.2 Whole lifestyle approaches in public health and prevention attempts

Chapter 1 of this thesis highlights the importance of considering whole lifestyles to support healthfulness, and this is supported by findings in **Chapter 2** and **3** of direct associations between adolescent obesity and inflammation or poor health behaviours and higher rates of diseases or conditions. Multiple health behaviour change approaches can yield the most efficient outcomes for public health[574, 662]. One reason for this is the bidirectional relationships

between many health behaviours, such that improving one health behaviour increases the likelihood of improvements in other health behaviours[574]. In adolescent programmes such as Health4Life which utilises multiple health behaviour change methods were found to significantly improve knowledge for each of The Big 6. Further public health and prevention attempts could focus on transitioning knowledge into practice to target multiple health behaviour change during adolescence.

Social stressors and pressures are largely unavoidable and are increasing in modern lifestyles. Social media is a contributing factor and whilst it has a variety of advantages, it is also an increasingly concerning issue for young people. Constant regular exposure to unregulated content and its addictive nature can be at the route of some unknown risks in this new era. One systematic review conducted in children and adolescents found that increased social media use was associated with skipping breakfast, increased intake of unhealthy snacks and SSB, and lower fruit and vegetable intake. The study also found those exposed to unhealthy digital food images compared to healthy digital food images had an increased reward response in the brain, overall summarising that limiting social media exposure in children and adolescents may improve food intake[663].

Poor mental health in adolescents being at historic highs, and its associations with chronic inflammation indicates that alongside multiple health behaviour change for The Big 6 (which should independently improve mental health), mental health should be considered as a vital 7th factor. Progress has been made in the last decade to open the conversations around mental health and wellbeing. In support of this the Australian department of education has built 'The Australian Student Wellbeing Framework' as a resource to support schools, students and parents and many secondary school's Australia wide have sufficient support and policies to employ a wellbeing officer[664]. Looking ahead all schools should have equal access to a wellbeing officer regardless of resources and a further suggestion for a new public health measure is to incorporate mindfulness and meditation in schools, this is discussed more in the 'future directions for research' section below.

6.3.1.3 Public health efforts to address poor dietary intake in adolescents

As highlighted throughout this thesis dietary intake in adolescents is of specific concern, poor dietary intake is pervasive and there are significant detrimental impacts of eating a substantial amount of non-nutritious foods. Public health and prevention attempts could be elevated to help

adolescents reach national dietary guidelines and reduce their intake of non-core foods. One suggestion could be for a surge of public health campaigns to highlight the unhealthful properties of UPFs, SSB and energy drinks and the healthful properties of anti-inflammatory foods such as fruit, vegetables, and whole gains. A recent review of the literature found almost all studies included found significant associations between food advertisement and adolescent obesity or overweight and/or choosing to consume unhealthy foods and beverages[665]. Furthermore, a recent umbrella review found mass media interventions to be effective in improving consumption of vegetables and fruits (in both young people and adults)[659].

To broaden the accessibility and increase the understanding of optimum dietary intake, public health messaging could deliver overarching and simplified content focusing on encouraging 80% or more core food consumption and less than 20% non-core food consumption, helping to relay concise and memorable messaging. Media campaigns could reinforce this messaging at point of purchase food environments such as supermarkets, food delivery apps and restaurants, thus aiding decision making in both the adolescent and their parent. As discussed earlier in this chapter, a critical aspect in food purchasing is food labelling, the general population could benefit from public health attempts to educate parents and adolescents on improving the understanding of food labelling, enabling more awareness of content within foods and hidden ingredients to be aware of. Leaflets with this information at supermarket entryways, at GPs, online food shopping websites and apps, and downloadable resources could help to have this information accessible for reference when required. **Chapter 5** highlights the importance of parenting on an adolescent's diet, findings indicate that favorable parenting practices are negatively associated with SSB and fruit intake, contrary to other dietary variables (vegetables and UPF). Adolescent SSB intake in particular has historically been more challenging to alter with parent-based interventions, even when other dietary variables have had positive outcomes[585]. Evidently, this isn't through lack of desire as a recent survey in adults found that out of all health behaviours parents chose dietary habits as the behaviour they would most like to change for themselves and their adolescents[575]. Public health attempts could emphasize the important of these snack-based foods, educating parents further on their importance and improving accessibility of fruit[659] whilst reducing accessibility and ease of purchasing of SSB.

6.3.2 Future directions for researchers

6.3.2.0 Requirement for more global and national epidemiological inflammatory data

The established relationship between health behaviours, mental health and inflammatory markers described throughout this thesis and in supporting literature supports the notion that epidemiology research and national data collection should regularly include inflammatory markers. There is disproportionately less inflammatory data currently collected in adolescence compared to inflammatory data collected in adults, and as explained in **Chapters 1** and **2** this is specifically lacking in Australia in comparison to other countries. Incorporating more inflammatory markers within data collection could enable improved cross-country comparisons, being particularly important when testing the efficacy of diets or new public health legislations. Historically successful international public health legislations, such as the indoor smoking ban originally implemented in Ireland in 2004[666], have been a great resource for Australia (and other countries) to learn from, adapt and utilise, and the addition of biomarkers for cross-country comparison could ultimately be a quantifiable health outcome accommodating this. This would also enhance the ability to track changes in inflammation overtime enabling improved indicators of population health, particularly as new behaviour trends emerge such as vaping or social media use. Alongside inflammatory marker collection, routine national monitoring of The Big 6 and mental health should also be encouraged to enable researchers to examine associations and trends. One such successful example of this routine monitoring is Canada's COMPASS initiative[667], which conducts regular ongoing data collection of The Big 6 and other important variables, within schools.

6.3.2.1 SES and sex relationships with inflammation in adolescents

Chapter 1 discusses how within adult data there can be variations in the prevalence of chronic inflammation depending on some socio-demographic variables. Adults from low SES communities and females generally experience higher inflammation, yet it is largely unknown whether this is also the case in adolescents. **Chapters 2** and **3** of this thesis aimed to help fill this gap. Whilst **Chapter 2** found no significant differences (notably the country level SES variable used was likely too broad), **Chapter 3** found some differing associations between sexes, SES and non-communicable disease and developmental condition prevalence. Building on **Chapter 3** and **4's** findings, there are many inflammatory risk factors that low SES communities could be exposed to such as poverty, low health literacy, low parental monitoring or increased stressors. This would suggest that future research should conduct in depth evaluations of SES differences in inflammation to determine if similar trends are being experienced in adolescents. Sex differences are evident in the parenting styles an adolescent experiences and in inflammation, which may be more complex due to female sex hormones (oestrogen), adult women can expect

to have slightly higher inflammatory levels than males. The differing hormones between males and females (at all ages) predisposes them to higher risks of different diseases, which became evident in **Chapter 3**. Importantly pubertal shifts could play a role in inflammatory levels, with some studies suggesting that males may innately have slightly higher inflammation prior to puberty and this role is reversed after puberty as oestrogen is pro-inflammatory and testosterone is anti-inflammatory[279-282]. However, it is inconclusive as to whether this is true for the general population due to the significant lack of data. Future research should examine inflammatory markers at different pubertal phases across males and females. A clearer understanding could contribute valuable insights into non-communicable diseases or developmental conditions that commonly emerge during adolescents such as IBS, asthma or ADHD[5, 14, 668]. By conducting research to better understand those at increased risk of heightened inflammation, future public health and prevention techniques could be tailored to yield maximum effectiveness and ultimately help to reduce health inequalities.

6.3.2.2 Longitudinal data required for causal analysis

This thesis examined cross-sectional data which is invaluable in contributing new knowledge in an under-researched topic and guiding future longitudinal research. Future progression examining longitudinal data of The Big 6, mental health, sociodemographic variables, and inflammation would accommodate causal analysis to be conducted. Examining data longitudinally could also assist in strengthening evidence to consolidate new public health policy suggestions and have increased leverage in their justification.

Chapter 2 found that of the adolescents with the inflammatory conditions, IBS and asthma, sufferers are generally experiencing high symptom severity. This is an important finding that requires further longitudinal research to better understand contributing factors to assist in alleviating or preventing symptoms that can have damaging social, emotional, and physical affects. Secondly, **Chapter 2** found the most prevalent associations with non-communicable diseases or developmental conditions were increased UPF, tobacco and alcohol intake and poor mental health (specifically depression, anxiety, and psychological distress), justifying the requirement for further longitudinal research examining the associations with these variables over time. **Chapter 4's** exploration of perceived-parental monitoring associations with adolescent dietary intake would benefit from further longitudinal analysis to decipher if perceived-parental monitoring causes improved or adverse dietary intake. Particularly as

parenting styles generally shift as a child transitions into adolescence and young adulthood, long-term analysis would help understand this shift and its subsequent impacts on dietary intake. **Chapter 5** explores crucial relationships between specific dietary variables and inflammation in adolescents, which is currently limited in longitudinal research. Determining adolescents' long-term associations with specific dietary variables can give valuable information about the most healthful dietary variables and overarching diets to prioritise in public health messaging. Furthermore, longitudinal data would enable the exploration of which specific dietary variables, health behaviours and mental health have the greatest impact on inflammation. For example, **Chapter 1** explains how there is some evidence suggesting that the sleep-inflammatory relationship may not be as strong as the SES and inflammation relationship (potentially driven by stressors), and high SES cohorts have higher inflammation when their sleep is poor compared to low SES cohorts, potentially caused by a dampened response system[189].

Given the associations identified between immunology and poor mental health and stressors throughout this thesis, there is a need for robust RCTs to explore their potential in preventing or reducing symptomology, specifically surrounding meditative techniques to calm the CNS. Examples to date include the My Resilience in Adolescence British study[337] which examined the effect of school-based mindfulness training and found no significant differences in mental health at the 1 year follow up in comparison to teaching as usual, however this programme had notable limitations. Much of the programme was not adhered to properly, the control group were schools with good 'Social Emotional Learning' programmes in place and long term follow up scheduled for mid-adolescents (where outcomes were anticipated due to increased onset of mental health conditions at this age) was prevented due to the pandemic. The European Union funded 'EUROPE' project[669] adopted transcendental meditation techniques in schools across three European countries and found significantly improved factors after 3 months, such as decreased anxious coping strategies, or anxiety of humiliation, increased cooperation with others, positive outlooks and help seeking behaviours. However, there was a lack of sustainability of these positive effects in the long term as participants reduced or stopped meditating, an important contribution to the literature as practices may likely require maintenance for long term results.

Future research conducted on public health nutrition should focus on the NOURISHING framework (Table 14), as current nutrition behaviour change literature (up to 2021) examined via an umbrella review[659] found that studies only utilised strategies across seven of the 10 broad

policy areas, and within these just 14 of the 65 specific sub-policy areas. This highlights the need for future research to incorporate more of these vital policy change techniques from varied domains. To summarise, understanding these relationships more clearly will allow for tailoring of future research, prevention, and public health programmes.

6.3.2.3 DBS for inflammatory marker collection

To encourage future immunological research in adolescents, accessible, feasible, and affordable options for bio sample collection are needed. **Chapter 5** provides a thorough explanation of using DBS for hsCRP collection in an adolescent population, specifically in a school setting. Future research should consider incorporating bio sample collection via DBS into protocols due to its ease, and affordability to enable more research resulting in an improved understanding in this field. More DBS resources are needed in Australia, following the USA and the UK with increased access to DBS resources. Increasing access to DBS resources in Australia would also help to reduce DBS costs further and therefore make them more accessible to researchers with lower budgets. One such suggestion is to explore the tools currently used in the Australian athletes, wherein a DBS kit is attached to the upper arm of young people[618]. To my knowledge this tool is currently not accessible outside of this context, however, would be efficient to help eliminate some of the limitations of conducting DBS described in **Chapter 5,** including the time taken to collect blood spots and the difficulty in collecting enough blood to fill all blood collection sheets. Such instruments show great promise for biobehavioural research in the future and are important elements for academic consideration. **Chapter 5** also contributes valuable sample size calculations for diet-inflammatory research conducted in adolescents, something that requires application to help power future studies.

6.4 Conclusions

This thesis advances the field of epidemiology and provides potential targets for prevention science through a multifaceted exploration of current adolescent lifestyle factors and their relationships with immunological health. Three key conclusions emerged from this thesis. First, the prevalence of health risk factors in adolescents is very high, particularly for poor dietary intake, sedentary behaviour and poor mental health, which poses a significant current and future public health concern. This highlights the need for increased public health interventions that consider a whole of lifestyle approach, including parenting and socio-demographic considerations. Emerging findings on the detrimental impacts of certain dietary components on

gut and immunological health (e.g., emulsifiers, artificial sweeteners, processed foods and meats) also requires replication in adolescent populations to determine potential detrimental health impacts in this critical developmental period. Secondly, associations between immunological health and poor health behaviours, mental health and social determinants of health are evidenced in adolescence, however, the adolescent population is vastly underrepresented in global data, justifying a substantial need for future adolescent biobehavioural research. Finally, the use of dried blood spots in biobehavioural research in adolescents is feasible, affordable and non-invasive, offering the potential for increased access to inflammatory marker retrieval within adolescents. Improved availability of dried blood spot resources is required in Australia to accommodate future, larger research studies. This thesis lays foundations for actionable recommendations for future research and policy, to work towards a healthier landscape for adolescents and contribute to disease prevention and reduction.

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Appendix A

Exploring the association between adolescent-perceived parental monitoring on dietary intake

Preface

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BO led the development of this Article. BO, LT, TB, MS, LG, KC and MT were involved in conceptualization. KEC and NCN secured funding and KEC led the development of the overall Health4Life RCT with oversight from NCN. KC, LAG and BO were responsible for ethics. BO was the primary lead in recruitment and data collection for this study which SS & EH assisted with. BO ran the statistical analysis and interpretation under the guidance of MS. MT & NCN oversaw project management. BO wrote the original manuscript, and all authors were involved in the review.

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Exploring the association between adolescent-perceived parental monitoring on dietary intake

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Abstract

Parenting practices such as parental monitoring are known to positively impact dietary behaviours in offspring. However, links between adolescent-perceived parental monitoring and dietary outcomes have rarely been examined and never in an Australian context. This study investigated whether adolescent-perceived parental monitoring is associated with more fruit and vegetable, and less sugar-sweetened beverages (SSB) and junk food consumption in Australian adolescents. Cross-sectional data was collected as part of baseline measurement for a randomised controlled trial in 71 Australian schools in 2019. Self-reported fruit, vegetable, SSB and junk food intake, perceived parental monitoring and sociodemographic factors were assessed. Each dietary variable was converted to "not at risk/at risk" based on dietary guidelines, binary logistic regressions examined associations between dietary intake variables and perceived parental monitoring while controlling for gender and socio-economic status. The study was registered in ANZCTR clinical trials. The sample comprised 6053 adolescents (M_{age} = 12.7, SD = 0.5; 50.6% male-identifying). The mean parental monitoring score was 20.1/24 (SD = 4.76) for males and 21.9/24 (SD = 3.37) for females. Compared to adolescents who perceived lower levels of parental monitoring, adolescents reporting higher parental monitoring had higher odds of insufficient fruit (OR = 1.03; 95% CI = 1.02–1.05) and excessive SSB (OR = 1.07; 95% CI = 1.06–1.09) intake, but lower odds of excessive junk food (OR = 0.96; 95% CI = 0.95–0.98) and insufficient vegetable (OR = 0.97, 95% CI = 0.96–0.99) intake. Adolescent dietary intake is associated with higher perceived parental monitoring; however, these associations for fruit and SSB differ to junk food and vegetable intake. This study may have implications for prevention interventions for parents, identifying how this modifiable parenting factor is related to adolescent diet has highlighted how complex the psychological and environmental factors contributing to dietary intake are.

KEYWORDS

adolescent, diet, Health4Life, parental monitoring, parenting

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1 | INTRODUCTION

Adolescence is a critical period characterised by increases in autonomy, shifting influences on dietary intake and greater consumption of junk foods and beverages (Ziegler et al., 2021). The occurrence of puberty during adolescence signifies a vital period of development, where balanced nutritional intake is of high importance to support neurological and physiological growth (Norris et al., 2022). This rapid growth period requires considerable nutrient demand as it is a time when 45% of skeletal growth takes place (Rees, 1989) and up to 37% of total bone mass may be accumulated (Key & Key Jr., 1994). However, adolescents are a nutritionally vulnerable group. Data show that 95% of 12–17-year-olds in Australia (Hardy et al., 2016) and 92% of 11–18-year-olds in the United Kingdom (Huang et al., 2019) do not meet the recommended daily guidelines for fruit and vegetable intake, while 9–13-year-olds in America have a mean Healthy Eating Index dietary score of 46.85 (SD 24.93), significantly below the score of 100, that is indicatcative of meeting dietary guidelines (Banfield et al., 2016) and similar patterns have been reported in Canada (Jarman et al., 2020) and Europe (Maneschy et al., 2022). This age group also consumes the most added sugars (Statistics, 2012), with 10% of this population consuming one cup of sugar-sweetened beverages (SSB) per day (Statistics, 2014). Poor dietary intake and nutritional patterns established in adolescence tend to track into adulthood and are associated with an increased risk of later chronic diseases, such as cardiovascular disease and some cancers (Kaikkonen et al., 2013).

To ensure adolescents lay strong nutritional foundations early in life to prevent diet-related disease in later life, an improved understanding of the modifiable parenting factors influencing adolescent dietary intake is needed. According to a comprehensive model proposed by Vaughn et al. (2016), there are three main types of food parenting practices: coercive control (e.g., restriction, pressure to eat), structure (e.g., monitoring, modelling) and autonomy support (e.g., encouragement, education). Research indicates that parental control (placing limits and restrictions on behaviours and insistence on compliance) (Rohner et al., 2005) is associated with restrained and emotional eating in offspring (DeCosta et al., 2017; Lau et al., 1990; van Strien & Bazelier, 2007) and increased intake of SSB and less nutrient-dense foods (Ma & Hample, 2018). Research indicates that parental autonomy support (providing options and meaningful justification during decision-making, alongside being empathetic to the youth's position; Deci et al., 1994) results in an adolescent being more likely to internalise and demonstrate greater self-determination, resulting in improved health behaviours such as dietary intake (Shannon Morrison et al., 2013). In terms of structural parenting practices there is good evidence that parental monitoring plays a key role in children's dietary behaviours when a child is young (Collins et al., 2014; Loncar, 2019); however, less is known about the influence of parental monitoring during the transitional adolescent period. Parental monitoring refers to a parent's awareness of their child's whereabouts and knowledge of their activities and friendships (Small & Kerns, 1993; Stattin & Kerr, 2000), along with the child's contribution and voluntary descriptions of their free-time activities. Open channels of communication and awareness of, but not control over, adolescents' whereabouts are key characteristics of parental monitoring. Parental monitoring has been associated with a significantly higher quality diet, as well as acting as a protective factor for positive adolescent eating patterns (Chilcoat & Anthony, 1996; DiClemente et al., 2001; Li et al., 2000; Pittman & Chase-Lansdale, 2001; Romer et al., 1999). Conducted among 4088 American adolescents, one of the only studies reporting adolescent-perceived parental monitoring and dietary intake in the general population, adolescents (Kim et al., 2019; Martinson et al., 2016) found high perceived parental monitoring was associated with healthy dietary intake while low perceived parental monitoring was associated with unhealthy dietary intake.

Gender is known to be associated with eating behaviours and dietary quality. Female adolescents are more likely to engage in restrictive eating behaviours, while male adolescents are more likely to consume SSB and junk food, and less likely to consume the recommended servings of fruit and vegetables (Askovic & Kirchengast, 2012). Emerging evidence suggests that gender is also associated with differing parenting approaches, with female adolescents reporting higher levels of parent dependability and trust in parents than males (Ying et al., 2015). Simultaneously, the food environment can be shaped by socioeconomic status (SES). Research consistently shows low SES is linked to lower fruit and vegetable consumption, coupled with increased saturated fat and refined sugar intake (Satia, 2009). While factors including lack of education, food insecurity and economic hardship play a role (Desbouys et al., 2020); differences in parental practices among lower SES populations may also impact adolescent

Key messages

- Little research has been conducted on adolescent-perceived parental monitoring, which is a factor contributing to overall parenting styles, and its relationship with adolescent's dietary intake. This study found that perceived parental monitoring is significantly associated with adolescent dietary intake, despite the increased autonomy and independence over food choices at this age.
- Our findings indicated that higher perceived parental monitoring is significantly associated with fruit, vegetable, sugar-sweetened beverage and junk food intake in different ways, highlighting how complex the psychological and environmental factors contributing to dietary intake are.
- Further research is needed incorporating parents' own diet and different parenting practices from both an adolescent and parents' perspective to help better depict the most recommended style for the optimum diet during adolescence.

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dietary intake (Sharon et al., 2015). For example, home environments where there is increased economic stress and work-related pressures (Pechey & Monsivais, 2016) may limit a parent's ability to effectively monitor their child's behaviour (Farley, 2011).

While some research documents how parent-reported parenting practices can impact dietary intake during adolescence, studies examining the impact of *adolescent-perceived* parental monitoring on diet are scarce. Literature suggests that parents and adolescents commonly perceive different parenting behaviours (Cottrell et al., 2003), therefore adolescent-perceived parental monitoring has the opportunity to accurately reflect the adolescents' actual experience of their parents' behaviours. Kim et al. (2019) found higher adolescent-perceived parental monitoring was associated with healthier dietary intakes among US adolescents. However, to date, no study has examined these links in an Australian sample. Further, there has been no research controlling for key demographic factors linked with parental monitoring, including gender and SES, which is critical to informing tailored prevention and intervention approaches. Therefore, the present study aims to explore the relationships between adolescent-perceived parental monitoring and dietary intake in a large sample of Australian adolescents (12–14 years old) controlled by gender and SES. We hypothesise that adolescents who perceive high parental monitoring will be more likely to meet dietary guidelines for fruit and vegetable intake and consume less junk food and SSB than those who perceive low parental monitoring.

2 | MATERIALS AND METHODS

2.1 | Participants

This study is a secondary analysis of cross-sectional baseline data collected for the Health4Life Study, a large cluster randomised controlled trial (RCT) among 71 schools across three Australian states of New South Wales (NSW; $n = 37$), Western Australia ($n = 16$) and Queensland ($n = 18$). This RCT aimed to improve six health behaviours (dietary intake, exercise, sleep, screen time, tobacco and alcohol use) in adolescents to prevent future chronic disease, full details of the RCT can be found in the published protocol (Teesson et al., 2020). In short, the sample consisted of Grade 7 students aged 11–14 years from independent ($n = 38$), government ($n = 24$) and Catholic ($n = 9$) secondary schools. Randomisation to either the intervention or control group was stratified by school location (metropolitan or regional) and school gender composition (coeducation, predominantly male [>60%] or predominantly female [>60%]) and conducted by a biostatistician with no role in school recruitment. Parental consent and student consent were obtained, and 6639 students participated in an online self-report survey in 2019. A full report on the baseline characteristics of the Health4Life sample has been published previously (Champion et al., 2023). Ethical approval was gained from the University Ethics Committees, NSW Department of Education, and relevant Catholic school committees.

2.2 | Measures

2.2.1 | Demographic information

Students self-reported their gender (male, female, nonbinary/gender fluid; Acon, 2019) and age. SES was assessed using the Family Affluence Scale (FAS) (Torsheim et al., 2016), an individual-level indicator of family affluence. The summed raw scores were then transformed into a normally distributed ridit score, which represents the relative SES position compared to the other individuals in this sample. Ridit transformation was originally developed by Bross (IDJ, 1958), our ridit scores ranged from 0 (most disadvantage) to 1 (most advantaged). Similar to the standard practice used in other studies (Corell et al., 2021), our ridit score was then used to convert adolescents into three groups: lowest 20% (low affluence), middle 60% (medium affluence) and highest 20% (high affluence), representing individuals who fall in a lower (ridit < 0.2), middle (ridit ≥ 0.2 and ≤ 0.6) or higher range (ridit > 0.6) (Elgar et al., 2017).

2.2.2 | Dietary intake

Dietary intake was assessed using the standardised questions derived from the NSW Health SPANS survey (Hardy et al., 2016). Participants were asked about their usual intake of fruit and vegetables ("I don't eat fruit/vegetables," "less than 1 serve per day," "1 serve per day," "2 serves per day," "3 serves per day," "4 serves per day," "4 serves per day," "5 serves per day," "6 serves per day," "more than 6 serves per day") and were provided with visual aids to represent a standard serve. Based on responses, a binary variable (0/1) was used to represent insufficient versus sufficient fruit and vegetable intake based on the Australian National Guidelines for their age group (consuming two or more serves of fruit a day and five or more serves of vegetables a day) (Government, 2021). To assess SSB consumption, students reported how many cups they usually consume per week ("never/rarely drink," "1 cup or less a week," "2 to 4 cups a week," "5 to 6 cups a week," "1 cup a day," "1 ½ cups or more a day" to "2 or more cups a day"), with Australian examples and visual aids provided. Based on responses, excessive SSB consumption was classified as drinking >5 cups per week. Frequency of junk food consumption, including one item each on takeaway meals or snacks (from places like McDonalds, KFC, Dominos or local fast food places), snack foods (sweet and savoury biscuits, cakes, donuts or muesli bars), potato crisps (or other salty snacks), hot chips (French fries, wedges or fried potatoes), ice cream or ice blocks and confectionary (lollies, or chocolate) was assessed ("Never/rarely," "1-2 times a week," "3-4 times a week," "5-6 times a week," "once every day," "two or more times a day"). Based on responses, excessive junk food consumption was classified as consuming more than one serving of junk food a day. Finally, a binary composite indicator of poor diet was calculated based on these individual binary dietary variables to describe participants as "at risk" or "not at risk" for poor overall diet for descriptive analysis, representing those who drank more than five

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cups of SSB a week, ate less than two serves of fruit and five serves of vegetables a day and more than one serve of junk food a day.

2.2.3 | Adolescent-perceived parental monitoring

A validated 6-item general parental monitoring scale (Small & Kerns, 1993) was used to assess adolescent-perceived parental knowledge of a child's whereabouts ("my parents usually know what I am doing after school," "my parents know who my friends are," "my parents know where I am after school," "if I am going to be home late, I am expected to call my parents to let them know," "I tell my parents who I'm going to be with before I go out," "I talk to my parents about the plans I have with my friends"). Each item is scored from 0 to 4 ("never," "rarely," "sometimes," "often," "always") and total scores range from 0 (lowest perceived parental monitoring) to 24 (highest perceived parental monitoring).

2.3 | Statistical analysis

Descriptive statistics were used to generate the frequency and percentage of the variables of interest in the total sample, grouping these by gender and SES. Due to low numbers of participants falling into the nonbinary/gender fluid category, these were omitted from the analyses, gender analysis therefore only included "male"/"female" genders. A series of binary logistic regressions were conducted to examine associations between perceived parental monitoring and each binary dietary outcome: fruit intake (<2 vs. 2+ serves per day), vegetable intake (<5 vs. 5+ serves per day), SSB intake (>5 vs. 0–5 cups per week) and junk food intake (>1 vs. 0–1 serve per day) while controlling for gender and SES. Before fitting the models, assumptions were tested and met. For each regression analysis, the dietary outcome was the dependent variable and parental monitoring was the independent variable. All regressions included a school cluster variable to account for the nonindependence of students clustered within schools and odds ratios (OR) and 95% confidence intervals (CI) are reported. Further demographic breakdown of this sample can be found elsewhere (Champion et al., 2022). Models used complete case analysis, and as the sample size is very large and missing data was negligible (below 5.4% for all dietary outcomes), no further examination of missing data was conducted as is standard practice (Smout et al., 2023). All analyses were conducted in Jamovi 1.6.16.

3 | RESULTS

3.1 | Sample characteristics

The baseline sample comprised a total of 6639 adolescents, of whom 6053 provided valid responses to the perceived parental monitoring questionnaire and were therefore included in analyses. Participants were aged 11–14 years, with a mean age of 12.7 (SD = 0.5) and 50.6% identified as male. 15.1% (12.6%–17.6%) of the cohort classified as low SES, 36.7% (34.3%–39.1%) as medium SES and 48.2% (44.2%–52.1%) as high SES.

TABLE 1 Dietary behaviours in the total sample.

Dietary behaviour	*n*	%	SE
Poor diet[a] (composite of high SSB, insufficient fruit & veg and high junk foods) (*n* = 5815)	2920	50.2	1.3
Excessive sugar-sweetened beverage consumption (>5 cups a week) (*n* = 6466)	705	10.9	0.9
Insufficient fruit intake (<2 serves/day) (*n* = 6444)	1492	23.2	1.1
Insufficient vegetable intake (<5 serves/day) (*n* = 6439)	5363	83.3	0.6
Excessive junk food intake (>1 serve/day) (*n* = 5728)	2357	41.1	1.1

[a]"Poor diet" is a binary variable (yes/no) and is a composite of having poor dietary consumption for each of the four dietary behaviours (excessive SSB, insufficient fruit, insufficient veg and excessive junk food).

TABLE 2 Perceived parental monitoring (out of 24 points) by sample characteristics.

		Mean (Pittman and Chase-Lansdale) perceived parental monitoring score
Gender[+]	Male (*n* = 3026)	20.1 (4.76)
	Female (*n* = 3027)	21.9 (3.37)
Relative family affluence	Low	20.3 (5.25)
	Medium	21.1 (4.04)
	High	21.2 (3.92)

As illustrated in Table 1, half of the sample (50.2%) reported poor diet based on the composite indicator, with the vast majority (83.3%) reporting insufficient vegetable intake. Excessive junk food intake (41.1%) and insufficient fruit intake (23.2%) were also common, with approximately one in ten (10.9%) adolescents consuming excessive SSB. Table 2 provides an overview of adolescent-perceived parental monitoring by demographic characteristics. Mean scores for perceived parental monitoring in the total sample were 21.0/24 (SD 4.22). Female adolescents reported higher levels of perceived parental monitoring compared to males, and adolescents of higher and medium relative SES reported higher levels of parenting monitoring compared to those of lower SES.

3.2 | Binary logistic regressions for dietary behaviours

A one-unit increase in perceived parental monitoring scores was significantly associated with increased odds of insufficient fruit intake (OR = 1.03; 95% CI = 1.02–1.05, $p < 0.001$). Similarly, a one-unit increase

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in perceived parental monitoring scores was associated with increased odds of excessive SSB intake (OR = 1.07; 95% CI = 1.06–1.09, $p < 0.001$). Conversely, a one-unit increase in perceived parental monitoring scores was associated with lower odds of reporting excessive junk food intake (OR = 0.96; 95% CI = 0.95–0.98, $p < 0.001$). Similarly, a one-unit increase in perceived parental monitoring scores was associated with lower odds of not meeting the guidelines for vegetable intake (OR = 0.97; 95% CI = 0.96–0.99, $p < 0.01$).

4 | DISCUSSION

This study examined whether adolescent-perceived parental monitoring was associated with dietary intake among Australian adolescents. As hypothesised, we found that adolescents who perceived *higher* levels of parental monitoring were more likely to not meet guidelines for fruit intake and consumed excessive SSB, whereas those who perceived *lower* levels of parental monitoring were more likely to not meet the guidelines for vegetable intake and consumed excessive junk food. Consistent with prior research (Çetinkaya, 2019), we found adolescents reported high levels of perceived parental monitoring, with females perceiving higher levels of parental monitoring compared to males (Mills et al., 2021), and adolescents of higher relative SES reporting higher levels of perceived parental monitoring compared to those of lower SES.

The finding that higher levels of perceived parental monitoring were associated with high SSB intake and insufficient fruit intake contradicts prior research, which has shown that adolescents with higher parent-perceived parental monitoring have more favourable dietary outcomes (DiClemente et al., 2001; Li et al., 2000; Pittman & Chase-Lansdale, 2001). One possible explanation is that SSB consumption is an autonomous behaviour that largely occurs outside the home (e.g., on the way to/from school, during leisure activities with peers) and therefore is less susceptible to the influence of parental monitoring (Vézina-Im et al., 2017). As the directionality of findings cannot be determined in our cross-sectional study, it is also possible that this relationship could be highlighting that parents of adolescents who are drinking more SSB have resulted in using higher parental monitoring in an attempt to reduce this. Contributing to this is the abundance of marketing from SSB companies to tactically target youth, alongside their high addictiveness and palatability, which could override the effects of parental monitoring when adolescents gain more autonomy over their food choices. These findings also support results from a recent meta-analysis, which found that parent-based interventions were not effective in reducing SSB intake among adolescents; however these interventions did significantly improve fruit, vegetable and junk food intake (Champion et al., 2022).

The unexpected associations between high perceived parental monitoring and insufficient fruit and excessive SSB intake could also be due to other factors in an adolescent's environment. First, a parent's own knowledge and beliefs about food, alongside food resources available to them (i.e., cost or food accessibility), will govern what foods are available in the adolescent's home. Additionally, parents act as role models for their adolescents' dietary behaviours, potentially contributing to ongoing cycles of poor dietary intake. As parental monitoring is only one factor contributing to an overall parenting style, it is important to consider how other parenting factors could contribute to poor fruit and SSB intake, including attitudes, beliefs and rules relating to a particular food group (e.g., vegetables), which may not apply to another food group (e.g., SSB).

Our finding that higher perceived parental monitoring was associated with lower odds of excessive junk food and insufficient vegetable intake aligns more closely with the literature (DiClemente et al., 2001; Li et al., 2000). The positive impact of perceived parental monitoring on these behaviours could be explained by some of these foods being predominantly consumed during meals, which a parent remains largely responsible for, particularly when compared to SSB and fruits, which are generally consumed when snacking. In line with this, it could be more difficult for an adolescent to purchase junk foods such as takeaway foods due to accessibility or cost in comparison to SSB, which are more affordable and could be sourced easily in local vending machines or convenience shops where adolescents are not reliant on a parent to drive them or even be aware of their purchasing. A further explanation could be that more traditionally, vegetables and "healthy meals" have been primarily emphasised and advertised to parents, and the risks of high SSB intake are still relatively under-appreciated, particularly when considering the existential growth in consumption over recent years.

The use of adolescent-reported perceptions of their caregivers' parenting practices allows for an accurate representation of how the adolescent themselves feel parented and reduces the bias of self-report from the parent's perspective. Future research could look at both parent and adolescent-perceived parenting practices as both views could provide different perspectives. The complexity of how parenting impacts adolescent dietary intake has also been explained previously by Basset et al. (2008) who witnessed that even when an adolescent is exercising autonomy over their food choice, if a parent is monitoring and controlling the environment by using coaxing and coaching strategies, an adolescent can respond by complaining or ignoring advice, while taking responsibility and reflected on their behaviours and keeping in mind their parents advice. Even if in some cases this does not transcend to immediate action, adolescent food choice is ultimately actively co-constructed by both adolescent and parent, proving adolescents may act in some ways immediately and in others can restore guidance which they may choose to act on at a later date.

4.1 | Strengths and limitations

The present results should be considered in light of several limitations. First, being a cross-sectional analysis, we are unable to determine the directionality of relationships and establish causality. For example, it is possible that parents who are concerned about

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their adolescents' eating behaviour may increase their parental monitoring. Additionally, although large and geographically diverse, our sample was not nationally representative, and students were predominantly English-speaking and living in major cities. Nonetheless, the sample comprised adolescents living across three Australian states and attending a diverse range of secondary schools (independent, government and Catholic). Our dietary outcomes were also collected via adolescent self-report, as objective assessment was not possible due to the scale of the RCT. We did not take into account parents' own dietary behaviours or home food environments, which could have resulted in some confounding factors being missed. Finally, SSB consumption could have been underreported as energy drink consumption was not part of the current analysis. Similarly, our perceived parental monitoring measure focuses predominantly on a child's whereabouts and general perceived parental monitoring, as opposed to the monitoring of an adolescent's diet specifically, therefore high adolescent-perceived parental monitoring could have been reported when a parent was prioritising other risky behaviours such as alcohol use, for example. Simultaneously our research has some considerable strengths, including the novel use of adolescent-perceived parental monitoring, which could be considered a more important format than parent-perceived monitoring due to reflecting the actual adolescent experience. In addition, most previous literature has only reviewed these relationships in relation to one food group, whereas our analysis of multiple food groups fills knowledge gaps on how perceived parental monitoring impacts different dietary variables in one cohort. Our large Australian sample size incorporated gender and SES, where no previous research on perceived parental monitoring of dietary intake in adolescents has been conducted. Future research should also monitor parenting practices specific to diet and explore different parenting styles in comparison with parental monitoring, such as initiatives like Triple P (teaching positive parenting practices) (Pickering, 2013), other food parenting practices or household food inventories. A recent survey of adults found that out of all health behaviours parents chose dietary habits as the behaviour they would most like to change for themselves and their adolescents (Champion et al., 2023), therefore combined interventions moving forward should aim to target both the parents and the adolescents to improving adolescent diet and overall food environments at home.

5 | CONCLUSION

Our results contribute knowledge specifically around perceived parental monitoring's association with adolescent dietary intake, a factor contributing to overall parenting style. However, our findings indicated that perceived parental monitoring is associated with different dietary variables in different ways. Despite increasing autonomy during adolescence, parents still have an important impact on aspects of their adolescent's dietary behaviours, thus dietary interventions among early adolescents should not overlook the role of parenting practices. Findings may have implications to inform further exploratory analysis, which could assist in guiding future prevention interventions for parents and adolescents, identifying how this modifiable parenting factor related to adolescent diet has highlighted how complex the psychological and environmental factors contributing to dietary intake are. Further research is needed incorporating parents' own diet and different parenting practices (Fleary & Ettienne, 2019) from both adolescent and parents' perspectives to help better depict the most recommended style for the optimum diet during adolescence.

AUTHOR CONTRIBUTIONS

Author Bridie Osman lead recruitment, data collection and analysis and writing of the manuscript. Katrina E. Champion, Lauren A. Gardner and Louise Thornton project-managed the recruitment and data collection, gave advice on the planning of this study and reviewed draft manuscripts. Tracy Burrows gave guidance during the planning of this study and reviewed draft manuscripts. Scarlett Smout and Emily Hunter assisted with recruitment and data collection and reviewed drafts of this manuscript. Matthew Sunderland gave guidance and reviewed the statistical analysis for this study and reviewed draft manuscripts. Maree Teesson & Nicola C. Newton oversaw project management and gave feedback on drafts of this manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study is available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions. Data can be made available upon request to the authorship team or by request via the online repository www.researchdata.edu.au/health.

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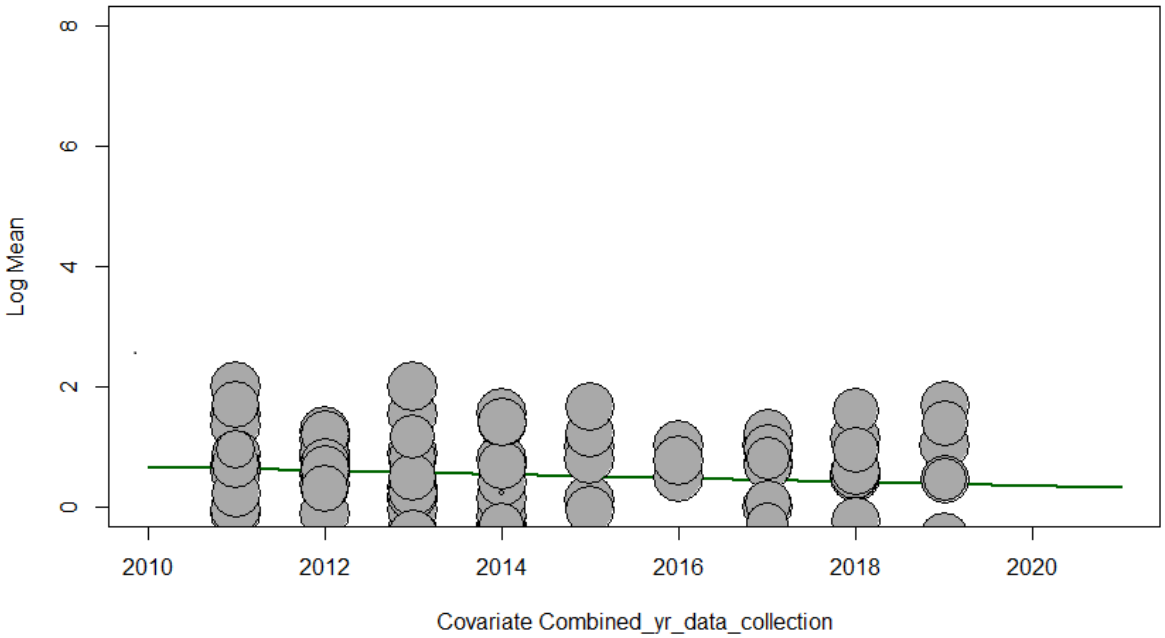
Appendix 1: Supplementary Materials for Chapter 2

Appendix 1.1 - Ovid MEDLINE search strategy

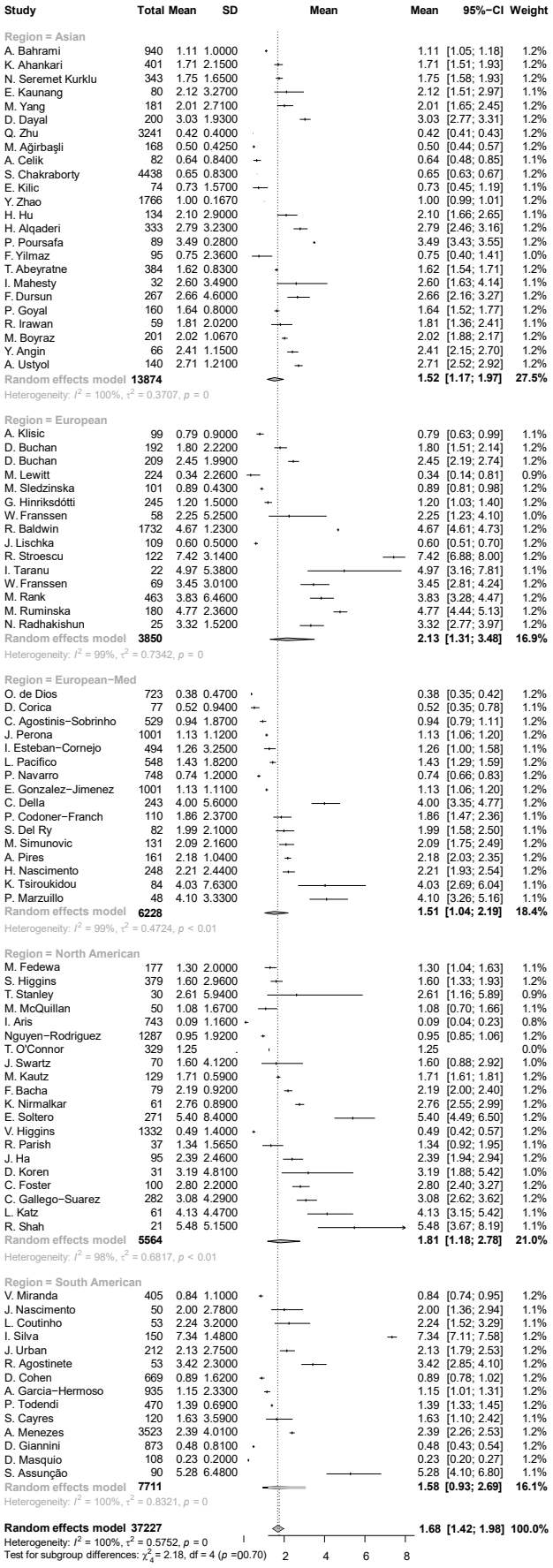
Ovid MEDLINE(R) ALL <1946 to September 13, 2021>

#	Query	Results from 13 Sept 2021
1	(C-Reactive Protein or c-reactive protein* or CRP or c-reaction protein or protein,c reactive or serum c-reactive protein).tw.	92,279
2	(adolescen* or youth* or early life or (young adj1 (person or people or adult*)) or teen* or p?ediatric* or juvenile or adolescent).tw.	896,386
3	(exp cohort studies/ or cohort$.mp. or exp Observational Study/ or exp case-control studies/ or (case$ and control$).mp. or exp cross-sectional studies/ or (cross$ and sectional$).mp.) not (exp animals/ not humans.sh.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3,549,182
4	1 and 2 and 3	2,563
5	limit 4 to humans	2,228
6	5 not (comment or editorial or letter).pt.	2,224

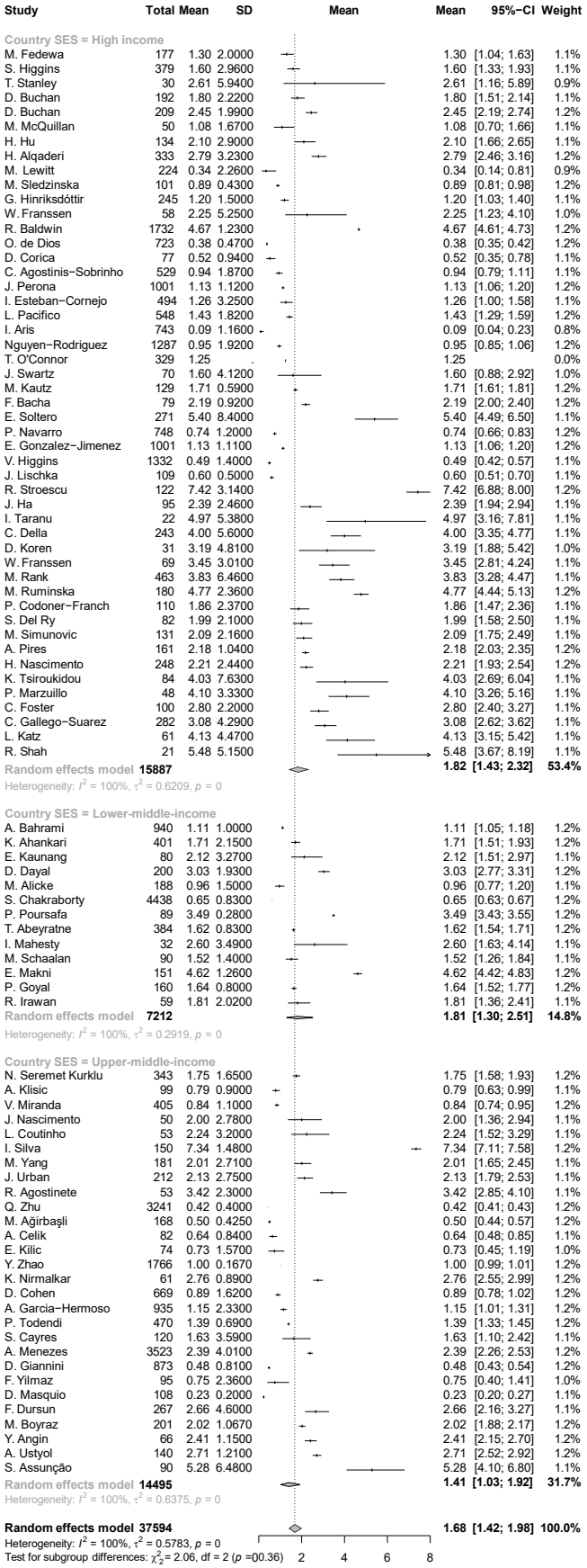
Appendix 1.2 - Meta-regression changes in adolescent CRP over the past 10 years, bubble graph



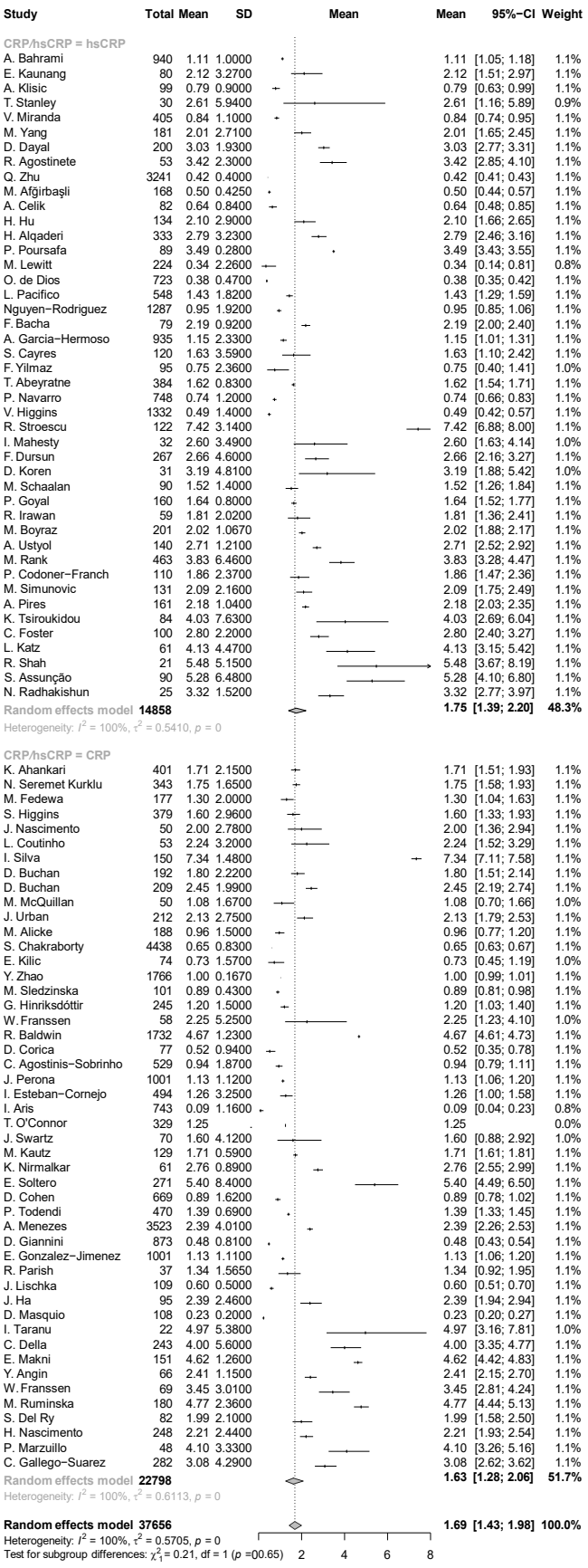
Appendix 1.3 - Meta-analysis determining differences in mean CRP levels between regional sub-groups



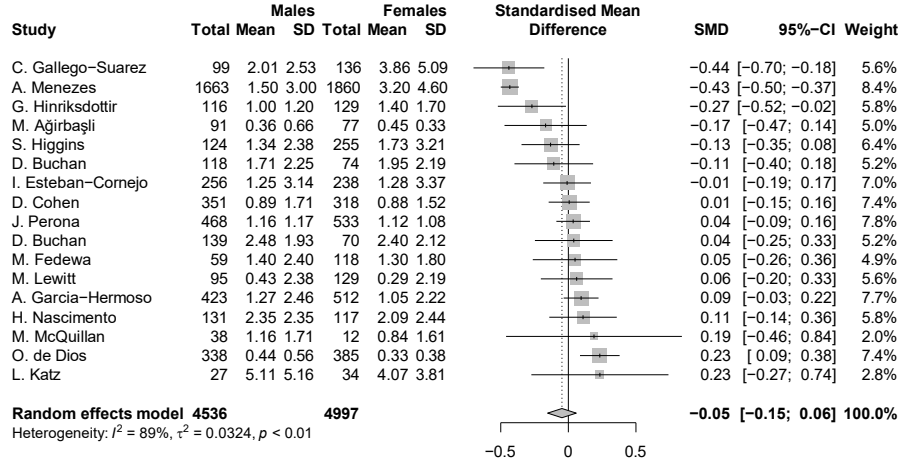
Appendix 1.4 - Meta-analysis determining differences in mean CRP levels between country SES sub-groups



Appendix 1.5 - Meta-analysis determining differences in mean CRP levels between CRP and hsCRP measuring sub-groups



Appendix 1.6 - Pooled standardised mean difference between male and female CRP levels



Appendix 1.7 - JBI risk of bias appraisal

B.J. Osman et al.

JBI risk of bias quality appraisal

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Abeyratne T et al.	0	1	1	1	1	1	1	0	6
Ağırbaşlı M et al.	0	0	1	1	0	1	1	1	5
Ahankari K et al.	1	0	1	1	0	1	1	1	6
Agostinete RR et al.	0	0	0	1	1	1	1	0	4
Alicke M et al.	0	0	0	1	0	1	1	1	4
Angin Y et al.	0	0	0	1	1	0	1	0	3
Assuncao SNF et al.	0	0	1	1	0	1	1	0	4
Bacha F et al.	0	0	1	1	1	1	1	1	6
Bahrami A et al.	0	1	0	1	0	1	1	0	4
Boyraz M et al.	0	0	1	1	1	1	1	0	5
Yilmaz et al.	0	0	1	1	1	1	1	0	5
Celik A et al.	0	0	0	1	1	1	1	0	4
Chakraborty S et al.	0	1	1	1	1	1	0	1	5
Corica D et al.	0	0	0	1	1	1	1	0	4
Codoner-Franch P et al.	0	0	0	1	1	1	1	0	4
Coutinho L et al.	0	0	1	1	1	1	1	0	5
Dayal D et al.	0	0	1	0	1	1	1	0	4

Della CC et al.	0	0	0	0	0	0	1	0	1
de Dios O et al.	1	0	0	1	1	1	1	0	5
Buchan DS et al.	0	0	1	1	1	1	1	0	5
Buchan DS et al.	0	0	1	1	1	1	1	0	5
Del Ry S et al.	0	0	0	1	1	1	1	0	4
Franssen W et al.	0	0	1	1	1	1	1	1	6
Esteban-Cornejo I et al.	1	0	1	1	1	1	1	0	6
Rank M et al.	0	0	0	1	1	1	1	1	5
Katz LE et al.	0	0	0	1	1	1	1	1	5
Mahesty IR et al.	0	1	1	0	0	0	1	0	3
Nascimento J et al.	0	0	1	1	1	1	0	0	4
Fedewa MV et al.	0	0	1	1	1	1	1	0	5
Franssen W et al.	0	0	1	1	1	1	1	1	6
Gallego-Suarez C et al.	0	0	1	1	1	1	1	0	5
Garcia-Hermoso A et al.	0	0	1	1	1	1	1	1	5
Foster C et al.	0	0	1	1	1	1	1	1	6
Gonzalez-Jimenez E et al.	0	0	1	1	1	1	1	1	6
Goyal P et al.	0	0	1	0	1	0	1	0	3
Ha J et al.	0	0	1	1	1	1	1	1	6
Hinriksdóttir G et al.	0	1	1	1	1	1	1	1	7
Higgins S et al.	0	0	1	1	1	1	1	1	6

Hu HJ et al.	0	0	0	1	1	1	1	0	4
Irawan R et al.	0	0	0	1	1	1	1	0	4
Kaunang E et al.	0	0	1	1	1	1	1	0	5
Kilic E et al.	0	0	1	1	1	1	1	0	5
Klisic A et al.	0	0	1	1	0	0	1	0	3
Koren D et al.	0	0	1	0	1	1	1	1	5
Lewitt MS et al.	0	0	1	1	1	1	1	1	6
Lischka J et al.	0	0	1	0	0	0	1	1	3
Makni E et al.	0	1	1	1	1	1	1	0	6
Marzuillo P et al.	0	0	0	0	1	1	1	0	3
Masquio DC et al.	0	0	1	1	1	1	1	1	6
McQuillan MT et al.	1	0	1	1	1	1	1	1	7
Menezes A et al.	0	0	1	1	1	1	1	1	6
Miranda V et al.	0	1	1	1	1	1	1	1	7
Nascimento H et al.	0	0	0	1	1	1	1	0	4
Nirmalkar K et al.	0	1	1	1	1	1	1	0	6
Pacifico L et al.	0	1	1	1	1	0	1	0	5
Parish RC et al.	0	0	1	1	1	1	1	1	6
Perona JS et al.	0	1	1	1	1	1	1	1	7
Pires A et al.	1	0	0	0	0	1	1	0	3
Poursafa N et al.	0	1	1	1	1	1	1	0	6
Radhakishun N et al.	0	0	0	1	1	1	0	0	3

Ruminska M et al.	0	0	1	1	0	1	1	0	4
Schaalan M et al.	0	0	1	1	1	1	1	1	6
Shah RV et al.	0	0	1	1	1	1	1	1	6
Silva IT et al.	0	1	1	1	1	1	1	0	6
Simunovic M et al.	0	0	1	1	1	1	1	0	5
Sledzinska M et al.	1	0	1	1	1	0	1	0	5
Soltero EG et al.	0	0	1	1	1	1	1	0	5
Stanley T et al.	0	0	1	1	1	0	1	1	5
Stroescu R et al.	0	0	1	0	0	1	1	0	3
Taranu I et al.	0	0	1	0	1	0	1	0	3
Ustyol A et al.	0	0	1	0	1	1	1	0	4
Tsiroukidou K et al.	0	0	1	1	1	1	1	0	5
Zhao Y et al.	0	1	1	1	1	0	1	0	5
Zhu Q et al.	0	1	1	1	1	1	1	1	7
Giannini DT et al.	0	1	1	0	0	1	1	0	4
Seremet Kurklu N et al.	0	0	1	1	1	0	1	0	4
Todendi PD et al.	0	0	1	1	1	0	1	0	4
Yang MC et al.	0	0	1	0	0	0	1	1	3
Dursun F et al.	0	0	1	1	1	1	1	0	5
Kautz MM et al.	0	0	1	1	1	1	1	1	6
Navarro P et al.	0	0	0	1	1	1	1	0	4
Higgins V et al.	0	0	1	1	1	1	1	0	5

Swartz JR et al.	0	0	1	1	1	1	1	1	6
Agostinis-Sobrinho CA et al.	0	1	1	1	1	1	1	1	7
Pires A et al.	0	0	0	0	1	1	1	0	3
O'Connor TG et al.	0	1	1	1	1	1	1	1	7
Cohen DD et al.	0	0	0	1	1	1	1	0	4
Baldwin JR et al.	1	1	1	1	1	1	1	1	8
Aris IM et al.	0	0	0	1	1	0	1	1	3
Alqaderi H et al.	0	0	1	0	0	1	1	1	4
Cayres S et al.	0	0	1	1	1	1	1	0	5
Urban J et al.	0	0	1	1	1	1	1	0	5
Nguyen-Rodriguez et al.	0	0	0	1	1	1	1	0	4
	1 = Yes		0 = No/Unclear						

JBI Critical Appraisal Checklist for studies reporting prevalence data	
1. Was the sample frame appropriate to address the target population?	
2. Were study participants sampled in an appropriate way?	
3. Were the study subjects and the setting described in detail?	
4. Was the data analysis conducted with sufficient coverage of the identified sample?	

5. Were valid methods used for the identification of the condition?
6. Was the condition measured in a standard, reliable way for all participants?
7. Was there appropriate statistical analysis?
8. Was the response rate adequate, and if not, was the low response rate managed appropriately?

Appendix 1.8 - MOOSE checklist

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	2-5
2	Hypothesis statement	-
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5-6
5	Type of study designs used	5-6
6	Study population	5-6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5-6, Title page
8	Search strategy, including time period included in the synthesis and key words	5-6, Table S1
9	Effort to include all available studies, including contact with authors	5-7
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	5-6

12	Use of hand searching (eg, reference lists of obtained articles)	-
13	List of citations located and those excluded, including justification	Table S3, Figure S1
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-8, Figure S2
22	Assessment of heterogeneity	7-8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	Tables 1-2, Figs 1-3, S2-S6
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 1-3, S2-S6
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Fig 2-3, S2-S6
28	Indication of statistical uncertainty of findings	21-24

Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	21, Table 1, S2

30	Justification for exclusion (eg, exclusion of non-English language citations)	6, Table S3
31	Assessment of quality of included studies	7, Figure S2
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	21-24
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	23
34	Guidelines for future research	24-25
35	Disclosure of funding source	2

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Appendix 2: Supplementary Materials for Chapter 3

Appendix 2.1 - Methods continued

Measures

Measures validated for use among adolescents were used where possible. Full details of all measures are available in the published study protocol for the larger RCT[1]and are briefly summarized below.

Sociodemographics:

Participants were asked to report their sex assigned at birth. SES was assessed using the six-item Family Affluence Scale (FAS-III)[2, 3] which asks a variety of socio-economic related questions and produces a continuous score (0-13), higher indicating more affluence.

Lifestyle behaviour's:

Four areas of dietary intake were assessed using items adapted from the NSW School Physical Activity and Nutrition Survey[4]; a total Ultra-processed food (UPF) intake score was summed from six items that were used to assess usual intake of UPFs, responses ranged from *'never'* to '*2 or more times per day'*. Fruit and vegetable intake were both accompanied by a standard serve pictorial chart and assessed usual number of serves per day, responses ranged from *'none'* to '*more than 6 serves per day'*. Sugar-sweetened beverages (SSB) intake was accompanied by a standard metric cups pictorial chart and assessed usual cups per week or day, responses ranged from *'never/rarely drink'* to *'2 or more cups a day'*. Alcohol use was assessed using a single item and accompanied by a standard drink pictorial chart[5, 6]; *'Have you had a full standard alcoholic drink in the past 6 months?'* (*'No'/'Yes'*). Tobacco use was assessed using a single item[5, 6]; '*In the past 6 months, have you tried cigarette smoking, even one or two puffs?'* (*'No'/'Yes'*). Screen time was assessed by average time (hours/minutes) spent engaging in sedentary recreational screen time per day over an average week[7] (TV, laptops or handheld devices outside of those used for school) and sleep durations were measured by average sleep duration per night (hours/minutes) over an average week [8], both coded as continuous scores. Physical

activity (PA) assessed moderate-to-vigorous physical activity (MVPA), measuring the number of days in the past week students engaged in at least 60 minutes of MVPA[9], and was coded as a continuous score.

Mental health:

Psychological distress was assessed using questions derived from the strengths and difficulties questionnaire (SDQ)[10], which provides broad and specific indicators of psychopathology. The SDQ generating a continuous score (0-40), a score of ≤17 indicates having psychological distress. From responses to the patient health questionnaire (PHQ)[11], categorical (mild, moderate, moderately severe or severe) depression scores were calculated. From responses to the patient-reported outcomes measurement information system for anxiety (PROMIS-A)[12], categorical (mild, moderate or severe) anxiety scores were calculated. All mental health measures have been extensively tested among adolescents and demonstrate strong psychometric properties[10-12].

Noncommunicable diseases and developmental conditions:

Noncommunicable disease and developmental conditions diagnoses were measured using questions derived from the longitudinal study of Australian Children survey[13] asking participants to report on the presence/absence of specific conditions. The following common and emerging conditions were included in this study: IBS, asthma, eczema, chronic fatigue, hay fever, food allergies, T2D, T1D, ADD/ADHD, and autism/Aspergers. A binary '≥1 common/emerging condition' variable was calculated if one or more common or emerging condition was reported. Participants with IBS or asthma responded to additional severity questions, including: the IBS severity scale (IBS-SSS) [14] which measures the severity of a range of IBS symptoms and from which a categorical score is calculated *('none'*, *'mild'*, *'moderate'*, and *'severe')*. Distribution and severity level similarities of responses were assessed and merged due to small sample sizes, producing a binary score (*'none'/'mild'* and *'moderate'/'severe'*. The asthma severity scale derived from WHO's Global strategy for asthma management and prevention survey[15] assessed the frequency of asthma attacks in the past 12 months (*'less than 1 per month'/ ' 1 per month (less than 1 per week)'/'1 per week (less than 1 per day)'/'1 per day or more'*), persisting symptoms between attacks in the past 12 months' (*'none'/' wheezing'/'wheezing and shortness of breath'/'activities limited by shortness of breath')*. Distribution and severity level similarities of responses from these two questions were assessed and merged due to small sample sizes, producing a binary score (*'less than 1 per month'/'1 per month'* and *'1 per week'/'1 per day'; 'none'/'wheezing'* and *'wheezing and shortness of breath'/'activities limited by shortness of breath')*. The final asthma severity questions asked, 'have you had any hospitalization for asthma in the past 12 months' (*yes/no*).

Appendix 2.2 - Prevalence and severity of each noncommunicable disease and developmental condition

Common and emerging condition	Prevalence	Total	Percentage prevalence
≥1 common/emerging condition	1683	3691	45.6%
No common/emerging conditions	2008	3691	54.4%
Irritable bowel syndrome	139	4651	3.0%
Asthma	701	4651	15.1%
Eczema	492	4651	10.6%
Chronic fatigue	93	4651	2.0%
Hay fever	1081	4651	23.2%
Food allergies	468	4651	10.1%
Type 2 Diabetes	45	4651	1.0%
Type 1 Diabetes	59	4651	1.3%
ADD/ADHD	435	4651	9.4%
Autism/Aspergers	152	4651	3.3%
IBS severity			
None	16	100	16.0%
Mild	32	100	32.0%
Moderate	21	100	21.0%
Severe	31	100	31.0%
Asthma severity – frequency of attacks			
Less than 1 asthma attack per month	395	513	77.0%

1 asthma attack per month	61	513	11.9%
1 asthma attack per week	32	513	6.2%
1 asthma attack per day	25	513	4.9%
Asthma severity – severity of symptoms			
No symptoms between attacks	177	514	34.4%
Wheezing between attacks	75	514	14.6%
Wheezing & shortness of breath between attacks	153	514	29.8%
Activities limited by shortness of breath	109	514	21.2%
Asthma severity – hospitalised by asthma in last 12 months			
No	68	512	13.3%
Yes	444	512	86.7%

Appendix 2.3 - Multivariable logistic regressions to estimate the associations between lifestyle behaviour's/mental health and individual common and emerging diseases/conditions, whilst controlling for sex at birth and SES for insignificant associations only

Variables	≥1 common /emerging condition		Irritable Bowel Syndrome		Asthma		Eczema		Type 2 Diabetes		Chronic Fatigue		Hay fever		Food Allergies		ADD/ADHD		Autism/ Aspergers		Type 1 Diabetes	
	OR[1]	99% CI[2]	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI	OR	99% CI
SES	1.01	0.97-1.06	1.06	0.92-1.22	0.95	0.89-1.02	0.98	0.92-1.06	0.97	0.82-1.13	0.98	0.85-1.13	1.02	0.97-1.09	1.01	0.93-1.09	1.06	0.98-1.14	0.96	0.86-1.06	0.89	0.71-1.10
Fruit intake	0.96	0.91-1.02	0.87	0.64-1.18	0.98	0.91-1.05	0.99	0.90-1.08	1.01	0.67-1.54	1.03	0.76-1.38	1.00	0.94-1.06	0.99	0.90-1.10	1.00	0.90-1.10	0.87	0.73-1.05	0.95	0.67-1.36

Vegetable intake	1.00	0.95-1.06	0.94	0.73-1.21	0.95	0.89-1.02	0.98	0.91-1.05	1.04	0.69-1.56	0.95	0.72-1.24	1.02	1.03-1.70	1.04	0.94-1.14	0.98	0.90-1.07	0.89	0.73-1.09	1.00	0.73-1.36

[1] Odds ratios
[2] 99% Confidence intervals

Appendix 2.4 - Sex at birth moderations of multivariable logistic regressions to estimate the associations between health behaviour's/mental health and individual common and emerging diseases/conditions, whilst controlling for SES

Variables	**≥1 common/ emerging condition**		**Irritable Bowel Syndrome**		**Asthma**		**Eczema**		**Type 2 Diabetes**		**Chronic Fatigue**		**Hay fever**		**Food Allergies**		**ADD/ADHD**		**Autism/ Aspergers**		**Type 1 Diabetes**	
	OR[1]	**99% CI[2]**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
UPFs	0.94 **	0.90-0.98	0.88	0.75-1.03	0.96	0.92-1.00	0.94	0.89-1.00	1.19 *	1.01-1.41	0.93	0.81-1.07	0.97	0.92-1.02	0.92 *	0.86-0.99	1.01	0.95-1.08	0.97	0.88-1.08	1.08	0.94-1.25
E-value	**1.21**								**1.67**				**1.39**									
Fruit intake	1.06	0.96-1.18	1.86 *	1.02-3.39	1.02	0.91-1.14	1.03	0.83-1.27	1.54	3.40-7.03	0.94	0.53-1.66	1.04	0.92-1.18	0.94	0.90-1.35	1.07	0.86-1.33	1.16	0.66-2.02	0.90	0.24-3.33
E-value			**3.12**																			
Vegetables intake	0.99	0.88-1.11	1.28	0.84-1.93	0.99	0.87-1.12	0.98	0.82-1.18	1.29	0.42-3.96	0.98	0.62-1.55	1.00	0.94-1.14	0.97	0.82-1.13	0.98	0.80-1.19	1.02	0.66-1.59	0.98	0.40-2.42
SSB	0.88	0.77-1.01	0.63	0.39-1.01	0.92	0.80-1.07	0.79	0.63-1.00	0.48	0.17-1.38	0.58 **	0.39-0.88	0.91	0.78-1.07	0.83	0.66-1.04	0.86	0.70-1.06	1.02	0.70-1.48	0.42	0.17-1.02
E-value											**2.84**											
Alcoholic drink <6mnths Yes[3]	0.71	0.42-1.19	0.25 **	0.09-0.68	0.57 *	0.32-0.99	0.49	0.26-0.92	0.22	0.00-5.40	0.17 **	0.05-0.63	0.94	0.54-1.64	0.66	0.32-1.34	0.92	0.49-1.73	0.42	0.12-1.49	0.44	0.05-4.02
E-value			**7.46**		**1.98**						**11.24**											
Tobacco <6mnths Yes[4]	0.50	0.20-1.22	0.22 *	0.06-0.80	0.40 *	0.18-0.90	0.38 *	0.16-0.90	0.83	0.04-16.30	0.15 *	0.03-0.70	0.60	0.30-1.19	0.44	0.18-1.04	0.88	0.40-1.93	0.55	0.17-1.79	0.49	0.05-4.36
E-value			**8.56**		**2.54**		**4.7**				**12.81**											
Screen time	0.98	0.94-1.02	0.91	0.82-1.00	0.98	0.94-1.03	0.96	0.92-1.01	0.98	0.90-1.06	0.90 *	0.81-0.99	0.99	0.95-1.03	0.94 *	0.90-0.99	1.01	0.96-1.06	0.99	0.93-1.05	0.95	0.85-1.05

E-value											**1.46**				**1.32**							
Sleep	1.01	0.88-1.17	1.42	0.95-2.13	1.10	0.91-1.34	1.22	0.96-1.54	1.08	0.44-2.63	1.01	0.88-1.17	0.94	0.81-1.08	1.19	0.96-1.47	1.03	0.83-1.28	1.24	0.79-1.95	1.01	0.52-1.96
Physical activity	1.02	0.93-1.12	1.34 *	1.00-1.80	1.03	0.93-1.14	1.02	0.89-1.16	1.17	0.56-2.43	0.95	0.71-1.27	1.00	0.93-1.09	1.10	0.95-1.27	0.91	0.80-1.03	0.94	0.71-1.24	1.09	0.72-1.64
E-value			**2.01**																			
Psychological distress Yes[5]	0.61 *	0.39-0.95	0.28 **	0.11-0.72	0.80	0.47-1.33	0.55	0.29-1.03	0.82	0.03-21.42	0.57	0.18-1.76	0.55 **	0.36-0.84	0.81	0.43-1.51	0.85	0.49-1.48	0.64	0.23-1.76	1.34	0.13-13.06
E-value	**1.88**		**6.6**										**2.03**									
Depression Mild [6]	1.03	0.67-1.57	1.28	0.20-8.04	0.88	0.52-1.49	1.03	0.53-2.01	1.82	0.02-115.55	1.78	0.21-15.00	0.87	0.55-1.39	1.23	0.65-2.33	1.01	0.47-2.17	2.22	0.37-13.17	1.07	0.03-38.71
Depression Moderate [6]	0.74	0.40-1.36	0.71	0.11-4.42	1.39	0.76-2.56	0.43 *	0.19-0.95	0.00	0.00-0.00	0.90	0.12-6.64	0.80	0.43-1.49	0.68	0.25-1.86	1.02	0.36-2.92	1.17	0.21-6.52	0.71	0.03-15.13
E-value							**4.08**															
Depression Moderately severe [6]	1.24	0.52-2.95	0.41	0.08-1.93	1.18	0.48-2.86	1.15	0.32-4.16	0.00	0.00-0.00	0.80	0.10-5.90	1.09	0.48-2.43	0.74	0.24-2.22	1.13	0.38-3.29	1.22	0.27-5.52	0.46	0.00-22.06
Depression Severe [6]	0.82	0.37-1.81	0.21 *	0.04-0.97	0.57	0.27-1.23	0.42	0.17-1.02	0.64	0.02-19.16	0.37	0.05-2.82	0.84	0.41-1.73	0.60	0.24-1.46	2.09	0.72-6.07	2.88	0.49-16.97	0.97	0.07-12.38
E-value			**8.99**																			
Anxiety Mild [7]	0.88	0.47-1.66	0.74	0.16-3.39	0.76	0.34-1.69	0.47	0.18-1.24	0.00	0.00-0.00	0.41	0.03-4.33	0.82	0.45-1.51	0.67	0.27-1.68	0.82	0.27-2.43	0.80	0.17-3.65	0.36	0.01-10.33
Anxiety Moderate [7]	0.73	0.41-1.27	0.33	0.08-1.35	0.70	0.36-1.35	0.85	0.35-2.02	0.65	0.02-19.92	0.59	0.09-3.56	0.78	0.43-1.40	1.11	0.58-2.13	1.22	0.57-2.58	1.58	0.40-6.24	0.52	0.05-4.79
Anxiety Severe [7]	0.50	0.20-1.24	0.12 **	0.03-0.50	0.36 *	0.16-0.84	0.35 *	0.15-0.80	0.23	0.00-10.28	0.15 *	0.02-0.93	0.82	0.45-1.50	0.37 *	0.16-0.87	0.80	0.33-1.95	0.61	0.13-2.88	0.11	0.00-2.40
E-value			**16.15**		**2.72**		**5.16**				**12.81**				**4.85**							

[1] Odds ratios
[2] 99% Confidence intervals
[3] These results are compared to those who have not drank alcohol in the past 6 months
[4] These results are compared to those who have not smoked tobacco in the past 6 months
[5] These results are compared to those who do not have psychological distress

[6] These results are compared to those with no depression
[7] These results are compared to those with no anxiety
* P>0.01
** P>0.001

Appendix 2.5 - SES moderations of multivariable logistic regressions to estimate the associations between health behaviour's/mental health and individual common and emerging diseases/conditions, whilst controlling for sex at birth

Variables	≥1 common/ emerging condition		Irritable Bowel Syndrome		Asthma		Eczema		Type 2 Diabetes		Chronic Fatigue		Hay fever		Food Allergies		ADD/ADHD		Autism/ Aspergers		Type 1 Diabetes	
	OR[1]	**99% CI[2]**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**	**OR**	**99% CI**
UPFs	0.99	0.98-1.00	0.98	0.96-1.00	0.99	0.98-1.00	0.99	0.98-1.00	0.98	0.96-1.00	0.98 *	0.96-0.99	0.99	0.98-1.00	0.99	0.97-1.00	0.99	0.98-1.00	1.00	0.99-1.01	0.98	0.97-1.00
E-value											**1.16**											
Fruit intake	0.99	0.96-1.03	0.99	0.85-1.17	1.00	0.96-1.03	0.98	0.94-1.02	0.57	0.80-1.14	0.97	0.82-1.16	0.97	0.82-1.16	0.97	0.92-1.02	1.01	0.95-1.08	0.95	0.90-1.00	0.99	0.82-1.20
Vegetable intake	0.99	0.96-1.01	0.97	0.85-1.09	0.99	0.96-1.03	0.97	0.94-1.01	0.94	0.84-1.05	0.99	0.89-1.10	1.00	0.97-1.03	0.96 *	0.93-0.99	1.00	0.95-1.04	0.93 **	0.88-0.97	0.98	0.86-1.12
E-value															**1.25**				**1.36**			
SSB	0.99	0.96-1.01	0.95	0.88-1.04	0.98	0.95-1.02	0.97	0.93-1.02	0.98	0.91-1.05	0.98	0.91-1.04	0.99	0.96-1.02	0.98	0.94-1.02	1.00	0.96-1.04	1.02	0.96-1.08	1.02	0.93-1.10
Alcoholic drink <6mnths Yes[3]	0.93	0.82-1.04	0.94	0.66-1.34	0.97	0.81-1.15	0.84	1.20	1.14	0.76-1.71	0.90	0.69-1.18	0.77	0.87-1.18	1.06	0.88-1.26	0.91	0.77-1.07	0.97	0.82-1.15	1.02	0.75-1.38
Tobacco <6mnths Yes[4]	0.97	0.79-1.19	1.05	0.75-1.47	1.00	0.82-1.22	0.97	0.77-1.24	0.99	0.67-1.46	0.83	0.63-1.09	0.93	0.74-1.16	1.03	0.79-1.35	0.89	0.72-1.08	1.13	0.92-1.37	0.96	0.69-1.33
Screen time	1.00	0.99-1.00	1.00	0.98-1.01	1.00	0.99-1.00	1.00	0.99-1.00	1.00	0.99-1.02	0.99	0.98-1.01	1.00	0.99-1.01	0.99	0.99-1.00	0.99	0.98-1.00	1.00	0.99-1.02	1.00	0.99-1.02
Sleep	1.00	0.95-1.05	1.07	0.94-1.22	1.07	0.94-1.22	0.97	0.92-1.04	1.04	0.84-1.28	1.03	0.91-1.15	0.98	0.94-1.01	1.05 *	1.00-1.11	0.98	0.91-1.05	1.00	0.91-1.09	1.06	0.89-1.26
E-value															**1.28**							

Physical activity	0.98	0.96-1.00	1.02	0.95-1.10	0.99	0.96-1.02	1.00	0.96-1.03	0.91	0.83-1.00	0.97	0.90-1.04	0.98	0.96-1.00	0.97	0.94-1.00	0.97	0.93-1.01	0.92 **	0.88-0.97	0.93	0.86-1.01
E-value																			**1.39**			
Psychological distress Yes[5]	1.01	0.89-1.15	0.74	0.53-1.03	1.00	0.87-1.14	1.00	0.85-1.17	0.74	0.52-1.05	0.88	0.66-1.16	0.99	0.88-1.12	0.94	0.83-1.07	0.89	0.75-1.05	1.01	0.79-1.29	0.76	0.48-1.21
Depression Mild[6]	0.99	0.88-1.12	1.16	0.65-2.08	1.04	0.90-1.20	1.02	0.87-1.20	0.58	0.26-1.30	1.06	0.68-1.66	1.03	0.90-1.19	1.03	0.85-1.24	0.96	0.75-1.22	0.84	0.61-1.17	0.96	0.35-2.59
Depression Moderate[6]	1.00	0.85-1.17	0.85	0.55-1.31	0.96	0.77-1.21	1.06	0.85-1.32	0.90	0.48-1.71	1.27	0.74-2.18	1.02	0.87-1.20	1.02	0.86-1.21	0.89	0.68-1.17	0.97	0.66-1.42	1.01	0.65-1.58
Depression Moderately severe[6]	1.12	0.90-1.39	0.92	0.55-1.54	1.03	0.84-1.26	1.01	0.81-1.26	0.78	0.38-1.58	1.57 **	1.14-2.17	1.09	0.89-1.33	0.95	0.79-1.14	0.94	0.71-1.24	0.95	0.74-1.21	0.93	0.58-1.49
E-value											**2.52**											
Depression Severe[6]	0.90	0.74-1.10	0.73	0.49-1.07	0.98	0.84-1.15	1.03	0.80-1.32	0.96	0.61-1.49	1.16	0.79-1.70	1.07	0.90-1.27	0.92	0.77-1.11	0.88	0.68-1.13	0.95	0.68-1.32	1.14	0.72-1.82
Anxiety Mild[7]	1.16	0.96-1.39	0.87	0.51-1.50	1.10	0.89-1.36	1.11	0.91-1.36	0.54 *	0.28-1.03	1.09	0.58-2.03	1.12	0.95-1.32	0.98	0.78-1.22	0.96	0.72-1.29	0.95	0.67-1.35	0.75	0.43-1.31
E-value									**3.11**													
Anxiety Moderate[7]	0.97	0.83-1.15	0.89	0.55-1.42	1.10	0.90-1.34	0.99	0.78-1.26	0.87	0.49-1.53	1.30	0.94-1.78	1.05	0.91-1.23	0.99	0.84-1.17	0.97	0.79-1.19	0.86	0.68-1.09	1.28	0.82-1.99
Anxiety Severe[7]	0.97	0.73-1.30	0.88	0.57-1.37	0.90	0.73-1.09	0.96	0.76-1.21	0.96	0.59-1.58	1.20	0.82-1.74	0.99	0.81-1.20	0.88	0.72-1.08	0.91	0.77-1.08	1.07	0.81-1.41	1.17	0.69-1.98

[1] Odds ratios
[2] 99% Confidence intervals
[3] These results are compared to those who have not drank alcohol in the past 6 months
[4] These results are compared to those who have not smoked tobacco in the past 6 months
[5] These results are compared to those who do not have psychological distress
[6] These results are compared to those with no depression
[7] These results are compared to those with no anxiety
* P>0.01
** P>0.001

Appendix 2.6 – Multivariable logistic regressions to estimate the associations between health behaviour's/mental health and IBS and asthma severity, whilst controlling for sex at birth and SES.

Variables	IBS severity (IBS-SSS)		Frequency of asthma attacks (past 12 months)		Persistence of asthma symptoms (past 12 months)		Been hospitalized for asthma (past 12 months)	
	OR[1]	**99%CI**[2]	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**
Sex Female[3]	1.43	0.45-4.52	1.05	0.59-1.89	2.04**	1.23-3.38	0.72	0.33-1.57
E-value					**2.21**			
SES	0.99	0.76-1.31	1.07	0.89-1.28	1.02	0.90-1.16	1.15	0.92-1.44
UPFs	1.08	0.99-1.17	1.11**	1.05-1.17	1.03	1.22-3.52	1.13**	1.07-1.20
E-value			**1.29**				**1.51**	
Fruit intake	1.15	0.91-1.44	0.95	0.76-1.19	1.02	0.89-1.18	1.14	0.86-1.50
Vegetable intake	1.01	0.84-1.24	0.91	0.75-1.10	0.95	0.82-1.10	1.09	0.88-1.35
SSB	1.16	0.92-1.47	1.44**	1.21-1.72	1.09	0.94-1.25	1.57**	1.29-1.91
E-value			**1.69**				**2.52**	
Alcoholic drink <6mnths Yes[4]	6.44**	1.68-24.56	3.34	1.57-7.10	1.88	0.99-3.55	4.49**	1.88-10.67
E-value	**4.51**						**8.45**	
Tobacco <6mnths Yes[5]	12.03**	2.29-63.11	5.53**	2.25-13.59	2.05	0.92-4.53	6.48**	2.43-17.29
E-value	**6.39**		**4.13**				**12.44**	
Screen time	1.05	0.99-1.11	1.09**	1.04-1.15	1.04	1.00-1.08	1.09**	1.04-1.14
E-value			**1.26**				**1.40**	
Sleep	0.79	0.45-1.39	0.76*	0.59-0.98	0.86	0.68-1.08	0.73	0.52-1.04
E-value			**1.56**					
Physical activity	0.90	0.67-1.20	0.90	0.76-1.07	1.00	0.89-1.12	0.93	0.75-1.14
Psychological distress Yes[6]	2.81	0.99-7.98	2.23*	1.16-4.28	1.56	0.93-2.62	2.50**	1.22-5.12
E-value			**2.35**				**4.44**	
Depression Mild[7]	0.93	0.20-4.32	0.92	0.40-2.08	0.91	0.51-1.62	2.25	0.77-6.54
Depression Moderate[7]	2.63	0.39-17.45	1.40	0.36-5.35	1.80	0.86-3.76	2.78	0.78-9.88

Depression Moderately severe[7]	1.73	0.38-7.89	3.62*	1.28-10.21	1.68	0.71-3.95	4.25*	1.08-16.62
	3.21				**7.97**			
Depression Severe[7]	2.23	0.50-9.94	3.21*	1.00-10.30	2.98**	1.39-6.36	13.78**	4.79-39.67
E-value	**2.98**				**2.85**		**27.05**	
Anxiety Mild[8]	1.06	0.13-8.33	1.47	0.56-3.83	1.45	0.69-3.02	1.36	0.40-4.60
Anxiety Moderate[8]	3.84	0.83-17.10	1.94	0.81-4.65	1.31	0.63-2.74	3.44*	1.17-10.08
E-value	**2.13**						**6.34**	
Anxiety Severe[8]	3.05	0.76-12.27	4.07**	1.66-9.95	2.85**	1.37-5.92	8.61**	3.11-23.77
E-value	**3.45**				**2.77**		**16.7**	

[1] Odds ratio
[2] 99% Confidence intervals
[3]These results are compared to males
[4] These results are compared to those who have not drank alcohol in the past 6 months
[5] These results are compared to those who have not smoked tobacco in the past 6 months
[6] These results are compared to those who do not have psychological distress
[7] These results are compared to those with no depression
[8] These results are compared to those with no anxiety
* P>0.01
** P>0.001

Appendix 2.7 – Sex at birth moderations of multivariable logistic regressions to estimate the associations between health behaviour's/mental health and IBS and asthma severity, whilst controlling for SES.

Variables	IBS severity (IBS-SSS)		Frequency of asthma attacks (past 12 months)		Persistence of asthma symptoms (past 12 months)		Been hospitalized for asthma (past 12 months)	
	OR[1]	**99%CI**[2]	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**
UPFs	1.01	0.87-1.16	0.91	0.80-1.03	1.01	0.91-1.13	0.99	0.87-1.12
Fruit intake	1.12	0.60-2.09	1.12	0.70-1.80	1.25	0.91-1.72	1.44	0.90-2.30
Vegetable intake	1.19	0.75-1.87	1.18	0.77-1.80	1.06	0.81-1.39	1.25	0.86-1.82
SSB	0.51*	0.27-0.93	1.10	0.72-1.69	1.04	0.71-1.54	0.95	0.64-1.43
E-value	**2.15**							
Alcoholic drink <6mnths Yes[3]	1.06	0.05-20.68	0.43	0.10-1.84	2.03	0.45-9.14	0.28	0.05-1.50
Tobacco <6mnths Yes[4]	0.51	0.01-20.98	0.47	0.07-3.20	2.05	0.24-17.30	0.43	0.07-2.45
Screen time	0.94	0.77-1.14	0.95	0.85-1.05	1.03	0.94-1.13	1.00	0.91-1.11
Sleep	0.74	0.29-1.90	1.11	0.59-2.07	0.96	0.65-1.43	1.04	0.55-1.97
Physical activity	0.88	0.47-1.65	0.96	0.71-1.32	1.00	0.80-1.25	1.11	0.74-1.67
Psychological distress Yes[5]	0.41	0.05-3.38	0.57	0.17-1.90	1.19	0.43-3.33	0.72	0.18-2.80
Depression Mild[6]	0.52	0.02-9.60	0.11*	0.02-0.61	0.36	0.10-1.22	2.30	0.28-18.54
E-values			**5.48**					
Depression Moderate[6]	16.41	0.25-1.036.41	0.17	0.02-1.25	0.98	0.16-5.74	1.02	0.06-15.84
Depression Moderately severe[6]	0.53	0.01-25.08	0.34	0.03-3.74	0.32	0.03-3.30	0.81	0.04-13.77
Depression Severe[6]	0.68	0.02-18.59	0.09*	0.00-0.92	1.13	0.16-7.79	0.16	0.01-1.64
E-values			**6.12**					
Anxiety Mild[7]	0.34	0.00-38.52	0.66	0.11-3.89	1.79	0.41-7.77	0.34	0.02-4.38
Anxiety Moderate[7]	3.34	0.14-76.76	0.35	0.06-2.02	3.15	0.64-15.49	0.92	0.11-7.64
Anxiety Severe[7]	1.66	0.07-34.66	0.21	0.03-1.24	1.20	0.24-5.95	0.03**	0.00-0.25
E-values			**3.79**				**66.16**	

[1] Odds ratios
[2] 99% Confidence intervals
[3] These results are compared to those who have not drank alcohol in the past 6 months
[4] These results are compared to those who have not smoked tobacco in the past 6 months
[5] These results are compared to those who do not have psychological distress
[6] These results are compared to those with no depression
[7] These results are compared to those with no anxiety

* P>0.01
** P>0.001

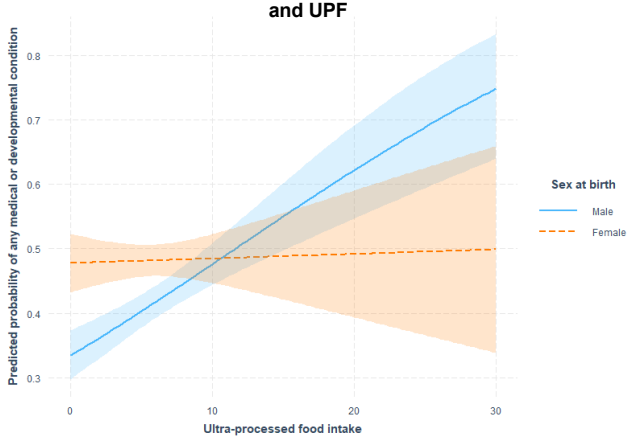
Appendix 2.8 – SES moderations of multivariable logistic regressions to estimate the associations between health behaviour's/mental health and IBS and asthma severity, whilst controlling for sex at birth

Variables	IBS severity (IBS-SSS)		Frequency of asthma attacks (past 12 months)		Persistence of asthma symptoms (past 12 months)		Been hospitalized for asthma (past 12 months)	
	OR[1]	**99%CI[2]**	**OR**	**99%CI**	**OR**	**99%CI**	**OR**	**99%CI**
UPFs	0.99	0.97-1.02	1.01	0.97-1.04	1.01	0.98-1.03	0.99	0.95-1.03
Fruit intake	0.96	0.86-1.07	0.95	0.85-1.06	1.01	0.92-1.10	0.99	0.88-1.12
Vegetable intake	0.94	0.84-1.06	0.96	0.87-1.05	1.00	0.94-1.07	1.03	0.92-1.16
SSB	0.99	0.89-1.09	1.00	0.90-1.10	1.00	0.91-1.09	0.99	0.90-1.09
Alcoholic drink <6mnths Yes[3]	1.23	0.70-2.16	0.92	0.60-1.40	0.94	0.62-1.42	0.78	0.46-1.25
Tobacco <6mnths Yes[4]	1.13	0.60-2.13	1.07	0.65-1.75	0.95	0.58-1.56	0.80	0.50-1.27
Screen time	1.01	0.98-1.04	1.00	0.98-1.03	0.98	0.96-1.01	0.98	0.95-1.01
Sleep	1.22	0.79-1.89	1.03	0.89-1.18	0.99	0.91-1.09	1.07	0.88-1.31
Physical activity	0.96	0.88-1.06	0.97	0.90-1.04	1.01	0.96-1.07	0.92	0.83-1.02
Psychological distress Yes[5]	0.82	0.48-1.41	0.89	0.63-1.27	1.07	0.78-1.47	1.06	0.69-1.63
Depression Mild[6]	1.19	0.48-2.94	1.47	0.87-2.48	1.04	0.74-1.45	1.73	0.77-3.86
Depression Moderate[6]	0.77	0.27-2.20	1.14	0.74-1.74	1.15	0.76-1.74	1.16	0.53-2.53
Depression Moderately severe[6]	1.03	0.36-2.87	0.79	0.48-1.31	0.80	0.45-1.40	1.15	0.59-2.22
Depression Severe[6]	0.77	0.36-1.65	0.81	0.42-1.56	0.86	0.43-1.71	0.84	0.45-1.55
Anxiety Mild[7]	0.84	0.25-2.74	0.84	0.55-1.28	1.06	0.74-1.52	1.10	0.44-2.73
Anxiety Moderate[7]	1.22	0.50-2.95	1.09	0.73-1.61	1.00	0.66-1.51	0.73	0.37-1.41
Anxiety Severe[7]	0.83	0.44-1.58	0.88	0.51-1.49	0.74	0.35-1.53	0.71	0.42-1.19

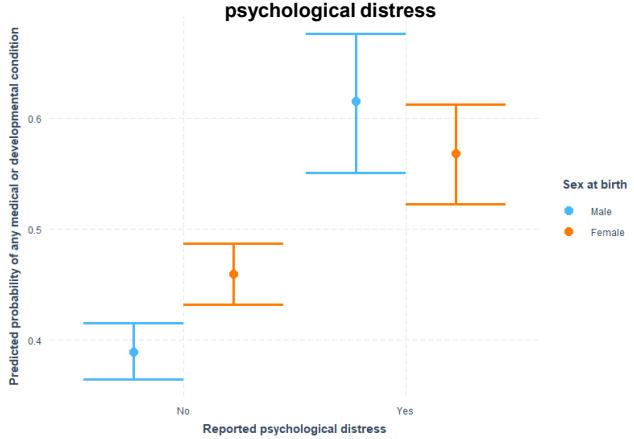
[1] Odds ratios
[2] 99% Confidence intervals
[3] These results are compared to those who have not drank alcohol in the past 6 months
[4] These results are compared to those who have not smoked tobacco in the past 6 months
[5] These results are compared to those who do not have psychological distress
[6] These results are compared to those with no depression
[7] These results are compared to those with no anxiety
* P>0.01
** P>0.001

Appendix 2.9 – Sex and SES moderation analysis

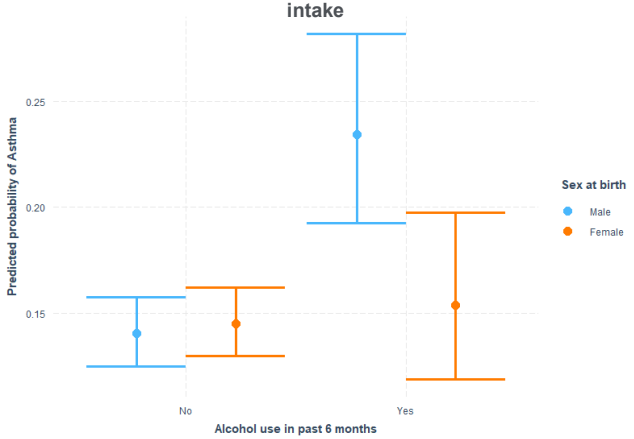
Sex moderation of the relationship between ≥1 disease/condition and UPF



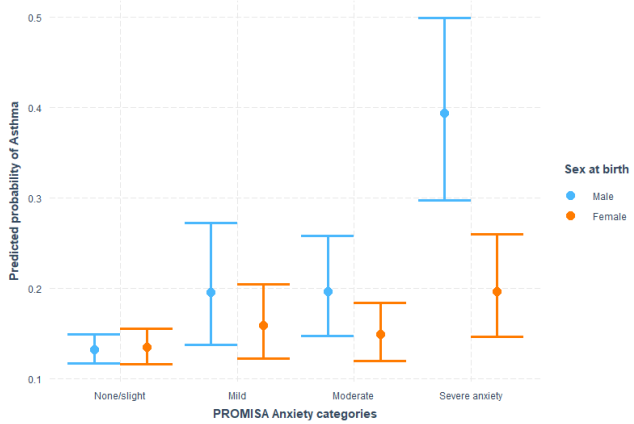
Sex moderation of the relationship between ≥1 disease/condition and psychological distress



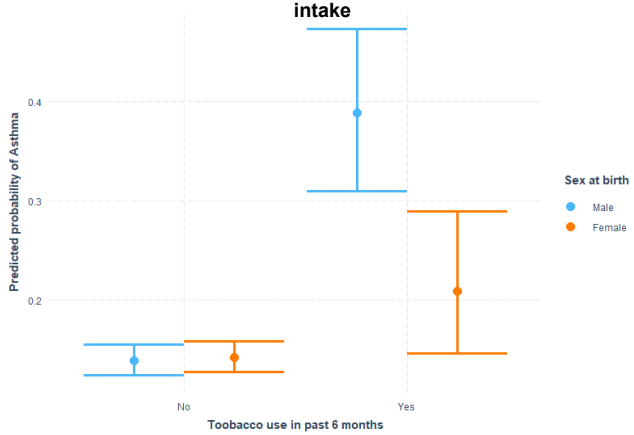
Sex moderation of the relationship between asthma and alcohol intake



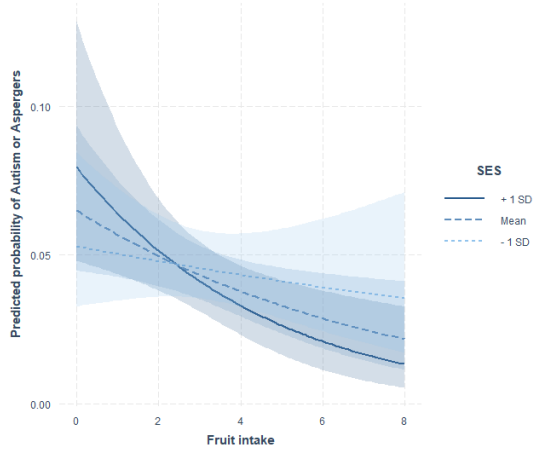
Sex moderation of the relationship between asthma and anxiety



Sex moderation of the relationship between asthma and tobacco intake

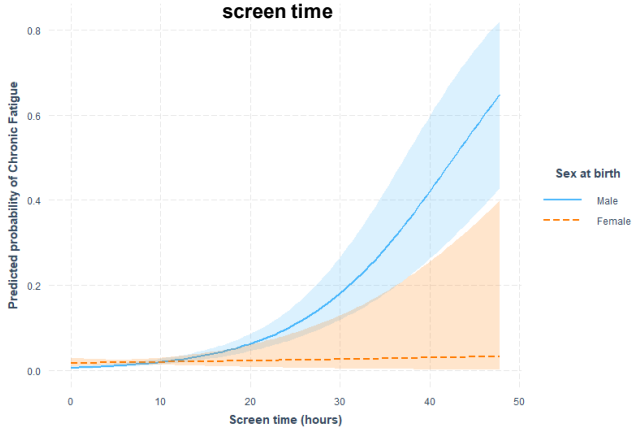


Sex moderation of the relationship between autism and fruit intake

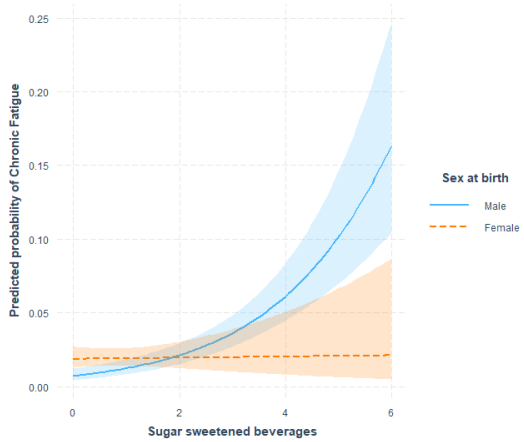


Appendix 2.9 cont.

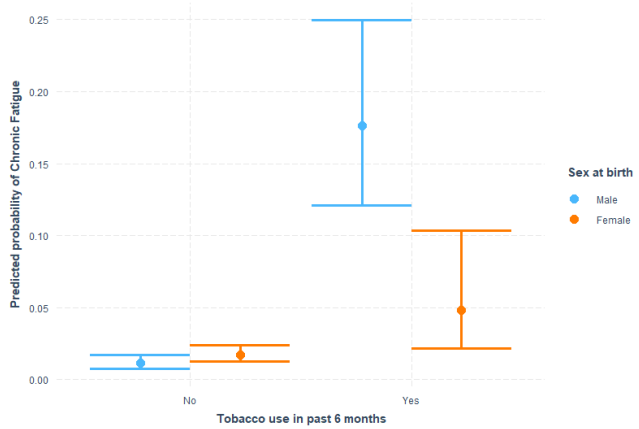
Sex moderation of the relationship between chronic fatigue and screen time



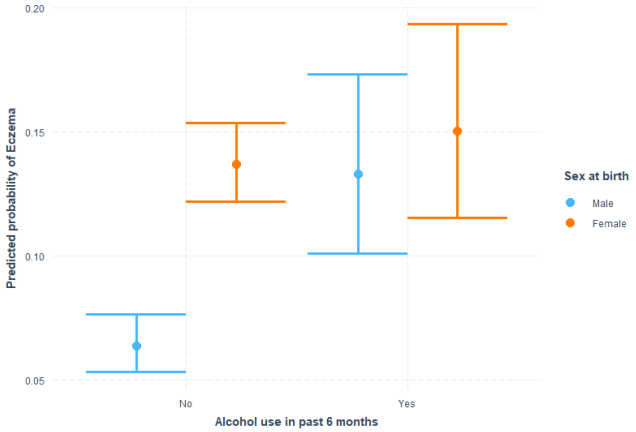
Sex moderation of the relationship between chronic fatigue and SSB



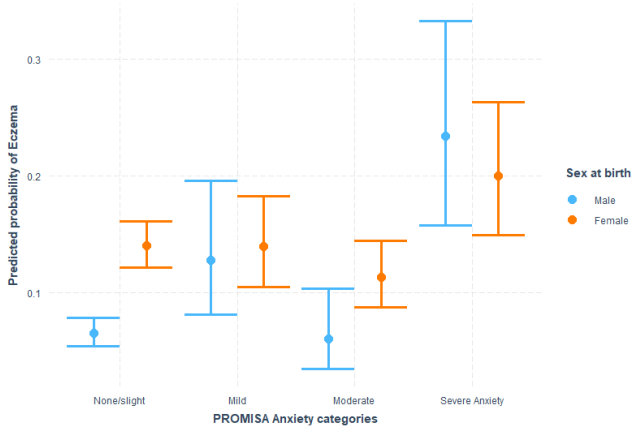
Sex moderation of the relationship between chronic fatigue and tobacco intake



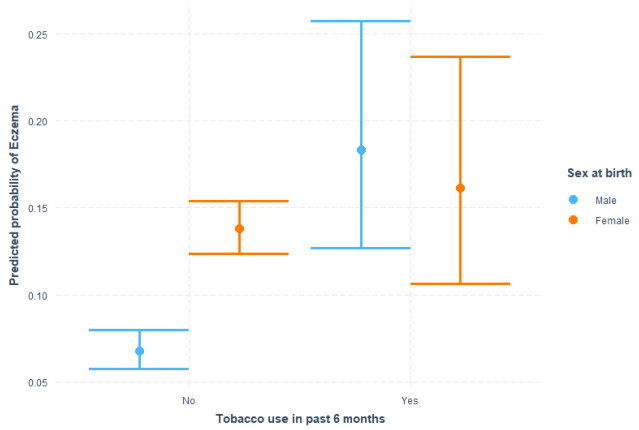
Sex moderation of the relationship between eczema and alcohol intake



Sex moderation of the relationship between eczema and anxiety

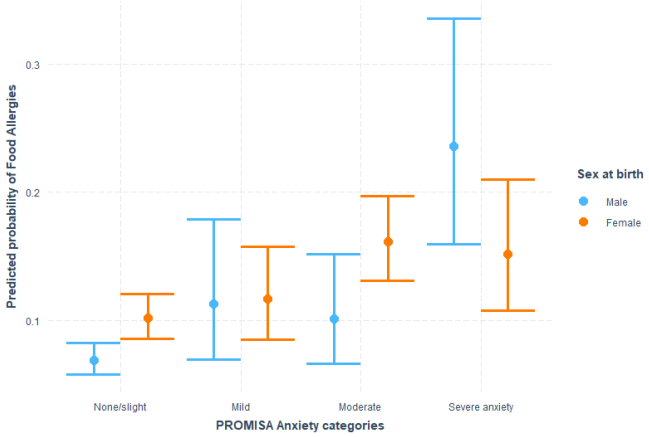


Sex moderation of the relationship between eczema and tobacco intake

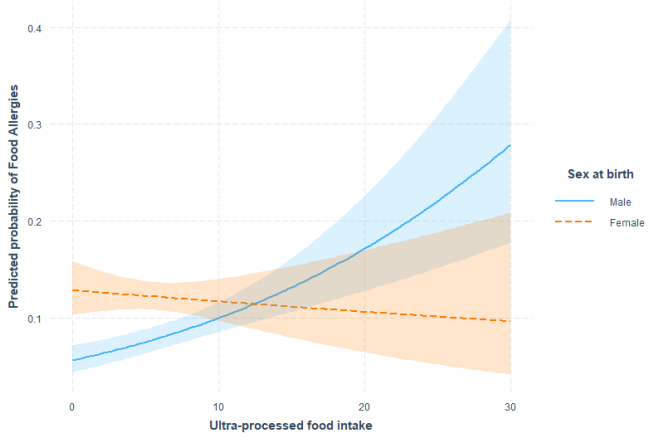


Appendix 2.9 cont.

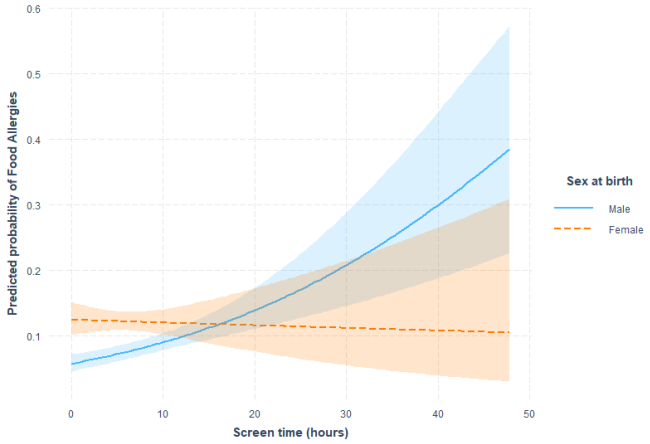
Sex moderation of the relationship between food allergies and anxiety



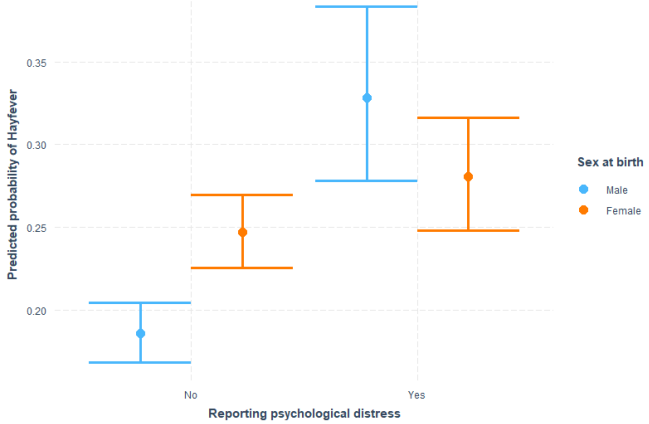
Sex moderation of the relationship between food allergies and UPF



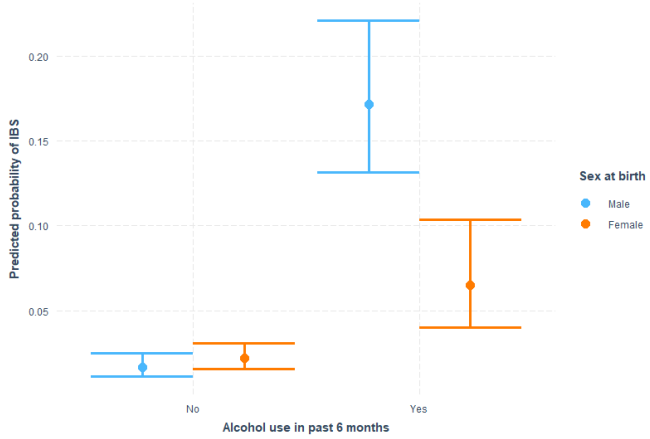
Sex moderation of the relationship between food allergies and screen time



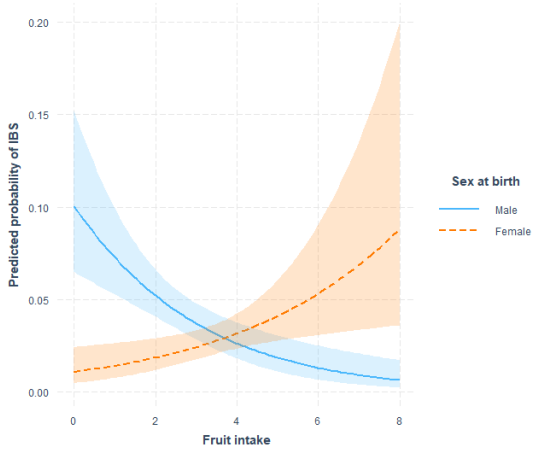
Sex moderation of the relationship between hay fever and psychological distress



Sex moderation of the relationship between IBS and alcohol intake

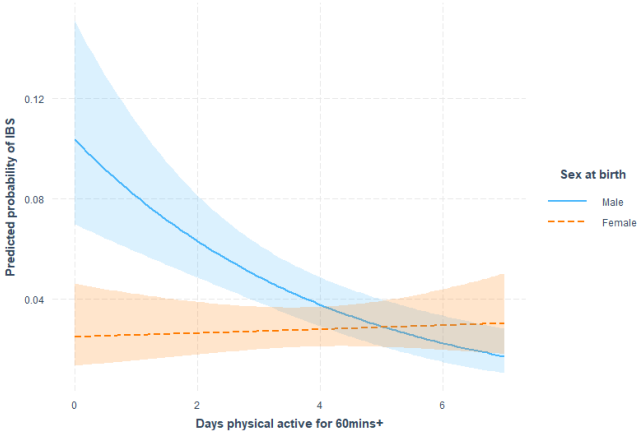


Sex moderation of the relationship between IBS and fruit intake

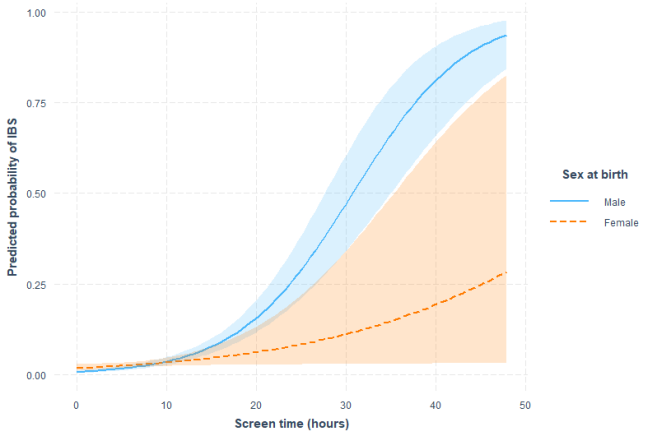


Appendix 2.9 cont.

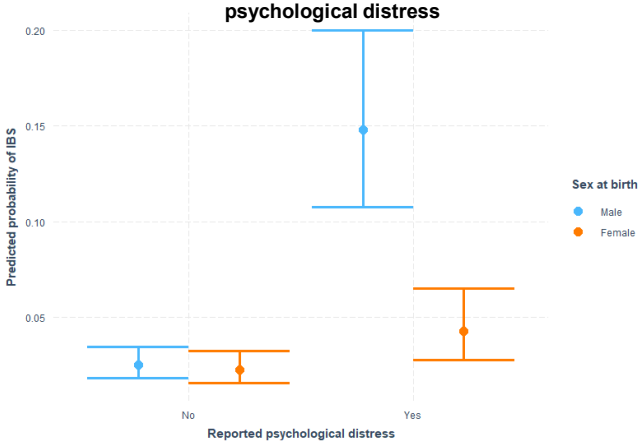
Sex moderation of the relationship between IBS and PA



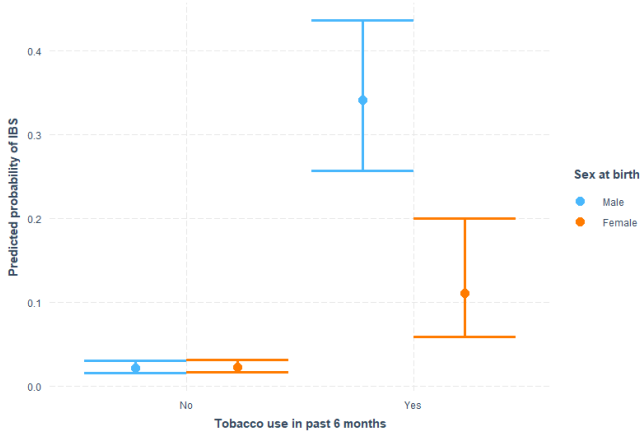
Sex moderation of the relationship between IBS and screen time



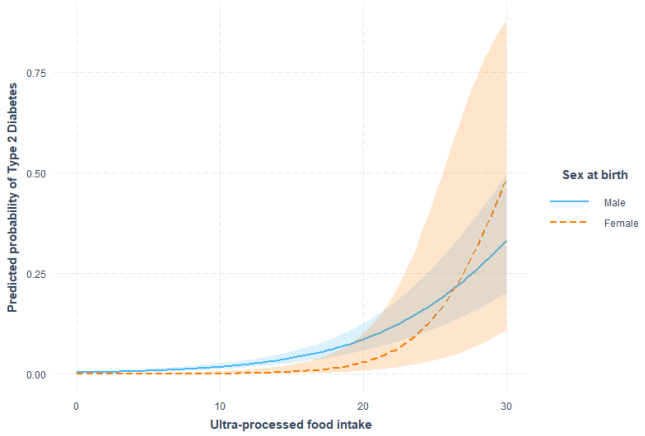
Sex moderation of the relationship between IBS and psychological distress



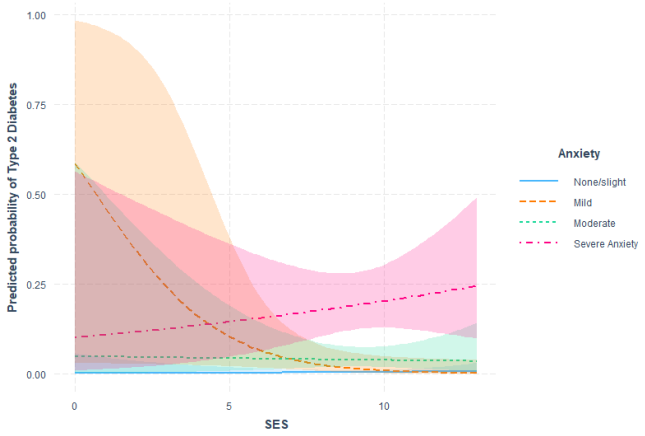
Sex moderation of the relationship between IBS and tobacco intake



Sex moderation of the relationship between TD2 and UPF

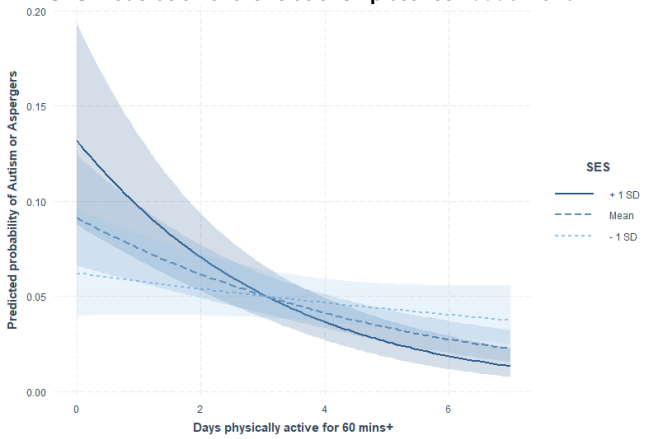


SES moderation of the relationship between T2D and anxiety

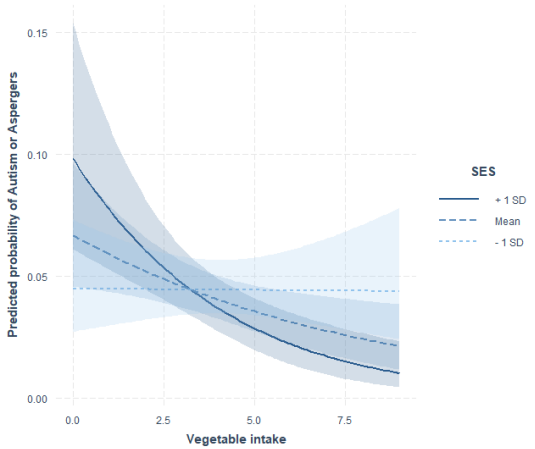


Appendix 2.9 cont.

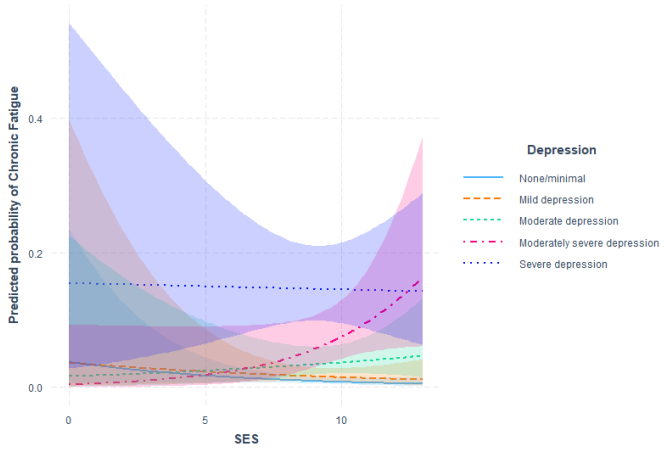
SES moderation of the relationship between autism and PA



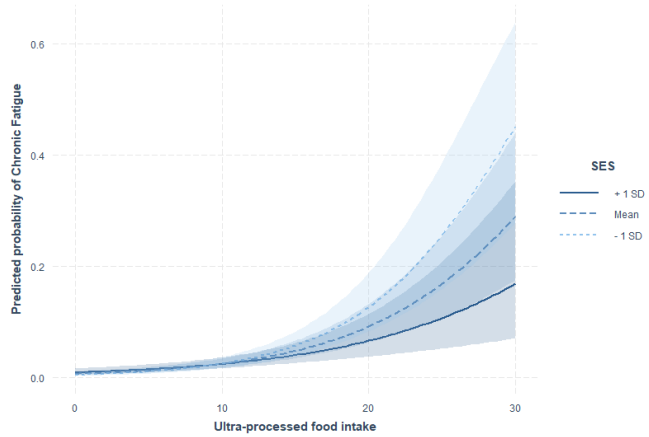
SES moderation of the relationship between autism and vegetable intake



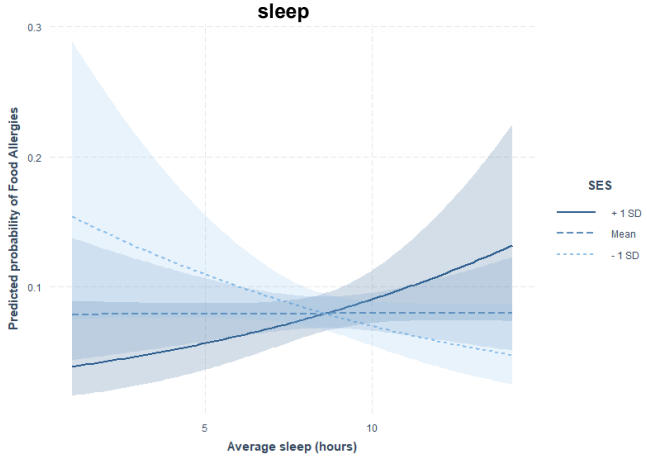
SES moderation of the relationship between chronic fatigue and depression



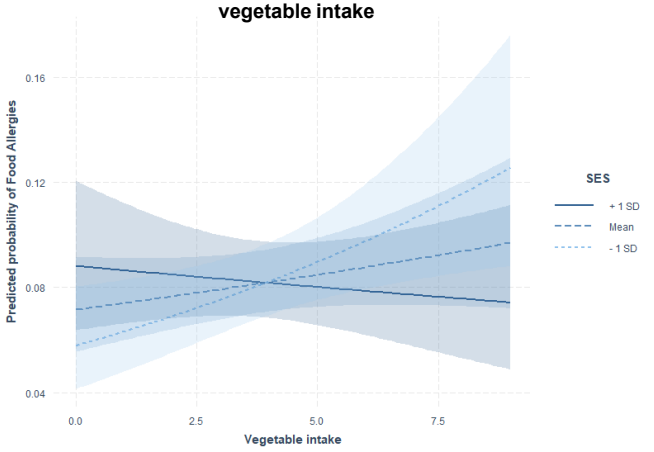
SES moderation of the relationship between chronic fatigue and UPF



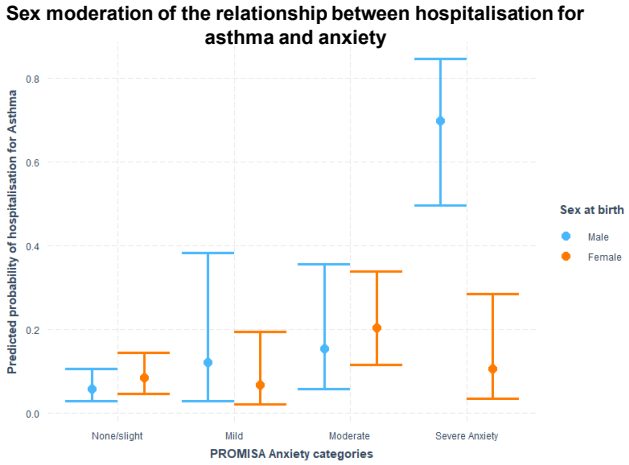
SES moderation of the relationship between food allergies and sleep

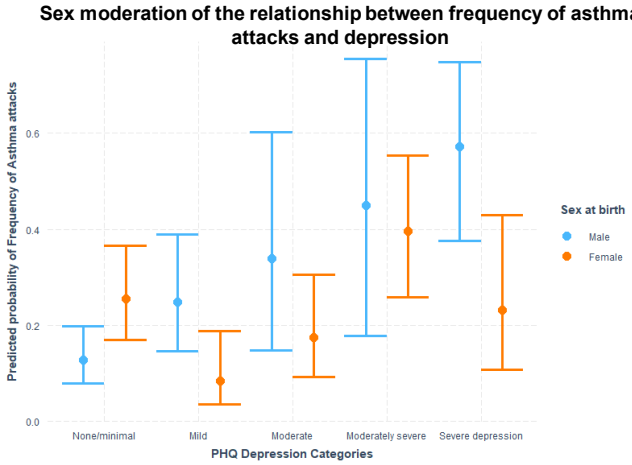


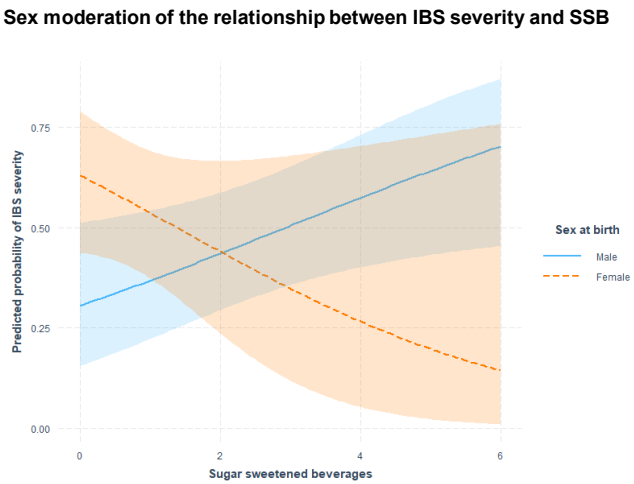
SES moderation of the relationship between food allergies and vegetable intake



Appendix 2.9 cont.







Appendix 3: Supplementary Materials for Chapter 5

Appendix 3.1 – Standard Operating Procedures (SOPs)

Health4Life Biomarker Checkpoint: standard operating procedures

Nutrition, mental health and other health behaviours on inflammation; an exploratory study in adolescents

24/11/2021

Background

Research question

What is the relationship between nutrition, mental health, other lifestyle behaviours and socio-demographics and C-reactive protein?

We are aiming to recruit 15–16-year-olds in New South Wales, that have previously participated in the Health4Life trial. Principal consent will be retrieved from all recruited schools.

Inclusion Criteria

- Students who are current participant in the Health4Life trial
- Students who have completed their 2022 Health4Life follow up survey
- Has parental consent

Previously retrieved survey data will also be linked to this trial, to give additional measures including socio-demographic data, exercise, sleep, screen time, alcohol and tobacco use behaviours and mental health and trauma data.

Summary of Outcome Measure

Measure	Format	Information retrieved
High sensitivity C-reactive protein	Dried blood spot	Inflammatory markers
Height/Weight	Anthropometric measurements	Body mass index
Body composition	Body composition analyser	Body composition, including body fat percentage
AES - Food frequency questionnaire	RedCAP Survey	Dietary intake and behaviour over the last 6 months
Medical conditions	RedCAP survey	Self-reported Medical condition diagnoses, and symptom severity

Table 1 – Summary of outcome measures

Booking assessment sessions and research staff

Participant assessment sessions will be scheduled in advance with teachers and managed via Outlook calendar invitations. Reminder emails and/or letters will be sent to teachers prior to the assessments to allow for them to remind participants.

All research staff will require proof of a current valid Working With Children Check. Research staff bookings for assessment sessions will be managed via Outlook calendar invitations.

Survey

Participants will first fill in hard-copy a contact details form and the special code attached. When participants first begin their online survey on a device, they will be asked to fill in the special code for the second time to enable for later linkage with contact details.

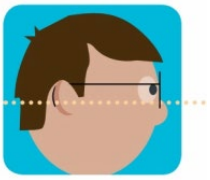
Participants will use their supplied contact IDs and complete The Australian Eating survey and medical conditions survey, hosted by RedCAP and take approximately 20-30 minutes to complete.

Anthropometry

Weight, height and waist circumference will be measured using standard protocols as follows [1]:

Standing Height

- Standing height will be measured using a stadiometer located in the assessment room.
- The same stadiometer should be used for all measures.
- Participants should stand barefoot (socks are okay), wearing light clothing so the positioning of the body can be seen.
- Anything that may interfere with the measurement should be noted on the case report form (e.g. hairstyles and accessories, or physical problems). You may also ask the participant to assist with this e.g. removing high ponytails or hair clips.
- The participant should stand straight with their back to the vertical backboard of the stadiometer and shoulders relaxed. Weight should be evenly distributed on both feet, with feet shoulder width apart and head positioned to look straight ahead. Check that the lower margins of the eyes are in the same horizontal plane as the ear canal. Arms should be hanging freely by the sides.



- The head, back, buttocks and heels should be positioned vertically.
- To obtain a consistent measure, ask the participant to inhale deeply and stretch to their fullest height. Adjust the participant's head if required. Bring down the moveable headboard onto the top of the head with sufficient pressure to compress the hair.
- Take the measure to the **nearest 0.1cm** – do not round up and read from the same height as the top of the head
- **Measure 2 times**. If measures differ by **≥0.5cm**, take a 3rd measurement.

Weight

[1] Davies PSW, Roodveldt R, Marks G. Standard methods for the collection and collation of anthropometric data in children. National Food and Nutrition Monitoring and Surveillance Project. Department of Health and Aged Care. Commonwealth of Australia 2001. ISBN 0 642 82058 9.

- Weight should be measured **once** to the **nearest 0.1kg**. Weight will be recorded during BIA measurements using the **Tanita UM-051 body composition analyser** (see details below).
- Heavy jewellery should be removed, and pockets emptied before weighing. Light indoor clothing should be worn excluding shoes, socks/tights, belts and sweaters.
- During weighing, any variations from light clothing (e.g. heavy clothes) should be noted on the data collection form.

Note: *Equipment should be checked before each measurement session to ensure consistency. Within and if relevant, between observer variability should be reported. The same equipment should be used between observers. The same piece of equipment should be used for all measurements of one participant.*

Body Composition Measurements

Bioelectrical impedance analysis (BIA)

BIA will measure body fat using a Tanita UM-051 body composition analyser. Body composition data will be recorded during the assessment.

Taking a Measurement using the Tanita MC-780MA

Setting Up

1. Turn the power on, check the **PT mark** is displayed. Press 'enter'.
2. The participant will be prompted to step onto the BIA scale. Weight will be measured to the nearest 0.1 kg. Ask the participant to remain on the scale for body composition measures.

For body composition measures:

3. Ensure a 'standard' body type is selected
4. Select gender
5. Enter age
6. Enter height
7. Have the participant stand on the scale ensuring correct positioning (see below)

The scale will measure impedance (body composition) after all personal information has been entered.

Positioning for body composition analysis

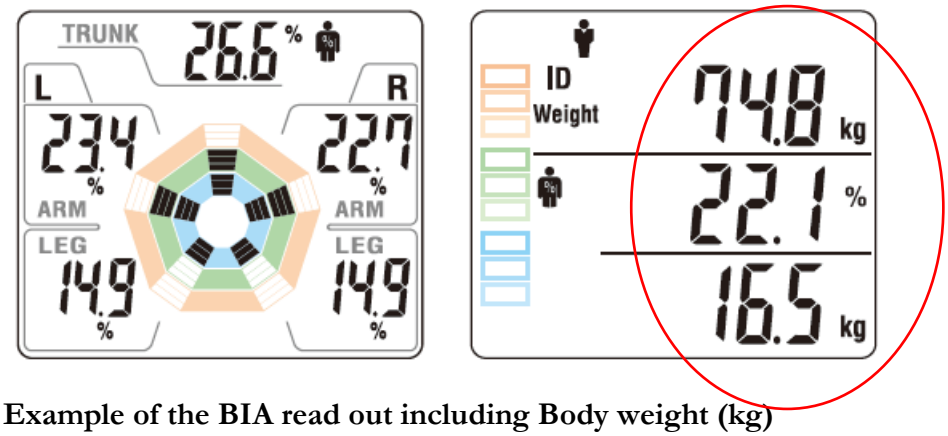
- Participants must be barefoot with soles of the feet in contact with the metal electrodes of the scale.
- The participant should be standing straight with weight equally distributed. Before starting the BIA ask the participant to take hold of the two handgrips and hold them straight down
- Ensure arms are not touching sides and inner thighs are not touching each other during measurement.

For Accurate measurements

- Avoid measuring after strenuous exercise
- Avoid measuring after excessive food or fluid intake or when dehydrated
- Do not take measurements while using transmitting devices such as mobile phones, which may affect readings
- Make sure the soles of the feet are free of excess dirt as this may block the mild electric current
- Check that the date and time is correct
- Check the scales are on a stable and level surface
- Stand clear of the participant during measurement to ensure accuracy

Measurement Results

The measurement results are displayed on the LCD screen after measurement is completed. The results are output to the laptop immediately after the measurement is completed.



Example of the BIA read out including Body weight (kg)

Please enter the participant's weight, % body fat and body fat (kg) on the case report form.

Dried blood spot

Labelling

Once contact ID and participant is cross checked

- Contact ID label the plain envelope
- Contact ID label the data form
- Write contact ID on each blood collection card, DOB and todays date
    - Ask participant to check DOB during collection

Collection

Dried blood spot collection

- Hands should be washed at the beginning of the assessment session for a minimum of 30 seconds

- Explain the process to the participant again and confirm they are happy to proceed
- Gloves should be worn, using a new pair of gloves for each participant
- Participant should be asked to shake hands and rub them together to help stimulate blood flow
- Alcohol prep pad, gauze and band aid should be opened up
- Choose either ring finger of middle finger of participant
- Alcohol wipe the tip of the finger, slightly off centre
- Use lancet and put at site of collection and push down until the lancet activates
- Use gauze to wipe away the first drop of blood
- Turn hand into vertical position
- Massage down the finger with the dried bloody spot sheet below
- When the blood is forming on the end and a blood drop is big enough for it to fall off the finger, touch the blood to the card (not finger).
- Keep massaging the finger and complete all the circles on the sheet
- *If there is not enough blood to fill a circle this could be invalid, so make sure the rest of the circles are full (blood spot should be enough to go through the sample card to the other side)*
    - If there is insufficient blood flow, try the second lancet on another finger – shaking and massaging again
- Once complete, use alcohol wipe on the finger and put the band aid on the finger
- Put sample collection card into the small envelope with contact ID on it, together with test request form
- Dispose of all research materials in regular household waste

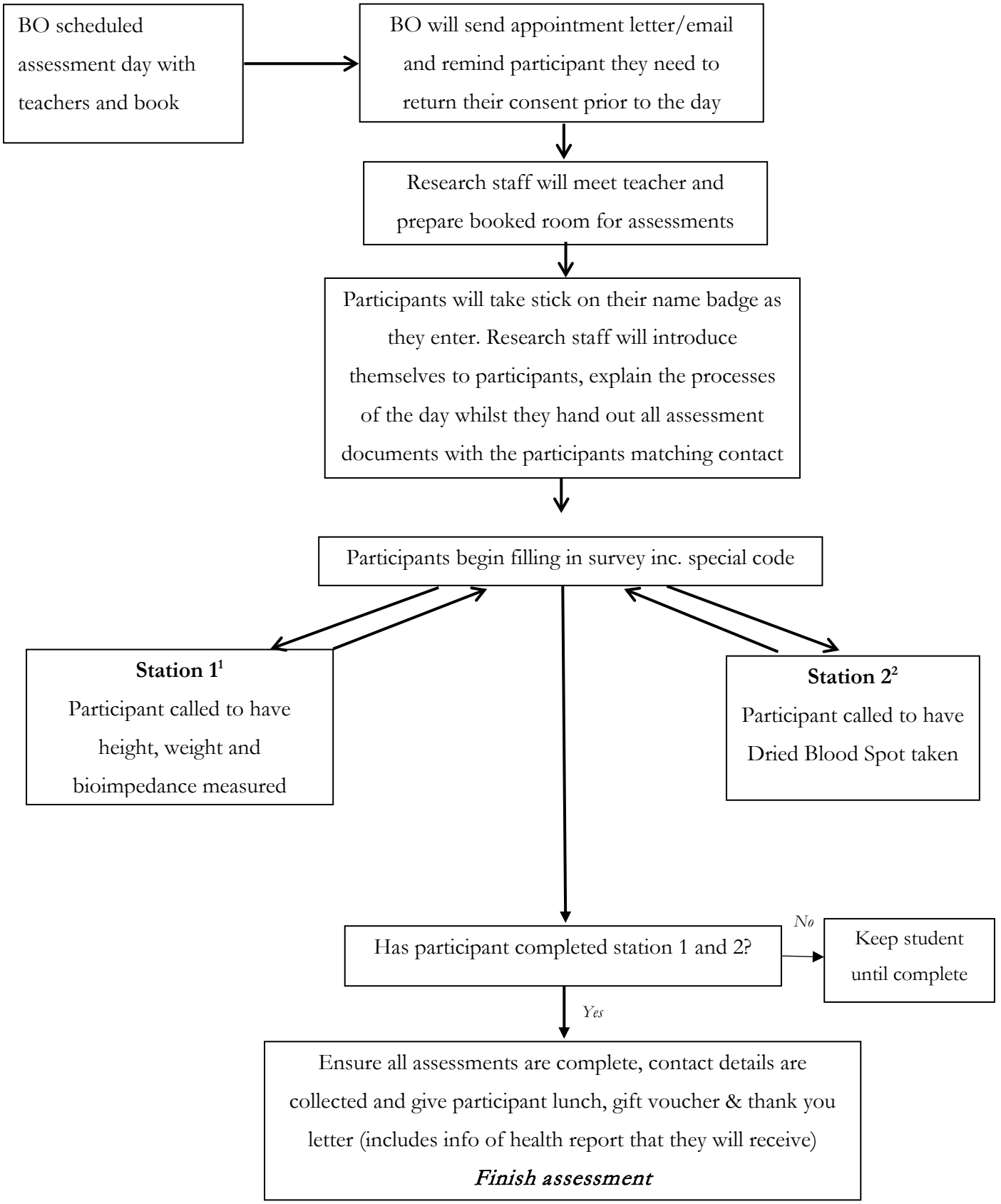
Processing

- Ensure all samples have a contact ID on them and are in an envelope
- Package all samples into one delivery package, prepared with NutriPATH address
- Post within 24 hours of sample collection

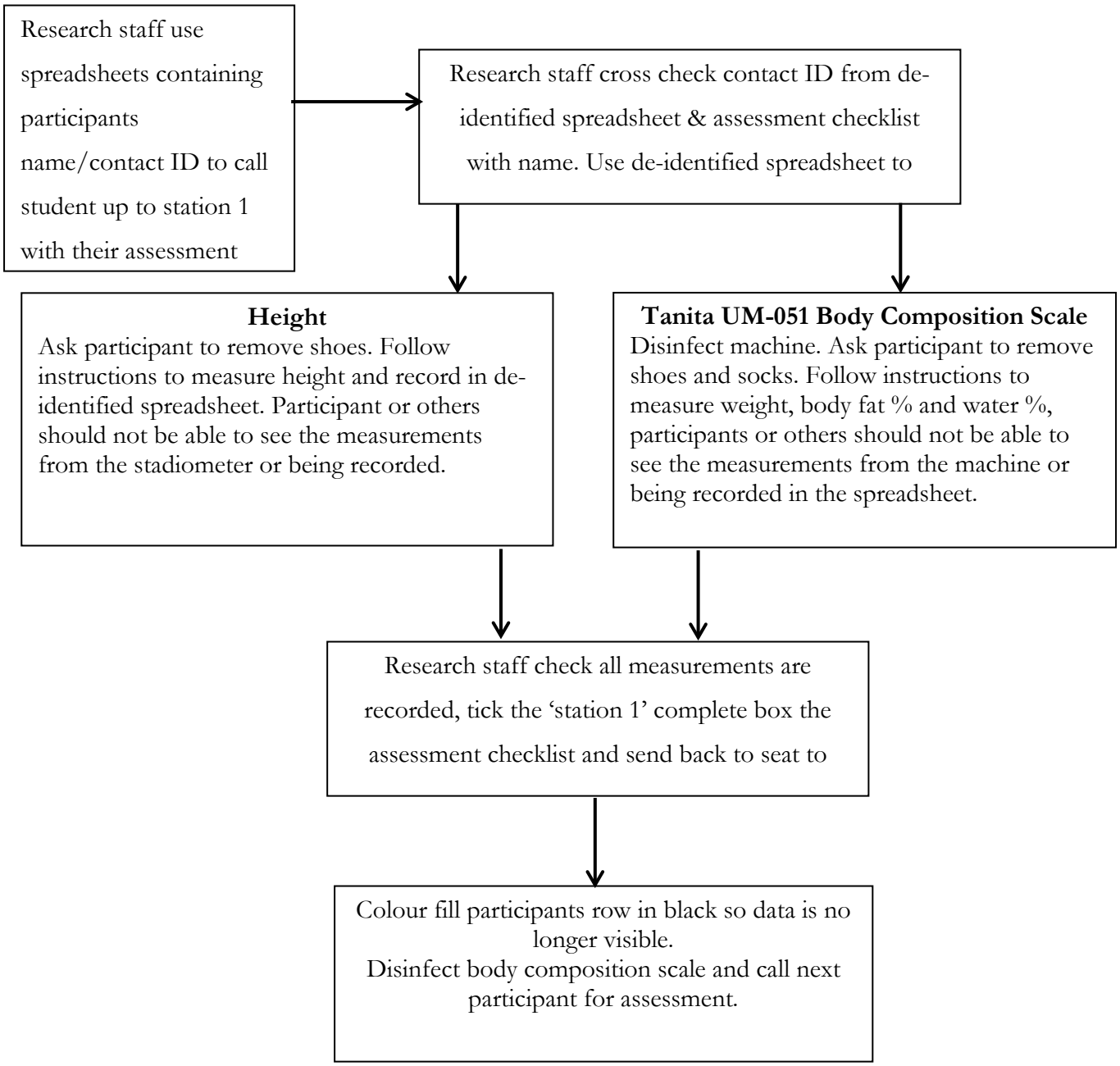
Difficult blood collection

- If there is insufficient blood flow, try the second lancet on another finger – shaking and massaging again

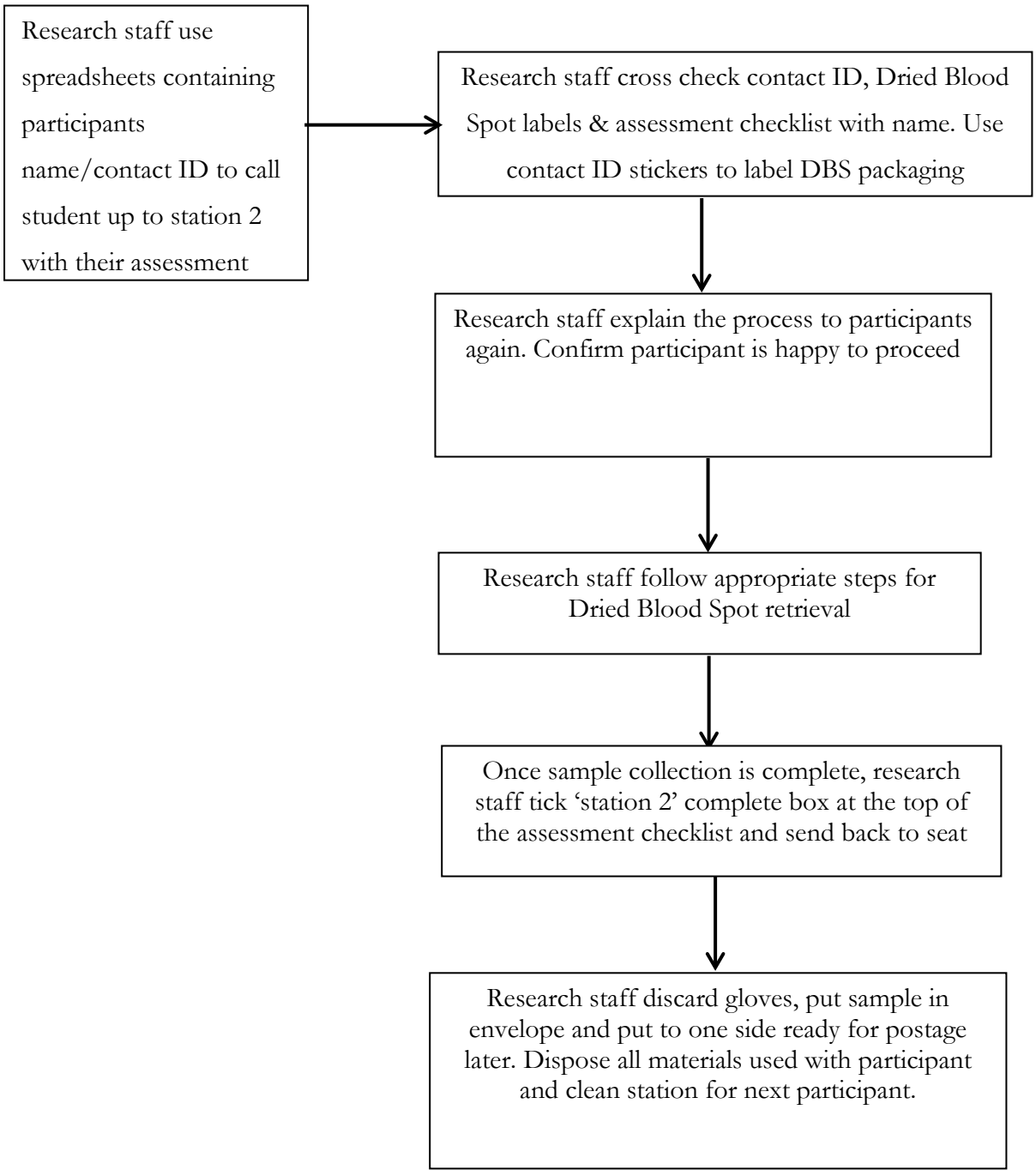
Summary of assessment day



Summary of station 1



Summary of station 2



Equipment required

Stationary

Labels

NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID
NAME CONTACT ID	NAME CONTACT ID	NAME CONTACT ID

Label sheet 1.

CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID
CONTACT ID	CONTACT ID	CONTACT ID

Label sheet 2.

Labelling required:

1 x Label sheet 1

3 x Label sheet 2

Usage:

Label sheet 1: Participant stick on top
Label sheet 2: Stick on contact details page
Label sheet 2: Stick on survey
Label sheet 2: Stick on dried blood spot (envelope/outer packaging)

Printing

- Assessment checklists (a form that includes the participants contact ID, space to fill in contact details and special code)
- Gift card cover letter
- Envelopes to hold gift cards

Hygiene

- Box of gloves
- 2 x disinfectant wipes
- 1 x disinfectant spray

Health report

After bio-samples are processed in the lab, research staff will generate the participants health report containing basic information on the health biomarkers, the participants results and the national ranges of 'healthy'.

This will be posted to the addresses participants have provided no longer than within a reasonable timeframe after their assessment day.

The same report will be sent to parents, through their chosen communication channel given on their consent forms.

Davies PSW, Roodveldt R, Marks G. Standard methods for the collection and collation of anthropometric data in children. National Food and Nutrition Monitoring and Surveillance Project. Department of Health and Aged Care. Commonwealth of Australia 2001. ISBN 0 642 82058 9.

Appendix 3.2 – STROBE-nut Checklist

STROBE-nut: An extension of the STROBE statement for nutritional epidemiology

Lachat C et al. (2016) STrengthening the Reporting of OBservational studies in Epidemiology – Nutritional Epidemiology (STROBE-nut): an extension of the STROBE statement. Plos Medicine 13(6) http://dx.doi.org/10.1371/journal.pmed.1002036 pdf or online version.

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	**nut-1** State the dietary/nutritional assessment method(s) used in the title, abstract, or keywords.	**1**
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported.		1,2
Objectives	3	State specific objectives, including any pre-specified hypotheses.		2
Methods				
Study design	4	Present key elements of study design early in the paper.		2
Settings	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	**nut-5** Describe any characteristics of the study settings that might affect the dietary intake or nutritional status of the participants, if applicable.	**2,3**
Participants	6	a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls.	**nut-6** Report particular dietary, physiological or nutritional characteristics that were considered when selecting the target population.	**3,4**

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed. Case-control study—For matched studies, give matching criteria and the number of controls per case.		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	**nut-7.1** Clearly define foods, food groups, nutrients, or other food components. **nut-7.2** When using dietary patterns or indices, describe the methods to obtain them and their nutritional properties.	**5**
Data sources - measurements	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).Describe comparability of assessment methods if there is more than one group.	**nut-8.1** Describe the dietary assessment method(s), e.g., portion size estimation, number of days and items recorded, how it was developed and administered, and how quality was assured. Report if and how supplement intake was assessed. **nut-8.2** Describe and justify food composition data used. Explain the procedure to match food composition with consumption data. Describe the use of conversion factors, if applicable. **nut-8.3** Describe the nutrient requirements, recommendations, or dietary guidelines and the evaluation approach used to compare intake with the dietary reference values, if applicable. **nut-8.4** When using nutritional biomarkers, additionally use the STROBE Extension for	**5**

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
			Molecular Epidemiology (STROBE-ME). Report the type of biomarkers used and their usefulness as dietary exposure markers. **nut-8.5** Describe the assessment of nondietary data (e.g., nutritional status and influencing factors) and timing of the assessment of these variables in relation to dietary assessment. **nut-8.6** Report on the validity of the dietary or nutritional assessment methods and any internal or external validation used in the study, if applicable.	
Bias	9	Describe any efforts to address potential sources of bias.	**nut-9** Report how bias in dietary or nutritional assessment was addressed, e.g., misreporting, changes in habits as a result of being measured, or data imputation from other sources	**5**
Study Size	10	Explain how the study size was arrived at.		6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	**nut-11** Explain categorization of dietary/nutritional data (e.g., use of N-tiles and handling of nonconsumers) and the choice of reference category, if applicable.	**5**
Statistical Methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—If applicable, explain how loss to follow-up was addressed. Case-control study—If applicable, explain how matching of cases and controls was addressed.	**nut-12.1** Describe any statistical method used to combine dietary or nutritional data, if applicable. **nut-12.2** Describe and justify the method for energy adjustments, intake modeling, and use of weighting factors, if applicable. **nut-12.3** Report any adjustments for measurement error, i.e,. from a validity or calibration study.	**6**

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.		
Results				
Participants	13	(a) Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	**nut-13** Report the number of individuals excluded based on missing, incomplete or implausible dietary/nutritional data.	**6, 4**
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) Cohort study—Summarize follow-up time (e.g., average and total amount)	**nut-14** Give the distribution of participant characteristics across the exposure variables if applicable. Specify if food consumption of total population or consumers only were used to obtain results.	**6, 7**
Outcome data	15	Cohort study—Report numbers of outcome events or summary measures over time. Case-control study—Report numbers in each exposure category, or summary measures of exposure. Cross-sectional study—Report numbers of outcome events or summary measures.		**6, 7, 8**
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval).	**nut-16** Specify if nutrient intakes are reported with or without inclusion of dietary supplement intake, if applicable.	**6, 7, 8**

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
		Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions and sensitivity analyses.	**nut-17** Report any sensitivity analysis (e.g., exclusion of misreporters or outliers) and data imputation, if applicable.	**6, 7, 8**
Discussion				
Key results	18	Summarize key results with reference to study objectives.		10
Limitation	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	**nut-19** Describe the main limitations of the data sources and assessment methods used and implications for the interpretation of the findings.	**12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	**nut-20** Report the nutritional relevance of the findings, given the complexity of diet or nutrition as an exposure.	**10, 11, 12**
Generalizability	21	Discuss the generalizability (external validity) of the study results.		**12**
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		**13 (or supplementary)**

Item	Item nr	STROBE recommendations	Extension for Nutritional Epidemiology studies (STROBE-nut)	Reported on page #
Ethics			**nut-22.1** Describe the procedure for consent and study approval from ethics committee(s).	**13 (or supplementary)**
Supplementary material			**nut-22.2** Provide data collection tools and data as online material or explain how they can be accessed.	**Supplementary**

Appendix 3.3 – CONSORT extension Pilot and Feasibility Trials Checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	1,2
	2b	Specific objectives or research questions for pilot trial	1,2
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	1
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	2
Participants	4a	Eligibility criteria for participants	1

	4b	Settings and locations where the data were collected	1
	4c	How participants were identified and consented	1
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	N/A
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	1,3,4
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	6
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	4,6(results)
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	6
Results			

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	4,6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3, 4
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	6, 7
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	6, 7
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	7, 8
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	7, 8
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9, 10
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	12, 13, 11
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	10, 11, 12, 13
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	10, 11, 12, 13
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	11, 12, 13
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	6

Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13
	26	Ethical approval or approval by research review committee, confirmed with reference number	3

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