Understanding Health Disparities in Genetic Heart Disease and Sudden Cardiac Death

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A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Faculty of Medicine and Health

The University of Sydney

June 2023

I. STATEMENT OF ORIGINALITY

This thesis is submitted in fulfillment of the requirements for the degree of Doctor of Philosophy 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 the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Name: Alexandra Butters

I. ACKNOWLEDGEMENTS

It is with a great sense of achievement and relief that I sit down to write this final section of my thesis. I am incredibly proud of myself for having completed a PhD in the crazy uncertain times we have experienced over the past few years due to the pandemic and the lab moving institutes. There are a bunch of people I want to thank who have provided me with encouragement, support and guidance over the past 4 years.

I want to begin by thanking Steve Nicholls for putting me in touch with Jodie back in 2017 when I was unsure of what my next step should be. Moving to Sydney to complete my Masters' whilst volunteering and then working for Jodie, which led to starting this PhD has been some of the best decisions I have made.

To Jodie, words cannot express how grateful I am to have you as a supervisor and mentor. It has been a real honour to be your 2nd ever PhD student. Thank you for you believing in me, supporting me and pushing me. I really could not have completed this PhD journey without you. Your unwavering passion and dedication to your work inspires me and countless others. With your guidance, I have grown both personally and professionally, and I am eager to witness the extraordinary accomplishments that await you in the future. I am so glad that I get to continue to work with you and the amazing team you have built.

Thank you to Jo for reminding me to "Just keep swimming" whenever I was feeling totally overwhelmed with the amount of work I needed to accomplish. Thank you also for spending the time to review and proofread my thesis. I look forward to your first senior author papers being published and furthering my skills in data linkage analysis with you. I would also like to thank Clare for helping me make sense of my sex-disaggregated analysis results. I was so grateful that you were able to be there in person to see me present this work at my first international conference in Barcelona last year.

Thank you to each and every member of the Clinical Genomics lab for your support, friendship, guidance, and eagerness for a blood orange margarita at Gino's or a boogie on the dancefloor.

Finally, I want to express my genuine appreciation to my family, especially my husband Jordan, for his unwavering love, encouragement, and understanding throughout this challenging and stressful journey. Your belief in me and constant presence have provided the emotional support that kept me going, even during the toughest times. I also want to thank my parents, Julie and Mark, especially Mum, for always being at the other end of the phone whenever I needed a chat or a reminder of just how capable I am.

This thesis is a result of the collective efforts and support of so many incredible people, and I am truly grateful for each and every one of you. Thank you for being a part of my journey and making it a memorable and fulfilling experience.

II. ABSTRACT

This thesis addresses health disparities among individuals with a genetic heart disease. Health disparities are avoidable inequities in provision of healthcare and can manifest in various ways including disease prevalence, morbidity and access to healthcare. They can occur due to factors such as sex, ethnicity and socioeconomic status. This thesis aims to improve understanding of health disparities in the context of genetic heart diseases, in order to achieve evidence-based and equitable healthcare.

Chapter 2 investigates sex differences in clinical and genetic factors associated with adverse outcomes in hypertrophic cardiomyopathy (HCM), the most common genetic heart disease. Significant differences were observed in disease course and outcomes, depending on genotype and sex. In addition to differences due to sex, this thesis examines health disparities with respect to ethnicity in two studies. ***Chapter 3*** focuses on a multiethnic HCM cohort, finding limited differences in clinical characteristics but crucial inequities in access to genetic testing and therapies between ethnicities. ***Chapter 4*** shows the critical need for openly accessible, large and diverse genomic reference databases, through in-depth analysis of a single nucleotide variant in a Pacific population. Finally, ***Chapter 5 & 6*** establishes a comprehensive clinical dataset through linking a genetic heart disease registry with state-wide routinely collected health datasets to identify healthcare utilisation patterns, uncovering disparities and opportunities for preventive care. This study highlights differences in healthcare utilisation by clinical diagnosis and disparities by socioeconomic status and sex.

Health disparities in genetic heart diseases are profound and this thesis highlights the lack of diversity in research participants, which limits knowledge and clinical management. By promoting inclusivity, equitable outcomes in diagnosing and managing genetic heart disease can be achieved.

III. TABLE OF CONTENTS

IV. LIST OF FIGURES

Chapter 6

Chapter 7

V. LIST OF TABLES

Chapter 4

None

Chapter 5

Chapter 6

Chapter 7

None

VI. LIST OF ABBREVIATIONS

ACC= American College of Cardiology

ACM= Arrhythmogenic cardiomyopathy

ACMG/AMP = The American College of Medical Genetics and Genomics and the Association for Molecular Pathology

AF= atrial fibrillation

AFR= African

AGHD= Australian Genetic Heart Disease

AHA = American Heart Association

BCPR= bystander cardiopulmonary resuscitation

BMI= body mass index

BrS= Brugada Syndrome

BSA = body surface area

CAD= coronary artery disease

CHeReL = Centre for Health Record Linkage

CI = confidence interval

CPVT= catecholaminergic polymorphic tachycardia

CVD= cardiovascular disease

DCM= dilated cardiomyopathy

EAS= East Asian

ECG= electrocardiogram

ED= emergency department

ESC= European Society of Cardiology

EUR= European

Fhx= family history

HCM= hypertrophic cardiomyopathy

HR= hazard ratio

ICD = implantable cardioverter defibrillator OR International Classification of Diseases

IQR = interquartile range

IRSAD= Index of Relative Socioeconomic Advantage and Disadvantage

LA= left atrial

LHD = local health district

LP/P = likely pathogenic or pathogenic

LQTS= Long QT Syndrome

LV = left ventricular

LVEF= left ventricular ejection fraction

LVNC= left ventricular non-compaction

LVOT= left ventricular outflow tract

LVOTO= left ventricular outflow tract obstruction

MDC= Major Diagnosis Category

MENA= Middle Eastern and North African

MI= myocardial infarction

MINOCA= MI with nonobstructive coronary artery disease

NSW = New South Wales

NYHA = New York Heart Association

OC=Oceanian

OSA= obstructive sleep apnoea

POA= People of the Americas

PPN = project-specific person number

PRS = polygenic risk score

RCM = restrictive cardiomyopathy

SAS= South Asian

SCD = sudden cardiac death

SHaRe= Sarcomeric Human Cardiomyopathy Registry

SNP= single nucleotide polymorphism

SRG= Service Related Group

STEMI= ST-elevation MI

SUD= sudden unexplained death

VF= ventricular fibrillation

VT= ventricular tachycardia

VUS= variant of unknown significance

VII. PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Chapters and work arising from this thesis have been published and presented in the following forums.

Peer-reviewed publications

1. **Butters A**, Lakdawala NK, Ingles J. Sex Differences in Hypertrophic Cardiomyopathy: Interaction with Genetics and Environment. Curr Heart Fail Rep. 2021 Oct;18(5):264-273. doi: 10.1007/s11897-021-00526-x. Epub 2021 Sep 3. PMID: 34478112; PMCID: PMC8484093.
2. **Butters A**, Arnott C, Sweeting J, Winkel BG, Semsarian C, Ingles J. Sex Disparities in Sudden Cardiac Death. Circ Arrhythm Electrophysiol. 2021 Aug;14(8):e009834. doi: 10.1161/CIRCEP.121.009834. Epub 2021 Aug 16. PMID: 34397259.
3. **Butters A,** Semsarian CR, Bagnall RD, Yeates L, Stafford F, Burns C, Semsarian C, Ingles J. Clinical Profile and Health Disparities in a Multiethnic Cohort of Patients with Hypertrophic Cardiomyopathy. Circ Heart Fail. 2021 Mar;14(3): e007537. doi: 10.1161/CIRCHEARTFAILURE.120.007537. Epub 2021 Mar 16. PMID: 33724884.
4. **Butters A,** Bagnall RD, Ingles J. Revisiting the Diagnostic Yield of Hypertrophic Cardiomyopathy Genetic Testing. Circ Genom Precis Med. 2020 Apr;13(2): e002930. doi: 10.1161/CIRCGEN.120.002930. Epub 2020 Apr 21. PMID: 32315220

Pre-prints

1. **Butters A**, Arnott C, Sweeting J, Claggett B, Cuomo A, Abrams D, Ashley EA, Day SM, Helms AS, Lampert R, Lin K, Michels M, Miller EM, Olivotto I, Owens A, Parikh VN, Pereira AC, Rossano JW, Ryan TD, Saberi S, Stendahl JC, Ware JS, Wittekind S, Atherton J, Semsarian C, Lakdawala NK, Ho CY, Ingles J. Sex-disaggregated analysis of risk factors for adverse outcomes in hypertrophic cardiomyopathy. medRxiv 2023.06.17.23291422; doi: https://doi.org/10.1101/2023.06.17.23291422

2. **Butters A,** Blanch B, Kemp-Casey A, Do J, Yeates L, Leslie F, Semsarian C, Nedkoff L, Briffa T, Ingles J, Sweeting J. The Australian Genetic Heart Disease Registry: Data Linkage Study Protocol. JMIR Preprints. 01/05/2023:48636

Peer-reviewed publications related to but not contained in this thesis

1. Leslie F, Avis SR, Bagnall RD, Bendall J, Briffa T, Brouwer I, **Butters A**, Figtree GA, La Gerche A, Gray B, Nedkoff L, Page G, Paratz E, Semsarian C, Sy RW, du Toit-Prinsloo L, Yeates L, Sweeting J, Ingles J. End Unexplained Cardiac Death (EndUCD) NSW Registry: A data linkage cohort study. Heart Lung Circ. Accepted 19th June 2023.

2. Stafford F, Krishnan N, Richardson E, **Butters A**, Hespe S, Burns C, Gray B, Medi C, Nowak N, Isbister JC, et al. The role of genetic testing in diagnosis and care of inherited cardiac conditions in a specialised multidisciplinary clinic. Genome Medicine. 2022;14:145.

3. Stafford F, Thomson K, **Butters A**, Ingles J. Hypertrophic Cardiomyopathy: Genetic Testing and Risk Stratification. Curr Cardiol Rep. 2021;23:9.

4. Isbister JC, Nowak N, **Butters A**, Yeates L, Gray B, Sy RW, Ingles J, Bagnall RD, Semsarian C. "Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest. Int J Cardiol. 2021;324:96–101.

5. **Butters A**, Isbister JC, Medi C, Raju H, Turner C, Sy RW, Semsarian C, Ingles J. Epidemiology and clinical characteristics of atrial fibrillation in patients with inherited heart diseases. J Cardiovasc Electrophysiol. 2020;31:465–473.

International conference presentations

Oral

1. *Moderated ePoster Presentation:* **Butters A,** Blanch B, Kemp-Casey A, Do J, Yeates L, Leslie F, Semsarian C, Nedkoff L, Briffa T, Ingles J, Sweeting J. The Australian Genetic Heart Disease Registry: Data linkage study protocol. European Society of Cardiology (ESC) Congress, Amsterdam, Aug 25th-29th 2023.

2. *Moderated ePoster Presentation*: **Butters A**, Arnott C, Sweeting J, Claggett B, Ashley EA, Colan SD, Day SM, Helms AS, Jacoby D, Michels M, Olivotto I, Owens A, Parikh VN, Pereira AC, Rossano JW, Saberi S, Ware JS, Wittekind S, Atherton J, Semsarian C, Lakdawala NK, Ho CY, Ingles J. Sex-disaggregated analysis of risk factors for adverse outcomes in hypertrophic cardiomyopathy. European Society of Cardiology (ESC) Congress, Barcelona, Aug 26th-30th 2022.

3. *Moderated ePoster presentation*: **Butters A,** Semsarian CR, Bagnall RD, Yeates L, Stafford F, Burns C, Semsarian C, Ingles J. Clinical Profile and Health Disparities in Patients with Hypertrophic Cardiomyopathy in a Multi-ethnic Cohort. American Heart Association (AHA) Scientific Sessions, Virtual 2020.

National conference presentations

Oral

1. *Mini Oral presentation:* **Butters A,** Blanch B, Kemp-Casey A, Do J, Yeates L, Leslie F, Semsarian C, Nedkoff L, Briffa T, Ingles J, Sweeting J. The Australian Genetic Heart Disease Registry: Data linkage study protocol. Cardiac Society of Australia

and New Zealand (CSANZ), Aug 3rd-6th 2023.

2. *Oral Abstract Presentation*: **Butters A**, Arnott C, Sweeting J, Claggett B, Ashley EA, Colan SD, Day SM, Helms AS, Jacoby D, Michels M, Olivotto I, Owens A, Parikh VN, Pereira AC, Rossano JW, Saberi S, Ware JS, Wittekind S, Atherton J, Semsarian C, Lakdawala NK, Ho CY, Ingles J. Sex-disaggregated analysis of risk factors for adverse outcomes in hypertrophic cardiomyopathy. Cardiac Society of Australia and New Zealand Annual Scientific Meeting, Gold Coast, Aug 11th-14th 2022. ***Multidisciplinary: Allied Health and Technology Prize Session Finalist.***

3. *Oral Abstract Presentation*: **Butters A,** Semsarian CR, Bagnall RD, Yeates L, Stafford F, Burns C, Semsarian C, Ingles J. Clinical Profile and Health Disparities in Patients with Hypertrophic Cardiomyopathy in a Multi-ethnic Cohort. Cardiac Society of Australia and New Zealand Annual Scientific Meeting, Sydney Hub, 2020. ***Cardiovascular Genetics Prize Session Finalist and Winner.***

4. *Oral Abstract Presentation:* **Butters et al**. A rare splice-site variant in *TNNT2*: cardiomyopathy and sudden death associated variant or common Polynesian polymorphism? Centenary Institute Showcase, Sydney, 2020.

Poster

1. *Poster Presentation:* **Butters A,** Thomson K, Harrington F, Henden N, McGuire K, Caleshu C, Dunn K, Bos JM, Ackerman MJ, Nowak N, Juang J, Tiemensma M, Ronan A, McGaughran, Atherton J, Semsarian C, Hayes I, Merriman TR, MacArthur DG, Skinner JR, Bagnall RD, Ingles J. A Rare Splice-Site Variant in TNNT2: The need for population-specific reference data. Human Genetics Society of Australasia (HGSA) 45th Annual Scientific Meeting, Perth, 24th-27th Nov 2022.

2. *Poster Presentation:* **Butters A,** Arnott C, Sweeting J, Claggett B, Atherton J, Semsarian C, Lakdawala NK, Ho CY, Ingles J. Sex disaggregated analysis of risk factors for adverse outcomes in hypertrophic cardiomyopathy. International Clinical Cardiovascular Genetics (ICCG) Conference, Brisbane 2022

Other oral presentations

1. *Invited Oral Presentation*: Sex differences in genetic heart disease and sudden cardiac death. University of Sydney, Young Leaders Program, Sydney 2019.

2. *Lightening Talk*. **Butters A**, Arnott C, Semsarian C, Ingles J. Sex disparities in Sudden Cardiac Death. Centenary Showcase, Sydney 2019.

I. AWARDS ARISING FROM THIS THESIS

2023 Paulette Isabel Jones PhD Completion Scholarship ($7000)

2023 CSANZ Complimentary Registration to attend the European Society of Cardiology (ESC) Congress, Amsterdam August 25th-August 28th 2023

2022 CSANZ Complimentary Registration to attend the European Society of Cardiology (ESC) Congress, Barcelona August 26th-August 29th 2022

2020 Cardiovascular Genetic Diseases Prize ($1000), Cardiac Society of Australia New Zealand (CSANZ)

CHAPTER 1

INTRODUCTION

1. CHAPTER 1: INTRODUCTION

1.1 Health disparities

Health disparities are recognised as avoidable inequities in the provision and availability of healthcare, resulting from social, political, and economic influences that disproportionately impact disadvantaged and underrepresented communities.[1] These disparities manifest in various aspects of health, encompassing inequalities in disease prevalence, incidence rates, morbidity, mortality, access to healthcare services, and the overall standard of care.[2]

Over the past decade, substantial effort has been made to improve the understanding of health disparities in cardiovascular diseases (CVD).[3–6] This has been driven by the recognition that specific populations, including women, underrepresented ethnic populations, socioeconomically disadvantaged individuals, and those living in regional or rural areas, experience higher rates of CVD and/or worse clinical outcomes than their counterparts.[3–5] The origins of disparities in CVD are numerous and wide-ranging, having largely evolved from societal inequalities related to the social determinants of health as shown in Figure 1.1.[7]

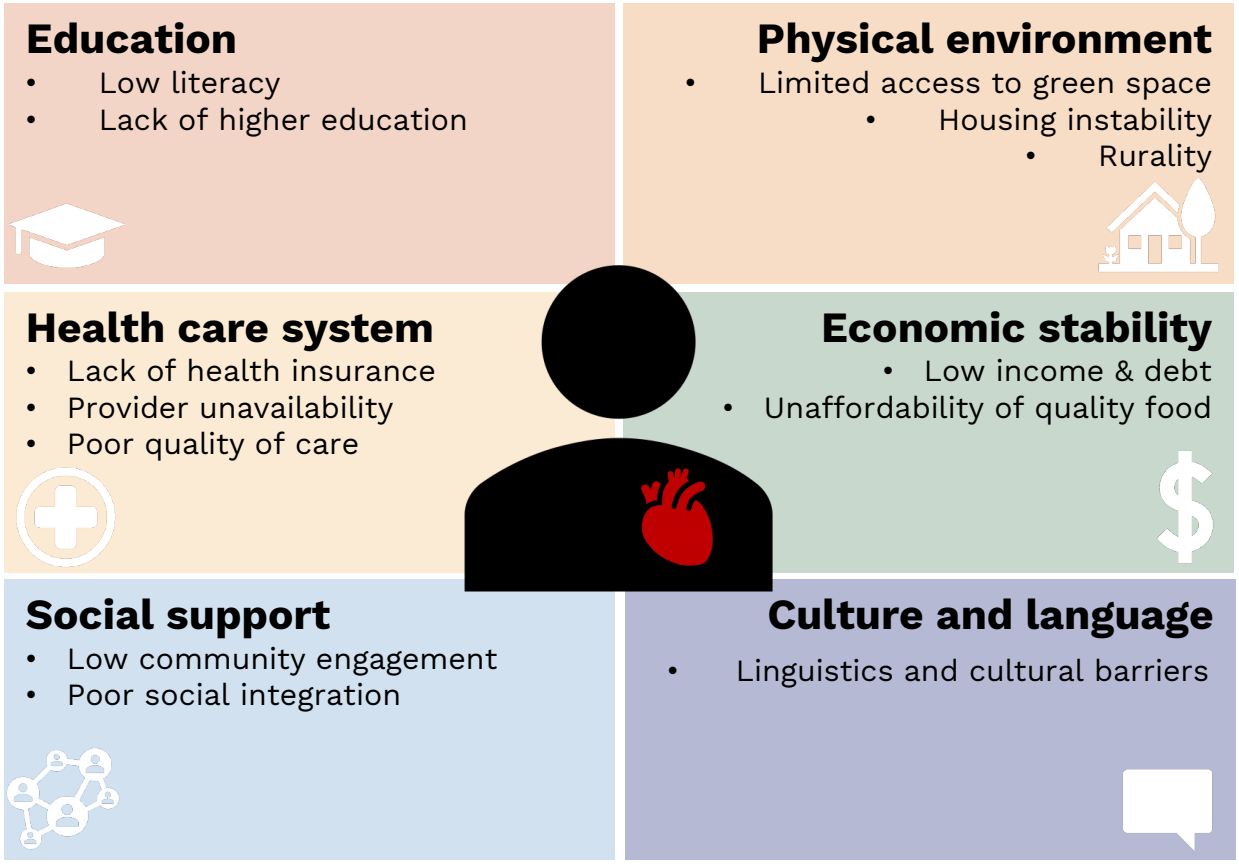

Figure 1.1: Social determinants of health in cardiovascular disease

Social determinants globally influence health outcomes, but the impact of these factors in the context of genetic heart diseases has rarely been investigated. Genetic heart diseases encompass a range of conditions, including inherited cardiomyopathies and primary arrhythmia syndromes with a clear genetic basis.[8–10] While various factors influence the development of these diseases, a comprehensive understanding of the aetiology and management of disadvantaged patient populations, including women, diverse ethnic populations and those from low socioeconomic and geographic groups, remains elusive.

The impact of sex on the cardiovascular system is complex, encompassing biological diversity and social and environmental disparities.[11] Genetic heart diseases are not immune to the impact of sex, and numerous clinical differences and disparities have been identified between the sexes. For instance, among patients with one of the most common genetic heart diseases, hypertrophic cardiomyopathy (HCM), women are underrepresented, older at diagnosis, have increased symptom burden, decreased exercise capacity, are more likely to be sarcomere variant carriers, and have higher rates of progression to heart failure and all-cause mortality.[12–15] Numerous groups have replicated these results, but the reason for these differences is still unclear.

Genetic heart diseases affect individuals worldwide, however, the majority of research to date has focused Predominantly on individuals of European ancestry. Efforts have been made to investigate racial and ethnic differences in African American/Black populations, however, research focused on individuals from other diverse populations is lacking.[16–18] Individuals from diverse populations are underserved in genetic testing due to a lack of

ancestry-matched population reference data, meaning they are less likely to have a causative variant identified.[19]

Socioeconomic status is an important determinant of health, including for patients with genetic heart diseases. Individuals from lower socioeconomic backgrounds often face barriers to accessing quality healthcare, including genetic testing, screening for early detection, and access to specialised multidisciplinary genetic heart disease clinics.[20,21] Due to their limited access to these services, relying on research from specialised centres likely means the full extent of the impact of disease on disadvantaged groups is unknown.

A comprehensive approach is required to address these disparities and understand their contributions to differences in disease progression and outcomes.[22] This includes raising awareness about genetic heart diseases among healthcare providers and the general public, promoting equal access to genetic testing and specialised care, implementing culturally sensitive interventions, and conducting and designing research to understand better the underlying mechanisms contributing to these disparities.[23] By addressing these factors, we can strive towards more equitable outcomes for genetic heart diseases, ensuring that individuals of all sexes, ethnicities, and socioeconomic backgrounds receive the care they need to manage their condition effectively.

This PhD aims to comprehensively understand the health disparities observed in genetic heart diseases. By investigating the complex interplay between sex, ethnicity, socioeconomic status, and disease outcomes, the research aims to uncover the underlying factors contributing to these disparities.

1.2 Genetic heart diseases

Genetic heart diseases encompass both inherited cardiomyopathies (e.g., HCM, dilated cardiomyopathy [DCM], arrhythmogenic cardiomyopathy [ACM], restrictive cardiomyopathy [RCM] and left ventricular non-compaction [LVNC]) and primary arrhythmia syndromes (e.g., Long QT Syndrome [LQTS], Brugada syndrome [BrS] and catecholaminergic polymorphic tachycardia [CPVT]). Each of these diseases is distinctly different; however, they are all mostly inherited as autosomal dominant traits, typically affect younger patients, have variable expressivity and penetrance, and require long-term clinical screening of at-risk relatives.[8,9,24] The most notable feature common to genetic heart diseases is the possible occurrence of sudden cardiac death (SCD).[25,26]

1.3 Inherited cardiomyopathies

Cardiomyopathies encompass diseases characterised by primary functional and structural irregularities within the heart muscle. The most optimal classification of cardiomyopathies is centred around their observable phenotypes: hypertrophic, dilated, arrhythmogenic, and non-compaction.[27]

1.3.1 Hypertrophic cardiomyopathy (HCM)

This PhD thesis will predominantly focus on HCM. HCM is defined by increased left ventricular wall thickness without abnormal loading conditions (e.g., hypertension, aortic stenosis).[24] The hallmark features include asymmetric hypertrophy of the interventricular septum, myocyte disarray, and fibrosis (Figure 1.2).[28–30] It has a prevalence of ~1 in 500 (0.2%) in the general population.[31] However, many patients may not be clinically apparent due to the absence of signs and symptoms.[28] Clinical diagnosis is made via 2-dimensional echocardiography (maximal left ventricular wall thickness ≥ 15mm), alongside clinical

examination, electrocardiogram (ECG) and review of the family history.[24] Cardiac magnetic resonance (CMR) imaging may be used to supplement echocardiography in a subset of patients with borderline hypertrophy or to further elucidate the risk of SCD. HCM is often first diagnosed through evaluation of symptoms such as dyspnoea, angina or syncope and presyncope, or asymptomatically due to family screening when HCM is diagnosed in another family member or incidentally during evaluation for another condition.[28] Diagnosis can occur at any age with incident cases described on prenatal evaluations through the fifth or sixth decade of life.[30]

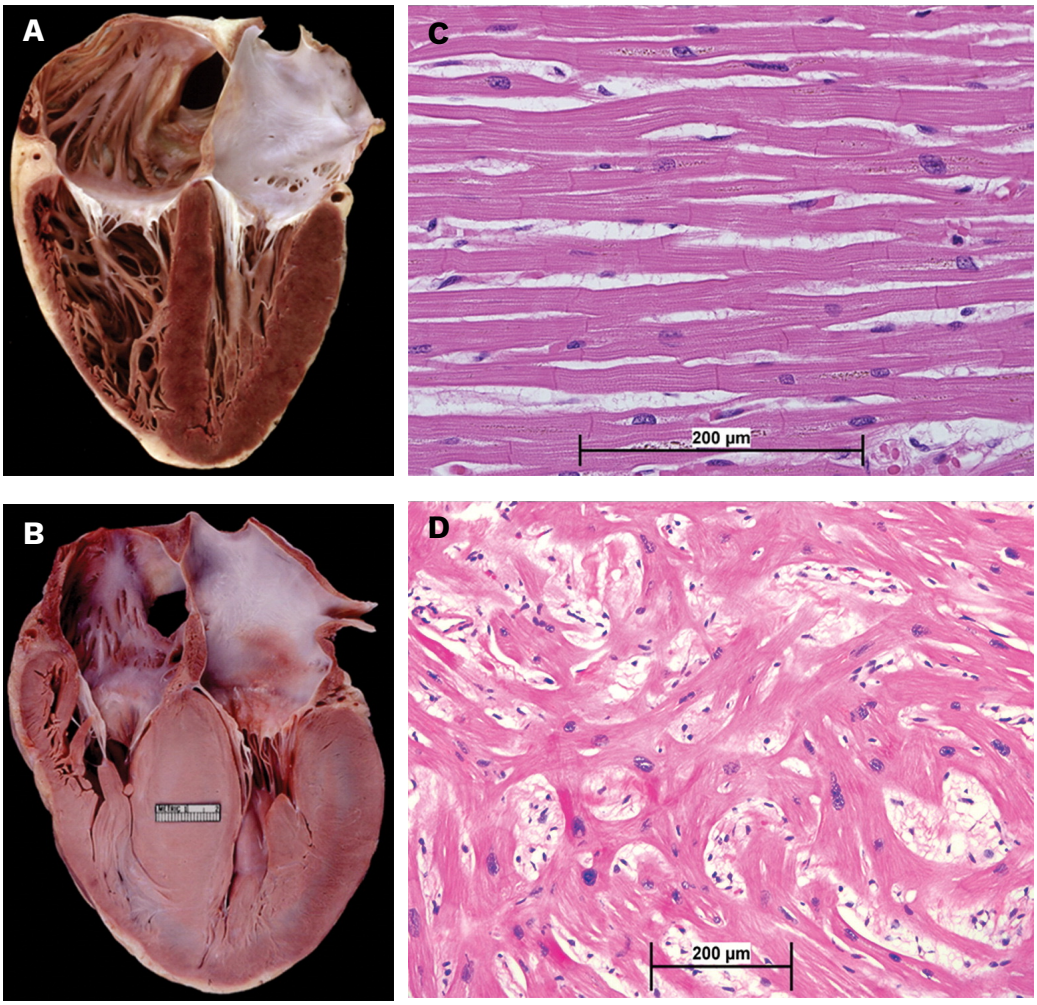

Figure 1.2: Gross and microscopic anatomy of normal heart and heart with HCM

(a) Normal heart

(b) Heart with HCM

(c) Normal cardiac myocytes (hematoxylin-eosin stain)

(d) Myocyte hypertrophy and disarray (hematoxylin-eosin stain)

Adapted from Baxi et al. 2016[29]

HCM exhibits significant clinical heterogeneity.[32,33] While a considerable number of patients remain asymptomatic, require no treatment, and live normal lifespans, there can be critical clinical implications such as the risk of SCD, the potential for arrhythmia including atrial fibrillation (20% of patients), stroke, symptomatic outflow tract obstruction at rest (25–30% of patients) or under provocation (60-70% of patients), and heart failure (Predominantly with preserved ejection fraction).[27,33–36] HCM is the primary underlying structural cause for SCD in individuals under 35 years.[25] Consequently, high-risk individuals are recommended an implantable cardioverter defibrillator (ICD) to detect life-threatening irregular heart rhythms and administer suitable therapy.[37] Additional commonly employed medical therapies include beta blockers, calcium channel blockers, and diuretics.[24] In cases where symptomatic outflow tract obstruction occurs, options such as alcohol septal ablation and surgical myectomy may be considered.[38] Recently, a disease-specific drug for obstructive HCM has been approved. Mavacamten, a novel myosin inhibitor, has shown substantial improvements in physical function, symptom relief, and quality of life in patients with symptomatic obstructive HCM in phase 3 clinical trials.[39–41]

1.3.2 Editorial: Revisiting the Diagnostic Yield of Hypertrophic Cardiomyopathy Genetic Testing

1.3.2.1 Preface to publication

The following editorial presents a contemporary summary of the genetics of HCM, including the diagnostic yield of genetic testing. It also includes an overview of HCM subgroups, including sarcomere-positive and non-familial HCM (i.e., sarcomere-negative HCM).
The published paper forms a section of this chapter. Author contributions are outlined in the author contribution statement.

Reference

Butters A[1,2], Bagnall RD[1], Ingles J[1,2,3]. Revisiting the Diagnostic Yield of Hypertrophic Cardiomyopathy Genetic Testing. Circ Genom Precis Med. 2020 Apr;13(2): e002930. doi: 10.1161/CIRCGEN.120.002930. Epub 2020 Apr 21. PMID: 32315220.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the editorial	AB, JI
Literature search	AB
Drafting the manuscript	AB
Review and critical comments on manuscript	All authors
Responding to reviewer comments	AB, JI
Coordination of submission and publication	AB, JI

As the candidate for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Candidate Name: Alexandra Butters

Signature: Date: 29/06/2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Supervisor Name: A/Prof Jodie Ingles

Signature: Date: 29/06/2023

Sources of funding
A/Prof Ingles is the recipient of an NHMRC (National Health and Medical Research Council) Career Development Fellowship (no. 1162929).

Disclosures
None

Circulation: Genomic and Precision Medicine

EDITORIAL

Revisiting the Diagnostic Yield of Hypertrophic Cardiomyopathy Genetic Testing

Alexandra Butters, MPH; Richard D. Bagnall, PhD; Jodie Ingles, PhD, MPH

Hypertrophic cardiomyopathy (HCM) is an inherited cardiomyopathy, characterized by left ventricular (LV) hypertrophy in the absence of blood flow-limiting coronary artery disease or abnormal loading conditions.[1,2] HCM affects at least 1 in 500 in the general population and displays significant phenotypic heterogeneity, ranging from asymptomatic individuals to those with heart failure and sudden cardiac death.[3] HCM is primarily caused by variants in genes that encode cardiac sarcomere proteins, although there is increasing evidence that ≈40% have a nonfamilial subtype where the underlying disease mechanism remains unclear.[4,5]

See Article by Hoss et al

It is well established that a small proportion of patients with HCM have a different underlying cause of their LV hypertrophy. It is known that other conditions can mimic HCM, where LV hypertrophy is present in the absence of overt syndromic or atypical features. Recent work by the ClinGen Cardiovascular Domain Clinical Working Group assessed the clinical validity of a number of syndromic genes, with 12 considered to have a definitive or strong association with a syndrome that could present with isolated, or seemingly isolated, LV hypertrophy.[6] These include metabolic storage phenotypes due to variants in *GLA* (Fabry disease), *PRKAG2* (*PRKAG2* cardiomyopathy), *TTR* (transthyretin amyloidosis), and *LAMP2* (Danon disease). Given the known occurrence of LV hypertrophy in patients with Noonan syndrome, *PTPN11*, *RAF1*, and *RIT1* should be included given the evidence that these patients may have only subtle extracardiac and dysmorphic features. Variants in *DES* cause a desminopathy associated with a range of features including progressive skeletal muscle weakness, cardiomyopathy including LV hypertrophy in some cases, cardiac conduction disease, and there can be heterogeneity in the phenotype features that initially present. *FHL1* causes Emery-Dreifuss muscular dystrophy, but some patients may have LV hypertrophy in the absence of any significant muscle weakness, and variants in *FLNC* lead to myofibrillar myopathy or dilated cardiomyopathy, although families with isolated LV hypertrophy have been reported. Autosomal recessive loss-of-function variants in *ALPK3* have recently been shown to cause severe infant-onset cardiomyopathy. Finally, variants in *ACTN2* and *PLN* can give rise to phenotypes that mimic HCM though often have other cardiac manifestations.

In this issue, Hoss et al[7] report the yield of causative variants in genes that cause conditions that can mimic HCM (*GLA, PRKAG2, TTR, LAMP2, PTPN11, RAF1, DES*). Among 1731 unrelated patients with HCM who underwent genetic testing, 16 (1.5%) had a likely pathogenic or pathogenic (LP/P) variant identified in *GLA, PRKAG2, TTR*, and *PTPN11*. A further 16 patients had a variant of unknown significance identified in *PRKAG2*, *TTR*, *LAMP2*, *RAF1*, and *DES*, although no patients had phenotypic evidence of the respective conditions suggesting the variants are unlikely causative. LP/P variants in syndromic genes may not account for a large proportion of gene-elusive HCM, but their clinical significance can be marked. Indeed, correct genetic diagnosis of a syndrome resulted in a major change in management in most patients and led to appropriate family screening in all. This work highlights why inclusion of these genes in routine HCM genetic testing is important, particularly

Key Words: Editorials ■ cardiomyopathies ■ coronary artery disease ■ genetic testing ■ hypertrophy ■ population

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For Sources of Funding and Disclosures, see page 78.

Circulation: Genomic and Precision Medicine is available at www.ahajournals.org/journal/circgen

when syndromes may present with no, or subtle, extracardiac manifestations.

Genetic testing for HCM is considered part of routine clinical management of patients, with a key role in cascade genetic testing of family members. Genotype positive relatives can be identified earlier for ongoing surveillance, whereas gene negative individuals can be released from lifelong clinical screening and worry. Even after decades of research and clinical experience, genetic testing of an HCM proband yields a causative variant in at best 30% to 40% of cases. But based on our contemporary understanding of HCM, do we ever expect the diagnostic yield to reach 100%?

DIAGNOSTIC YIELD OF HCM GENETIC TESTING

A contemporary summary of the diagnostic yield of HCM genetic testing is shown in the Figure. The yield of an LP/P result in sarcomere genes is estimated to be ≈32%, with the majority of causative variants found in the 2 most common genes *MYBPC3* (17%) and *MYH7* (10%). Variants in other sarcomere genes, including *MYL2, MYL3 TNNT2, ACTC1, TPM1,* and *TNNI3,* account for ≈5% of the remaining genetically confirmed cases.[4,8] Variant of unknown significance in sarcomere genes are reported to occur in 9% of HCM probands,[4,5] and recent work suggests many of these may be causative, although do not meet stringent variant classification thresholds.[9] Inclusion of syndromic genes, as illustrated by Hoss et al,[7] identifies LP/P variants in a further 1.5% of apparent HCM cases. For the remainder of probands with a family history of disease, there is strong suspicion of an underlying genetic cause that is yet to be solved. In the ≈40% of patients with HCM having a nonfamilial subtype, where a mendelian cause is unlikely, then it could be argued that these patients do not require further genetic analysis.

In many respects, careful reassessment of the phenotype would raise suspicion for a syndromic cause of LV hypertrophy, although the role of genetic testing in signaling a potential misdiagnosis seems particularly useful in this setting. Indeed, Hoss et al[7] showed that in the majority of patients, the clinical diagnosis of a syndrome would have been challenging without genetic testing, especially for those with Fabry disease, where 4/11 had no extracardiac manifestations even when investigated specifically for the phenotype. Importantly, a positive family history of HCM was reported in almost half of those diagnosed, raising suspicion that a genetic cause beyond the sarcomere genes should be investigated. In all cases, clarifying the clinical diagnosis with genetic testing had a direct impact on either management or more appropriate clinical screening recommendations for family members.

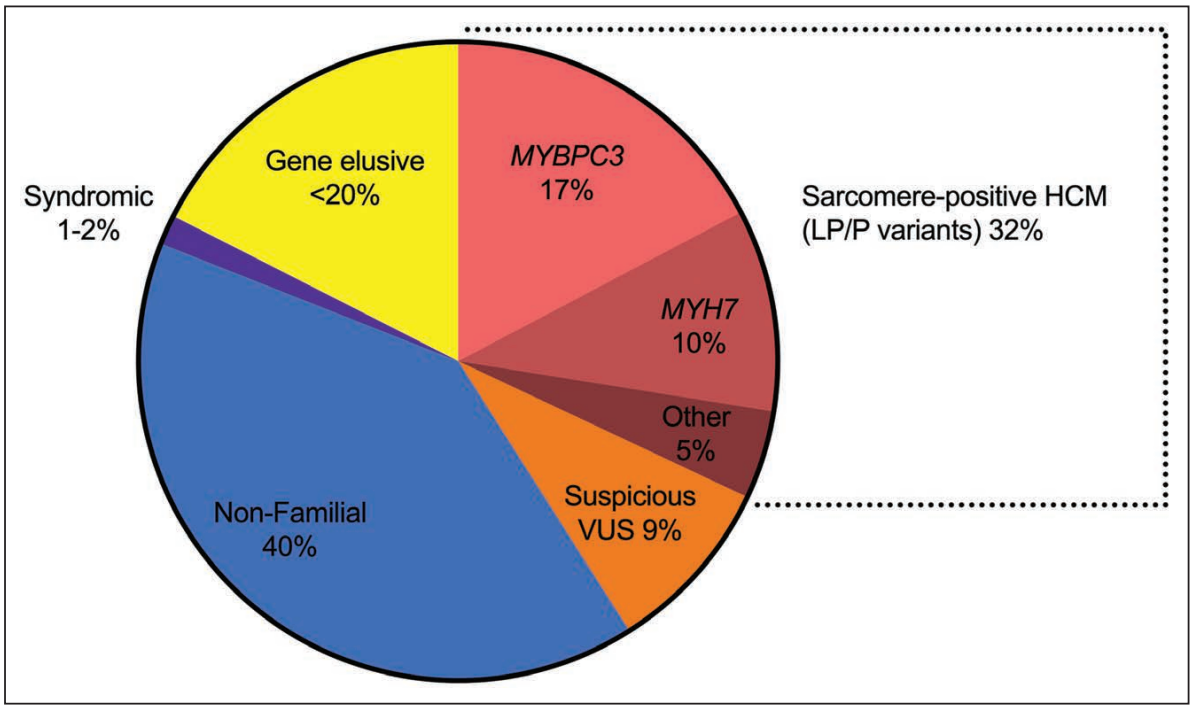

Figure. Contemporary summary of the approximate diagnostic yield of hypertrophic cardiomyopathy (HCM) genetic testing. Other includes TNNT2, TNNI3, TPM1, ACTC, MYL2, and MYL3. LP/P indicates likely pathogenic and pathogenic; and VUS, variant of uncertain significance.

THE SOLVED HCM CASES

The well-established sarcomere genes have the most robust association with HCM.[6] Among cases with a sarcomere variant, most will have variants in *MYBPC3* or *MYH7*, while the remainder will be identified in *TNNT2, TNNI3, TPM1, ACTC, MYL2*, and *MYL3*. Recent work from the Sarcomeric Human Cardiomyopathy Registry demonstrated sarcomere positive HCM is associated with worse outcomes when compared with sarcomere negative HCM.[5] Those with sarcomere variants have significantly earlier onset of events and are more likely to have clinical outcomes of heart failure and atrial fibrillation. They are also more likely to experience ventricular arrhythmia, including cardiac arrest, appropriate implantable cardioverter-defibrillator shock, sudden cardiac death. The greatest clinical utility of genetics in these cases is for cascade genetic testing of at-risk family members, although there are emerging scenarios where knowing the precise genetic cause will have medical or therapeutic benefit in future.

NONFAMILIAL HCM

A subgroup of patients with HCM have no genetic variant identified despite comprehensive genetic testing, and family screening does not identify an affected relative even after decades of clinical surveillance.[4] The nonfamilial HCM subgroup has a different clinical course compared with sarcomere positive HCM, being typically male, diagnosed later in life, milder LV hypertrophy, and more likely to have hypertension. The implications of recognizing nonfamilial HCM extend beyond the clinical differences. For the first-degree at-risk relatives, who under current recommendations must undergo lifetime periodic clinical surveillance, there may be an argument to lessen this. Furthermore, given our ability to reasonably identify nonfamilial HCM clinically and genetically, they should not be considered gene-elusive as it is very unlikely that a mendelian genetic cause exists. The underlying cause of LV hypertrophy in this group is currently unknown but may be due to a combination of polygenic and nongenetic factors. Indeed, many factors can contribute to a small degree of LV hypertrophy, and it is possible that in combination, these may give rise to an HCM-like phenotype.

SOLVING GENE-ELUSIVE HCM

Identifying an underlying genetic cause of disease can have significant benefits. For the patient, it can confirm an uncertain clinical diagnosis, and as Hoss et al[7] have shown, it can identify a misdiagnosis. For the family, the overarching impact predominantly relates to clarifying inheritance risks through cascade genetic testing. In some cases, for example, in a family found to have Fabry disease after genetic testing, the inheritance pattern is clarified to be X-linked. Therefore, sons of a male patient are no longer at risk. Early identification of Fabry disease can also prompt initiation of enzyme replacement therapy. Indeed, Hoss et al[7] report that 8/10 patients identified to have Fabry disease were treated with enzyme replacement therapy, while 2 patients were eligible but declined treatment.

As research efforts begin to move us towards a more precision-based approach to disease management, efforts to elucidate the precise underlying cause of the disease become even more critical. Reporting of large clinic experiences such as that by Hoss et al[7] allows us to gain a contemporary understanding of the profile of patients currently being seen in specialized clinics. It also shines a spotlight on the remaining gene-elusive HCM group, where a mendelian, familial cause is highly suspected yet a genetic diagnosis cannot be made. Recent work suggests some of the answers will be in key genes we already understand, with deep intronic *MYBPC3* variants contributing an additional yield of 1% to 2%, while others may be solved as new genes causing HCM-like phenotypes become better understood.[10]

CONCLUSIONS

HCM genetic testing has been the focus of intense research efforts and is now considered a mainstream aspect of patient management. In some respects, there have been transformational advances in our knowledge of the genetic architecture of HCM and yet despite this, the overall diagnostic yield has not substantially improved. Further subclassification of the phenotype, by better recognizing syndromes misdiagnosed as HCM or better understanding the causes of nonfamilial HCM, are necessary next steps, and will help to guide who we expect to find an LP/P variant in. For the true gene-elusive group, dedicated and focused efforts to delineate the clinical and genetic basis of their disease are so important, not just in giving the family more certainty in their diagnosis and inheritance risks, but in our understanding of the genetic causes of LV hypertrophy.

ARTICLE INFORMATION

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Acknowledgments

Dr Ingles is the recipient of an NHMRC (National Health and Medical Research Council) Career Development Fellowship (no. 1162929).

Sources of Funding

None.

Disclosures

Dr Ingles receives research grant support from Myokardia, Inc. The other authors report no conflicts.

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1.3.3 Dilated cardiomyopathy (DCM)

DCM is a myocardial disease characterised by ventricular dilation and impaired contraction, often leading to heart failure. It is estimated to affect 1 in 250 individuals.[42] Different underlying aetiologies exist, with DCM occurring due to familial, infectious, and inflammatory causes.[43] DCM is familial or determined to have a genetic aetiology in approximately 30% of cases.[44] Familial DCM stands out as the most genetically and phenotypically diverse of the inherited cardiomyopathies, posing challenges for diagnosis and elucidating causal genetic variants.[45]

DCM genes encode proteins of broad cellular functions. Variants in genes encoding cytoskeletal, sarcomeric, mitochondrial, desmosomal, nuclear membrane, and RNA-binding proteins have all been linked to DCM, with variants in greater than 100 genes asserted to cause DCM.[46,47] While each of these genes has some degree of evidence suggesting a relationship with the DCM phenotype, only 19 genes have robust evidence supporting a definitive-strong gene-disease relationship.[48–50]

1.3.4 Arrhythmogenic cardiomyopathy (ACM)

ACM results in progressive fibro-fatty cell infiltration of the right and left ventricular myocardium.[8,51] Arrhythmogenic right ventricular cardiomyopathy (ARVC), a sub-type of ACM, is the term originally designated to describe a myocardial disease Predominantly affecting the right ventricle, with hallmark clinical presentation of malignant ventricular arrhythmias. ARVC is diagnosed using the 2010 ARVC Taskforce criteria, which requires the fulfilment of either two major, one major and two minor, or four minor criteria.[52] However, over the years, autopsy investigations, genotype-phenotype correlation studies, and increased use of contrast-enhancement CMR have shown fibro-fatty replacement

affecting either the right or left ventricles or both.[53] This has led to the development of the Padua criteria for ACM, recognising left-sided and biventricular conditions.[53] These criteria are still yet to be validated and therefore are not yet included in clinical guidelines. For the scope of this thesis, ACM refers to ARVC, arrhythmogenic left ventricular cardiomyopathy, and biventricular disease.

1.3.5 Left ventricular non-compaction (LVNC)

LVNC is primarily distinguished by the presence of excessive trabeculations, often observed in the apex of the left ventricle. The trabeculations may be accompanied by left ventricular dilatation or hypertrophy, systolic or diastolic dysfunction and occasionally congenital heart disease.[54] Due to the overlapping features with other cardiomyopathies and the prevalence of hypertrabeculation in the general population, it has been debated whether LVNC should be considered a separate disease entity.[55] However, it is clear that true familial isolated LVNC cases do exist. Outside such families, LV trabeculation identified in an individual may be an incidental finding or indeed be a feature of a syndrome.[56,57]

1.4 Primary arrhythmia syndromes

Primary arrhythmia syndromes are a group of primary electrical disorders (LQTS, BrS and CPVT) caused by genetic variants in ion channels and their interacting proteins, predominantly involving potassium, sodium, and calcium handling.[58] They are an important cause of SCD in the young, and on autopsy, the heart is structurally normal with no evidence of disease macroscopically.[25,59] Only a brief description of these diseases is provided here, as they are discussed in relation to SCD in a following review, and are not a major focus of this thesis.

1.5 Review: Sex Differences in Hypertrophic Cardiomyopathy: Interaction with Genetics and Environment

1.5.1.1 Preface to publication

Sex-based differences in HCM have gained attention in recent years. There is overwhelming evidence that sex differences are vital in explaining some of the clinical heterogeneity seen among HCM patients. The following literature review discusses sex differences in HCM.
The published paper forms a section of this chapter. Author contributions are outlined in the following author contribution statement.

Reference

Butters A[1-3], Lakdawala NK[4], Ingles J[1-3,5]. Sex Differences in Hypertrophic Cardiomyopathy: Interaction with Genetics and Environment. Curr Heart Fail Rep. 2021 Oct;18(5):264-273. doi: 10.1007/s11897-021-00526-x. Epub 2021 Sep 3. PMID: 34478112; PMCID: PMC8484093.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the study	AB, JI
Literature search	AB
Drafting the manuscript	AB
Review and critical comments on manuscript	All authors
Responding to reviewer comments	AB, JI
Coordination of submission and publication	AB, JI

As the candidate for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Candidate Name: Alexandra Butters

Signature: Date: 29/06/2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the

authorship attribution statements above are correct.

Supervisor Name: A/Prof Jodie Ingles

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Sources of funding
A/Prof Ingles is the recipient of an NHMRC Career Development Fellowship (no. 1162929).

Disclosures
A/Prof Ingles receives research grant support from Myokardia Inc. Dr Lakdawala has received modest consulting incomes from Myokardia Inc., Bristol Myers Squibb, Pfizer Inc. and Tenaya.

Current Heart Failure Reports (2021) 18:264–273
https://doi.org/10.1007/s11897-021-00526-x

SEX AND GENDER ASPECTS IN HEART FAILURE (G. FIGTREE AND C. ARNOTT, SECTION EDITORS)

Sex Differences in Hypertrophic Cardiomyopathy: Interaction With Genetics and Environment

Alexandra Butters[1,2,3] · **Neal K. Lakdawala**[4] · **Jodie Ingles**[1,2,3,5]

Accepted: 22 July 2021 / Published online: 3 September 2021

Abstract

Purpose of Review We explore the sex-specific interaction of genetics and the environment on the clinical course and outcomes of hypertrophic cardiomyopathy (HCM).

Recent Findings Women account for approximately one-third of patients in specialist HCM centres and reported in observational studies. As a result, evidence informing clinical guideline recommendations is based predominantly on risk factors and outcomes seen in men. However, disease progression appears to be different between the sexes. Women present at a more advanced stage of disease, are older at diagnosis, have higher symptom burden, carry greater risk for heart failure and are at greater risk of mortality compared to men. Women are more likely to be gene-positive, while men are more likely to be gene-negative. The risk of sudden cardiac death and access to specialised care do not differ between the sexes.

Summary Reporting sex-disaggregated results is essential to identify the mechanisms leading to sex differences in HCM.

Keywords Hypertrophic cardiomyopathy · Sex · Genetics · Environment

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease affecting 0.5% of the adult population [1]. It is a primary myocardial disorder characterised by left ventricular hypertrophy, which is not explained by abnormal loading conditions such as hypertension [2]. Clinical heterogeneity is common with many individuals experiencing minimal symptoms, while others can develop heart failure, atrial fibrillation or sudden cardiac death (SCD). Traditionally HCM has been considered a monogenic disease caused by variants in genes encoding the cardiac sarcomere [3]. Despite ongoing research over three decades, the underlying genetic basis of HCM is incompletely understood. At least 40% of HCM patients have no family history and no causative variant identified [4, 5]. In some cases, patients remain gene-elusive despite evidence for heritability, and there is growing awareness that a proportion of HCM is due to a complex interplay between genetic and environmental factors. Indeed, results from two recent genome-wide association studies in large HCM cohorts suggest that common variants account for an important proportion of heritability (SNP heritability ~ 30%), suggesting a role for genetic and non-genetic factors in penetrance and expression [6, 7].

Sex-based differences in HCM have gained attention in recent years. There is overwhelming evidence that sex is vital in explaining some of the clinical heterogeneity seen among HCM patients. Despite an autosomal dominant inheritance pattern, males consistently account for approximately 60% of published cohorts

This article is part of the Topical Collection on *Sex and Gender Aspects in Heart Failure*

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[8–15]. Indeed, the penetrance of sarcomere variants may be lower in women; however, diagnostic biases and under-recognition of HCM may also play a role. We know women are older at the time of diagnosis, have a higher prevalence of an obstructive phenotype, worse diastolic function and more severe heart failure symptoms at presentation [8–15]. Women are also more likely to be sarcomere variant positive (sarcomere-positive), i.e. have a disease-causing variant identified in one of the eight key sarcomere genes as opposed to men who are more likely to be sarcomere variant negative (sarcomere-negative), i.e. no family history and no causative variant identified [4]. Under-representation of females in cohort studies means that the evidence informing clinical guideline recommendations is based predominantly on risk factors and outcomes seen in men (Fig. 3). We aim to explore the sex-specific interaction of genetics and the environment on the clinical course and outcomes of HCM.

Sex Differences in Natural History and Clinical Course

Prevalence

HCM is typically caused by variants in genes encoding proteins of the sarcomere and inherited as an autosomal dominant trait. Therefore, the prevalence of HCM in the general population is expected to be equal among the sexes. However, studies frequently report an overrepresentation of males, ranging from 55 to 70% [8–15]. This has not changed over the last three decades, or since the first significant publication, examining sex differences in HCM (37% vs. 38%, $p = 0.34$) [14]. Over the life course, the male predominance persists across all age groups until 60 years of age when females become the more prevalent group [9, 10, 16]. It is unknown if this finding represents decreased disease penetrance in women or reflects differences in clinical recognition, slower disease progression due to the protection of sex hormones or lack of sex-specific diagnostic criteria (Fig. 1).

Fig. 1 Complex relationship of factors that determine the sex-related differences in hypertrophic cardiomyopathy

Age at Diagnosis

Women have consistently been shown to be older at diagnosis than men, ranging from 6 to 13 years [9, 10, 12–14]. Furthermore, the age of diagnosis differs by sex depending on genotype. A recent study of $n = 5873$ patients (38% female) by the Sarcomeric Human Cardiomyopathy registry (SHaRe) found that the age of diagnosis varies by sex, genotype and disease gene. Sex-specific differences in age at diagnosis were more pronounced in sarcomere-negative HCM than sarcomere-positive HCM (7.1 years older vs. 3.6 years older) [14]. Differences also existed depending on the gene status of sarcomere-positive patients. Those with a disease-causing variant in *MYBPC3* or a thin-filament gene (i.e. *TNNT2*, *TNNI3*, *TPM1*, *ACTC*) were 4.8 and 6.7 years older than men at diagnosis, respectively ($p < 0.02$). Age at diagnosis was comparable for patients with variants in *MYH7*. Using age at diagnosis as a proxy for penetrance, the authors suggested that sex does not appear to modify the penetrance of *MYH7* variants to the same degree as variants in other sarcomere genes. Age at diagnosis has been explored in those with left ventricular outflow tract obstruction. Olivotto et al. studied $n = 969$ HCM patients (41% female) and found the delay to diagnosis even more striking with female patients, who were up to 14 years older than their male counterparts [9].

Symptoms at Initial Evaluation

Women are more likely to present with heart failure symptoms, particularly exertional dyspnoea, fatigue, palpitations and chest pain and New York Heart Association (NYHA) functional class III to IV, compared to men [8–15]. Determinants of initial HCM diagnosis differ between men and women [9, 13]. A multi-centre study of $n = 2123$ HCM patients (38% female) [13] found that heart failure symptoms led to diagnosis more commonly in women (51% versus 41% in men, $p = 0.02$), while in men, the diagnosis often followed a routine medical assessment that identified an abnormal electrocardiogram or heart murmur (32% versus 23%, $p < 0.01$). There was no difference in the proportion of patients diagnosed due to clinical screening for family history. Specifically, 73% of women were symptomatic in NYHA functional classes II to IV, characteristically with exertional dyspnoea or fatigue, with or without chest pain compared to 53% of men ($p < 0.001$).

Morphology

While measurement of maximum left ventricular (LV) wall thickness, LV cavity size and left atrial diameter is often statistically greater in males, these are typically not clinically significant differences [9, 12–14]. The female heart is smaller than males after correction for body surface area (BSA) [17–21], and corrected SHaRe registry data showed that women have a greater maximal LV wall thickness, LV cavity size and left atrial diameter [14]. HCM diagnostic criteria do not currently account for the fact that women have relatively smaller hearts than men [2, 22]. This means that women require relatively more hypertrophy to reach current diagnostic criteria of at least 15-mm maximal LV wall thickness. Smaller heart size may explain the delay in recognising the disease and advanced symptoms seen in women. No difference exists in the prevalence of severe hypertrophy (LV wall thickness ≥ 30 mm) [9, 12, 13].

Despite similar degrees of hypertrophy, women more commonly demonstrate dynamic LV outflow tract obstruction (≥ 30 mmHg) than men [9, 12–14]. In a study of $n = 2123$ patients (38% female), Rowin et al. found that women more commonly demonstrated dynamic LV outflow tract obstruction caused by mitral valve systolic anterior motion than did men (65% versus 57%; $p < 0.001$). LVOT obstruction was present most commonly at rest (45% versus 31% in men; $p < 0.001$) and less frequently provoked with stress exercise echocardiography (20% versus 26% in men; $p < 0.001$) [13]. Similarly, Geske et al. showed that women have a higher LVOT gradient when compared with men [36 (IQR 10–81) vs. 23 (IQR 0–61) mmHg] and were more likely to demonstrate resting obstruction when compared with men (54% vs. 46%, $p < 0.0001$). Consistent with these results, women had more mitral regurgitation (moderate to high in 28% vs. 18%, $p < 0.0001$) [12]. This finding is likely related to the smaller cavity size in females. This hypothesis is supported by the SHaRe registry, which found that after controlling for LV end-diastolic diameter, the sex-based difference in LVOT obstruction did not persist ($p = 0.17$) [14].

Echocardiographic assessment of diastolic function using spectral and tissue Doppler imaging was available for a subset of patients in two studies [12, 14]. Both studies found relatively impaired diastolic function in women. Data from the SHaRe registry highlight that although the peak early diastolic septal tissue Doppler velocity (e') was lower in women (6.1 ± 2.6 versus 7.0 ± 2.7, $p < 0.0001$), the peak velocity of early diastolic inflow (E wave; 83.5 ± 32.7 versus 75.0 ± 23.7, $p < 0.0001$) and the ratio of E/e' (15.6 ± 9.2 versus 11.9 ± 6.3, $p < 0.0001$) were higher in women [14]. However, these differences were not significant after controlling for age and hypertension. LVOT obstruction is a powerful predictor of adverse outcomes due to heart failure. Therefore, the more frequent occurrence of obstruction in women likely contributes to their more significant adverse outcomes.

Clinical Outcomes

Female patients with HCM have a greater risk than male patients of progression to NYHA III–IV symptoms and heart failure. Recent data showed that incident heart failure was 87% more common in women even after controlling for obstruction, systolic dysfunction, hypertension and age (HR 1.87, CI 1.48–2.32, $p < 0.001$). The authors hypothesised that the increased burden of heart failure in women may be related to LVOT obstruction and diastolic function differences. Systolic dysfunction is infrequent in HCM and not more common in women [14, 23]. Understanding contributors to the higher frequency of heart failure in women is essential to improve overall outcomes (Fig. 2).

Rowin et al. showed that during follow-up, women are more likely to develop advanced drug-refractory heart failure (NYHA class III/IV) (53% versus 35% men; $p < 0.001$). This diagnosis occurred on average 6 years later than in males. However, women were still relatively young, with 48% of women < 50 years of age at onset (range, 14–49) [13]. They also found that despite greater use of beta-blockers, verapamil and disopyramide in women, the rate of progression to heart failure was higher in women (4.8%/year versus 3.4%/year; HR 1.6, CI 1.2–2.1, $p < 0.001$). Advanced heart failure symptoms secondary to outflow obstruction were reported in the same number of women and men.

Consistent with the higher prevalence of heart failure, women were more likely to undergo septal reduction therapy, including septal myectomy and alcohol septal ablation. Improvement to NYHA I–II symptoms following these procedures has been reported to be similar between the sexes [24]. Of the 283 women and 347 male patients who underwent septal myectomy with NYHA III–IV symptoms, 94% of female patients and 97% of male improved to NYHA I–II by the end of follow-up ($p = 0.18$). Septal reduction therapy is therefore just as successful in controlling LVOT obstruction in both women and men and has likely resulted in a reduction in mortality from heart failure associated with HCM.

Arrhythmias

Patients with HCM are at high risk of developing ventricular and atrial arrhythmias. Female sex was not a predictor of SCD events (i.e. SCD, resuscitated out-of-hospital cardiac arrest or appropriate ICD shock for ventricular tachycardia or ventricular fibrillation) (HR 0.69, CI 0.51–0.94, $p < 0.05$) or atrial fibrillation (AF) (HR 0.72, CI 0.60–0.87, $p < 0.001$) [5]. The prevalence of SCD events is similar between the sexes in numerous studies. One study found that the occurrence of SCD events is 5% (0.9%/year) in women and 6% (0.8%/year) in men (HR 0.92; CI 0.6–1.5, $p = 0.73$) [13]. Accordingly, the investigators also found no difference in primary prevention ICD insertions between the sexes. Despite women being older at diagnosis, the age at ICD implantation also did not differ.

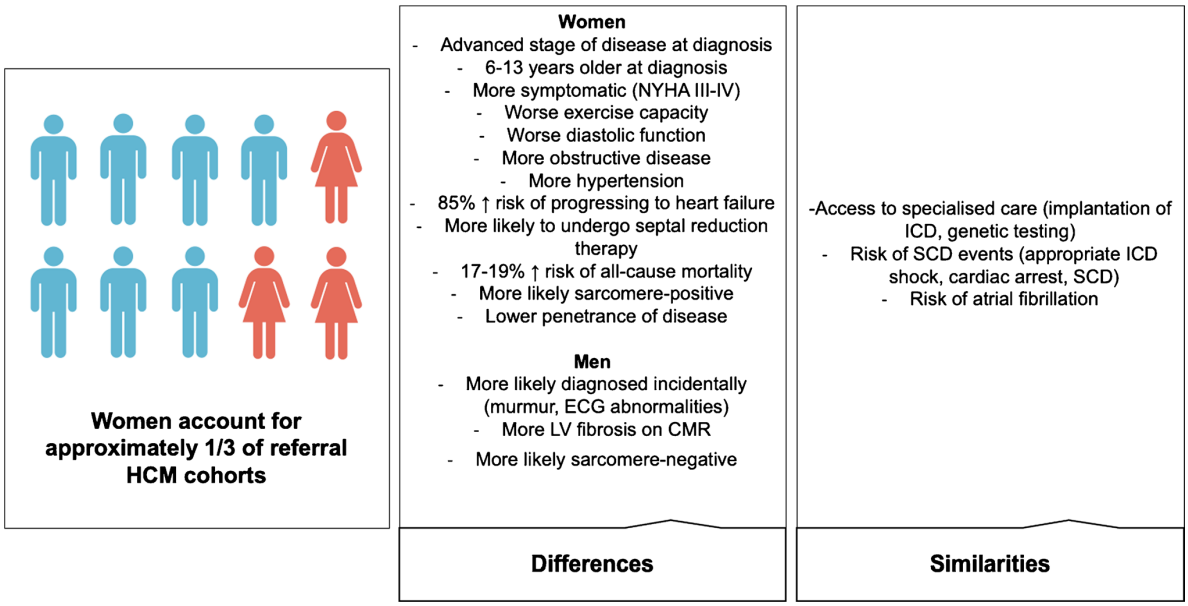

Fig. 2 Sex differences in clinical profile, genotype and outcomes in hypertrophic cardiomyopathy

The prevalence of symptomatic AF is similar between women and men at baseline [9, 12–14]. Lakdawala et al. found the incidence of AF to be 22% in both sexes. However, in a multivariate model controlling for age, left atrial diameter and hypertension, they found women to be at a moderately increased risk of incident AF (HR 1.21, CI 1.01–1.46, $p = 0.04$).

Mortality

Several studies have been conducted in HCM patients to determine whether women with HCM have poorer outcomes than men with HCM [9, 11–15, 25]. Geske et al. recently reported outcomes of HCM patients attending the Mayo Clinic. This study had a large sample size of 3673 adult patients (45% female) and the most extended follow-up so far [10.9 years (IQR 7.4–16.2 years)]. Women had a significantly higher incidence of all-cause mortality than both men with HCM and the general population. Furthermore, female sex was associated with all-cause mortality in multivariable and propensity-matched analyses (HR 1.17, 95% CI 1.07–1.25; $p < 0.001$).

A multi-centre report by the European HCM Outcome Investigators' collaboration included 4893 patients (36% women) with a follow-up of 6.2 years (IQR, 3.1–9.8 years) [25] showed that excess mortality was greater among women than men (HR 1.19, 95% CI:1.06–1.30; $p = 0.007$). This persisted into the later decades of life, whereas mortality rates in men aged more than 65 years were similar to the general population. The authors suggest that this may be related to increased heart failure death rates (HR 1.44, 95% CI:1.25–1.59; $p < 0.001$). The SHaRe registry, $n = 5873$ patients (38% female) and median of 7.7 years (IQR, 3.1–15.4 years) follow-up, reported that all-cause mortality is 50% higher in women after controlling for age, sarcomere status, systolic dysfunction (LVEF < 50%) and left atrial diameter [HR, 1.50 (95% CI, 1.13–1.99), $p < 0.01$] [14]. Of all deaths, 43% were HCM-related (caused by heart failure, sudden death or stroke), with a similar frequency of causes in women and men. This study provides further insights into HCM-specific mechanisms contributing to decreased survival in women. It is not a reflection of the greater prevalence of sarcomeric HCM as the difference persisted after controlling for genotype. Excess mortality is also not due to stroke or sudden death. The investigators, therefore, suggest that excess heart failure is the most plausible mechanism.

Other studies have not found any difference in all-cause mortality. In a 2005 study of 969 patients with HCM (41% female), female sex was associated with progression to severe heart failure and death from heart failure or stroke [1.50 (1.11–2.00), $p < 0.001$], but not all-cause mortality [9]. Similarly, a recent study of 2123 patients (38% female) referred to the Tuft's HCM Institute between 2001 and 2016 [13] showed that age-adjusted all-cause mortality did not differ between women and men (HR 1.32, 95% CI 0.92–1.91, $p = 0.13$). Both studies report small samples and may lack statistical power to see an effect.

Genetic Basis of HCM

There is growing awareness that a proportion of HCM is due to a complex interplay between genetic and environmental factors. Incomplete penetrance and variable expressivity are hallmark features of the disease, and recent work has begun to identify the role of common genetic variants and non-genetic/environmental factors in contributing to the phenotype.

Sarcomere-Positive HCM

HCM is traditionally a Mendelian disease inherited in an autosomal dominant manner. Eight sarcomere genes have the most robust gene-disease association (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC*, *MYL2* and *MYL3*) [3].

Women are more likely to have a disease-causing variant identified and are therefore more likely to be sarcomere-positive. Sex differences related to genetics have recently been comprehensively reported, with genetic testing performed in 3788 (65%) patients. Females were 17% more likely to have a causative sarcomere variant ($p < 0.001$). The distribution of disease genes, however, did not vary between the sexes. As expected, the most commonly involved genes were *MYBPC3* and *MYH7* [14]. A study by Terauchi et al. investigated the penetrance of MYBPC3 mutations in 61 patients from 28 families [26]. They found that disease penetrance in those ≤ 40 years of age was 92% in males and 67% in females. Another retrospective study of sarcomere variant carriers found that male sex and an abnormal ECG are associated with a higher risk of developing HCM [27]. The underlying mechanisms for sex-based differences in the penetrance and expression of sarcomeric HCM are not well understood.

Sarcomere-Negative HCM

A subgroup of patients with HCM have no genetic variant identified despite comprehensive genetic testing, and family screening does not identify an affected relative even after decades of clinical surveillance [4, 5]. This subgroup has a different clinical course compared with sarcomere-positive HCM, being typically male, diagnosed later in life, with milder LV hypertrophy and more likely to have a pre-existing diagnosis of hypertension [4–7]. This sub-group of patients likely have an underlying complex disease aetiology. Recent genome-wide association studies performed in

large international cohorts of patients with HCM have shown SNP heritability up to 34%, and individuals with sarcomere-negative HCM are more likely to be in the extreme polygenic risk score (PRS) distributions [4].

Non-genetic Risk Factors in HCM

Hypertension

Based on the high population prevalence, many HCM patients will develop hypertension in their lifetime. Hypertension at diagnosis with HCM is an independent predictor of outcomes, irrespective of ethnicity, sex or age (HR 2.02, 95% CI 1.05 to 3.88, $p=0.036$) [28]. Women are, however, more likely to carry a prior diagnosis of hypertension compared to men (49% vs. 43%, $p=0.0010$) [12]. Hypertension has been found to be a predictor of sarcomere-negative status (OR, 2.80; 95% CI, 1.57–5.00; $p=0.0005$) [4], and more recently a one standard deviation increase in diastolic blood pressure (11.3 mmHg) was shown to confer a four-fold risk of HCM (OR 3.93, 95% CI 2.86–5.41, $p=3.74\times10^{-16}$) independent of other factors [6]. The authors noted that this is more than double the risk typically observed for other diseases associated with diastolic blood pressure [29–33] and raises the possibility that sarcomere-negative HCM may constitute an exaggerated response to hypertension in genetically susceptible individuals. Given known differences in frequency of sarcomere variants and prevalence of hypertension between sexes, how this effect might be different for males and females should be explored.

Obesity

Obesity is a significant public health problem and a known risk factor for cardiovascular disease. Notwithstanding the limitations of using body mass index (BMI) to define obesity, this problem is widespread among adult patients with HCM, with > 70% being pre-obese with a BMI > 25 and > 30% obese with a BMI > 30 [34–36]. Obesity is common in paediatric patients, with approximately 30% having a BMI in the 99th percentile for age and sex [37]. Excess weight is associated with increased left ventricular hypertrophy and mass and is a prognostic factor for rapid clinical progression and worsening of heart failure symptoms [34, 36]. LV obstruction is more common in obese patients and observed in more than 50% with body mass index > 30 [35]. Obese patients were less likely to carry a sarcomere gene variant; however, obesity increases the risk of significant outcomes in both sarcomere-positive and sarcomere-negative patients. Little is known about sex-specific differences in obesity in HCM. Lakdawala et al. found no difference in BMI between males and females ($p=0.72$) [14]; however, Geske et al. found a statistically significant, but very small difference (28.3 ± 6.7 female versus 28.9 ± 5.0 male, $p=0.0053$) [12]. Due to the influence of obesity on the progression of HCM, more research is required to identify if differences between men and women exist.

Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) is exceedingly prevalent in HCM, affecting 32–70% of patients [38, 39]. This wide range is likely due to differences in the definition of sleep-disordered breathing. Patients with OSA are older, have more hypertension and have greater limiting symptoms and exercise capacity [38–41]. OSA has also been associated with a greater prevalence of AF (40% vs. 11%, $p=0.005$) [39] and apnoea-hypopnea index is associated with an increased risk of non-sustained VT (OR 1.07; 95% CI 1.02–1.12; $p=0.001$) [40]. Sex-related differences in OSA have not yet been investigated, likely due to the small sample size of the published cohorts. More research is needed to investigate if sex differences exist.

Pregnancy

Pregnancy places substantial burden on the cardiovascular system, triggering increased circulating blood volume, stroke volume and heart rate [42]. Pregnancy in HCM is well tolerated, however, does still carry maternal and foetal risks [43–47]. A meta-analysis of data from 9 cohorts, including 237 women and 408 pregnancies, demonstrated that most pregnancies in women with HCM are uneventful [44]. The risk of maternal mortality is low occurring in only 0.5% of cases. Complications or worsening symptoms occurred in 29% of cases and included heart failure in up to 30% and arrhythmias in up to 48%. A study of 276 women with cardiovascular disease, including 8% cardiomyopathies, found that the risk of adverse outcomes during delivery is very low (3–4%) with no differing risk between natural delivery and caesarean section [42]. In terms of foetal outcomes, the risk of premature birth is increased occurring in 26% of births. Foetal mortality is comparable to the general population [44]. The impact of parity is largely unknown in HCM; however, there is an association between the number of pregnancies and the risk of cardiovascular disease [48]. This warrants further investigation in HCM cohorts.

Health Disparities

Health disparities likely play an important role in the differences observed between males and females. However, little is known about the impact of health disparities concerning sex in HCM. Women have been consistently

underrepresented in published studies, leaving a paucity of pre-specified sex-disaggregated evidence (i.e. evidence where sub-group analyses are specified by sex before data collection enabling the collection, analysis and reporting of data separately for men and women). This has resulted in clinical guideline recommendations informed largely by male-dominated datasets. Figure 3 shows the proportion of women and men in original research studies used to form 2020 AHA/ACC guideline recommendations to diagnose and treat patients with hypertrophic cardiomyopathy. Of the 219 studies, 13 provided no breakdown of sex within their cohorts, despite controlling sex in their analysis. Five studies with 100% female participants were specifically investigating pregnancy. Women tended to be over-represented in studies relating to septal reduction therapies. The single study with 100% males consisted of $n = 10$ males and investigated VT ablation in HCM. While this is possibly representative of disease prevalence, ensuring relatively equal numbers of males and females in studies is necessary to identify why these differences exist. It is crucial that we more often report sex-disaggregated results for all studies on HCM, even if this is not the study's primary focus. It is also essential to highlight that women from non-European populations are likely to have more severe outcomes and will be even more underrepresented in the literature. These data can inform research and patient care to the benefit of both sexes.

Despite this lack of female data in clinical guidelines, limited disparities have been identified in access to HCM-based management once women present to a specialised HCM clinic. Women are just as likely to have an implantable cardioverter defibrillator (ICD) [9, 12–14]. Additionally, despite the older age at diagnosis, women undergo ICD implantation at a similar age to men [13]. ICD use in HCM differs from population-based studies, which have consistently found women to be less likely to receive an ICD, even after adjustment for known clinical confounders, including age and comorbidities [49, 50]. No bias exists between the sexes in regards to genetic testing [14]. Rates of septal reduction therapy do, however, appear to differ. Women are more likely to undergo alcohol septal ablation and septal myectomy [51, 52]. This likely relates to the increased age at diagnosis and higher prevalence of obstruction and heart failure symptoms in females.

Physiological or Social Causes?

The causes of sex-specific differences in HCM are primarily unknown. Several mechanisms have been suggested relating to underlying physiological differences and societal factors. The endocrine effects of sex hormones are the most widely accepted physiological mechanism for sex differences in a range of cardiovascular diseases [53–55]. The contribution

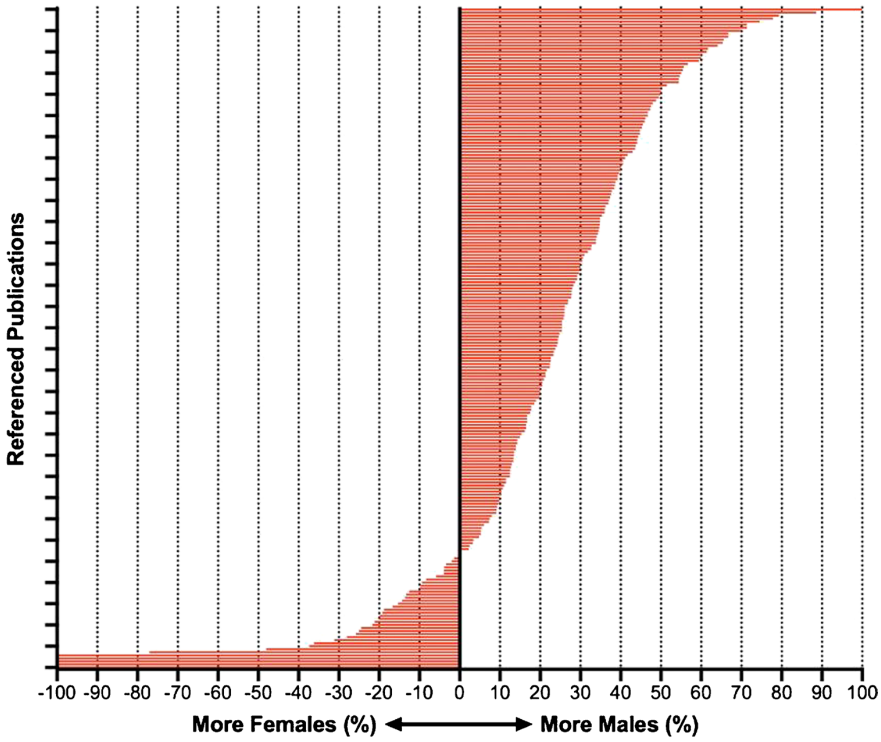

Fig. 3 Sex distribution of original research studies used to inform clinical recommendations in the 2020 AHA 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy [2]

of hormonal and reproductive factors to HCM risk is still incompletely understood. There is limited evidence in humans and animal models that sex hormones may delay development of the HCM phenotype or its clinical manifestations. Oestrogens have a protective role in hypertrophy [56], while exposure of cardiomyocytes to androgens may result in hypertrophy [57]. This suggests that pre-menopausal women may be protected against developing HCM compared to men. One study suggested that the high number of younger women reported (< 50 years) with heart failure is perhaps suggestive that menopause is unlikely to play a part in HCM [13].

Delayed diagnosis and worse symptoms in females may also relate to the assumption that men are more at risk of cardiovascular disease than women [58].

Within the general cardiovascular literature, there is little awareness or prioritisation of cardiovascular disease by women. A 2018 survey by the Australian National Heart Foundation found that compared to 55% of men, only 39% of women aged > 45 years in Australia had undergone a heart risk assessment by a health professional in the prior 2 years [59]. Additionally, physician bias contributes to less cardiovascular disease screening and reduced primary and secondary prevention in women than men. An Australian study showed that women were 12% less likely to be screened for cardiovascular disease in general practice than men. Women were, therefore, less likely to have risk factors assessed to allow overall risk to be determined [60]. However, following initiation of patient care at HCM referral centres, there is generally no sex-based differences in HCM-specific management [9, 12–14]. More work is required to elucidate the mechanisms contributing to the sex differences observed in HCM.

Future Directions

Underlying these sex differences in HCM is a lack of sex-disaggregated research. Women have been consistently under-represented in studies representing only a third of published cohorts, including those informing clinical recommendations (Fig. 3). While this is likely representative of disease prevalence, ensuring a relatively equal sex representation is necessary to identify why these differences exist. Understanding the cause of these differences will only be possible if the evidence is presented for both sexes via pre-specified sex-disaggregated analysis. This requires planning sub-group analyses before data collection and enabling the collection, analysis and reporting of data separately for men and women, even if this is not the study's primary focus. These data have the potential to inform research and patient care to the benefit of both sexes.

Conclusion

There is overwhelming evidence that sex is vital in explaining some of the clinical heterogeneity seen among HCM patients. Better female representation coupled with sex-disaggregated analysis is essential to understanding these differences. Further understanding of the sex-specific interaction of genetics and the environment, especially the impact of reproductive health and sex hormones on HCM outcomes, will be largely beneficial.

Acknowledgements J. Ingles is the recipient of an NHMRC Career Development Fellowship (no. 1162929).

Declarations

Conflict of Interest J. Ingles receives research grant support from MyoKardia Inc. N. Lakdawala has received modest consulting incomes from MyoKardia Inc., Bristol Myers Squibb, Pfizer Inc. and Tenaya.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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1.6 Review: Sex Disparities in Sudden Cardiac Death

1.6.1.1 Preface to publication

SCD is a tragic event common to each of the genetic heart diseases. The following literature review discusses sex differences in sudden cardiac death.
The published paper forms a section of this chapter. Author contributions are outlined in the following author contribution statement.

Reference

Butters A[1,2], Arnott C[3,4], Sweeting J[1], Winkel BG[5], Semsarian C[2,3,6], Ingles J[1,2,3]. Sex Disparities in Sudden Cardiac Death. Circ Arrhythm Electrophysiol. 2021 Aug;14(8): e009834. doi: 10.1161/CIRCEP.121.009834. Epub 2021 Aug 16. PMID: 34397259.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the study	AB, CA, JI
Literature search	AB
Drafting the manuscript	AB
Review and critical comments on manuscript	All authors
Responding to reviewer comments	AB, JI
Coordination of submission and publication	AB, JI

As the candidate for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Candidate Name: Alexandra Butters

Signature: Date: 29/06/2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Supervisor Name: A/Prof Jodie Ingles

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Sources of funding
A/Prof Ingles is the recipient of an NHMRC Career Development Fellowship (No. 1162929). Prof Semsarian is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (No. 1154992).

Disclosures
A/Prof Ingles receives research grant support from Myokardia, Inc.

Circulation: Arrhythmia and Electrophysiology

REVIEW

Sex Disparities in Sudden Cardiac Death

Alexandra Butters, MPH; Clare Arnott, MBBS, PhD; Joanna Sweeting, PhD; Bo Gregers Winkel, MD, PhD; Christopher Semsarian, MBBS, PhD, MPH; Jodie Ingles, PhD, MPH

ABSTRACT: The overall incidence of sudden cardiac death is considerably lower among women than men, reflecting significant and often under-recognized sex differences. Women are older at time of sudden cardiac death, less likely to have a prior cardiac diagnosis, and less likely to have coronary artery disease identified on postmortem examination. They are more likely to experience their death at home, during sleep, and less likely witnessed. Women are also more likely to present in pulseless electrical activity or systole rather than ventricular fibrillation or ventricular tachycardia. Conversely, women are less likely to receive bystander cardiopulmonary resuscitation or receive cardiac intervention post-arrest. Underpinning sex disparities in sudden cardiac death is a paucity of women recruited to clinical trials, coupled with an overall lack of prespecified sex-disaggregated evidence. Thus, predominantly male-derived data form the basis of clinical guidelines. This review outlines the critical sex differences concerning epidemiology, cause, risk factors, prevention, and outcomes. We propose 4 broad areas of importance to consider: physiological, personal, community, and professional factors.

Key Words: arrhythmias ■ death ■ pregnancy ■ resuscitation ■ sex ■ sudden ■ women

Sudden cardiac death (SCD) is the leading cause of cardiovascular mortality, responsible for approximately half of all deaths.[1] SCD refers to the sudden unexpected death after a cardiac arrest either within 1 hour of symptom onset, if event witnessed, or within 24 hours of having been observed alive and symptom-free, if unwitnessed.[2] The overall incidence of SCD is estimated to be considerably lower among women than in men.[3] As a result, women are underrepresented in studies leading to a paucity of prespecified sex disaggregated-evidence (ie, evidence where sub-group analyses are specified by sex before data collection enabling the collection, analysis and, reporting of data separately for men and women; Table 1). The limited data available suggest that the underlying pathophysiology and risk factors of SCD are different in women than in men. Further, the phenotype causing SCD can be influenced by both sex and the age at death.[10,15] These differences have important implications for clinical management and guideline development to the benefit of both sexes.

Here, we describe sex differences in the epidemiology, risk factors, management, and outcomes of SCD. We refer to sex as the biological definition, with gender; the broader connotations concerning identity at a societal level, not discussed here. We propose 4 broad areas of importance for consideration: physiological, personal, community, and professional factors (Figure 1). We explore the sex-related differences in SCD, the reasons contributing to these disparities, and highlight key areas where women remain consistently underrepresented.

EPIDEMIOLOGY

The annual incidence of SCD in women is estimated to be almost half that of men.[4,11,12] As such, the overall lifetime risk of SCD differs between the sexes, with men having a significantly higher risk than women, estimated at 10.9% for men and 2.8% for women.[3] The incidence of SCD increases with age in both sexes; however, the 2:1 ratio remains throughout life.[3] The difference in incidence is most striking in the middle-age, premenopausal, and early postmenopausal years, where men are at 3.9 times greater risk of SCD than women of the same age.[3] This gap seems to have decreased over the last 30 years through improved awareness of prevention measures for coronary artery disease (CAD) and sudden cardiac

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Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

Nonstandard Abbreviations and Acronyms

BCPR	bystander cardiopulmonary resuscitation
CAD	coronary artery disease
CVD	cardiovascular disease
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter defibrillator
MI	myocardial infarction
MINOCA	MI with nonobstructive coronary artery disease
SCD	sudden cardiac death
STEMI	ST-elevation MI
VF	ventricular fibrillation

arrest.[8] The decline of SCD in women has been significantly slower than in men (34% decline in men versus 10% in women over 30 years).[14,16–18] While the reasons for this changing trend are still primarily unknown, numerous investigators speculate that this reflects the altered sex distribution in prevalence and mortality from CAD.[19–21] This suggests that modifiable risk factors for ischemic heart disease are more predominant in men, and perhaps the underlying cause of SCD is predominantly heterogeneous in women.

In those <35 years, SCD is a tragic and devastating event occurring in previously healthy individuals, significantly impacting the community and families involved.[9] SCD contributes ≈7% of all deaths in this age group, with an average age-dependent incidence of 1.3 cases per 100 000 persons per year.[9,22,23] In the young, males continue to have a higher incidence of SCD than women at 1.8 versus 0.7 cases per 100 000 persons.[9]

It is important to note that there are inherent challenges in estimating the incidence of SCD, depending on the data source used for case ascertainment, the definitions used, and the methods employed.[24–26] The probability of establishing the underlying cause of SCD is contingent on many factors, including whether postmortem examination is undertaken, local cardiac pathology expertise, the extent of cardiac investigations in the victim or family, and the availability of genetic testing.[24,26] Study design is also crucial here, with most studies reporting single-center experiences or post-mortem series, which each have their own bias. Without diminishing the importance of previously published articles, understanding their limitations is critical and helps us piece together key insights into sex disparities in SCD.

PHYSIOLOGICAL FACTORS

Cause of SCD

The cause of SCD differs depending on the age of the cohort (Figure 2). In the young, SCD predominately occurs in the setting of structural heart disease (hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy, arrhythmogenic cardiomyopathy, and myocarditis), or inherited arrhythmia syndromes (long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia). In contrast, the most common clinical finding associated with SCD in older cohorts is CAD.

SCD in the young

Many of these causes of SCD in the young have a genetic basis and are generally inherited in an autosomal dominant pattern.[9] Approximately 40% of SCDs in this age group have no cause of death detected on postmortem examination and are attributed to inherited arrhythmia syndromes.[9,10] A prospective study of SCD of those aged 1 to 35 years conducted between 2010 and 2012 in Australia and New Zealand (28% female) found that

Table. Sex Differences in Key Published SCD Studies

	Baseline study dates	Country of cohort	Participants (% female)	Age range at baseline, y	Sex-specific multiple-adjusted relative risks provided
Kannel et al[4]	1948–86	United States (Framingham Cohort)	94 (29)	30–62	Yes
Chugh et al[5]	1989–98	United States	45 (63)	>20	No
Chugh et al[6]	2002–2005	United States (Ore-SUDS study)	556 (36)	…	No
Adabag et al[7]	2001–2004	United States	10 (19)	25–60	No
Niemeijer et al[8]	1990–2010	Netherlands (Rotterdam Study)	304 (32)	≥55	No
Bogle et al[3]	1948–2001	United States (Framingham Cohort)	197 (53)	28–62	No
Bagnall et al[9]	2010–2012	Australia and New Zealand	137 (28)	1–35	No
Winkel et al[10]	2000–2009	Denmark	205 (32)	1–35	No
Haukilahti et al[11]	1998–2017	Finland (Fingesture Cohort)	1238 (21)	…	No
Albert et al[12]	1976–1998	United States (Nurse's Health Study Cohort)	244 (100)	30–55	Yes
Bertoia et al[13]	1993–1998	United States (Women's Health Initiative)	418 (100)	50–79	Yes
Mehta et al[14]	1996–2000	United States (Women's Ischemia Syndrome Evaluation (WISE) Study]	904 (100)	>18	Yes

SCD indicates sudden cardiac death.

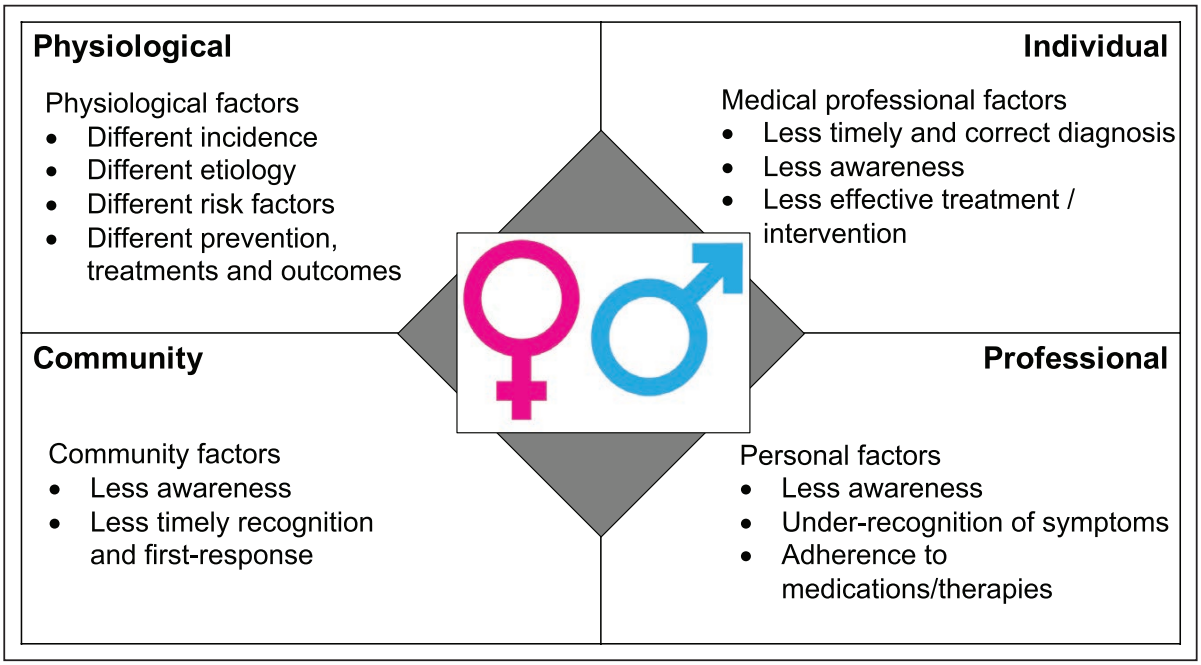

Figure 1. Contributors to sudden cardiac death disparities between the sexes.

while males in this age group are twice as likely to experience SCD, female sex was associated with death being unexplained after postmortem investigation, that is, likely attributed to an inherited arrhythmia syndrome.[9] This has been reported across numerous other studies.[22,23]

Sex-specific differences in the outcomes of inherited arrhythmia syndromes are increasingly recognized. In long QT syndrome, adult women carry a greater risk of *torsades de pointes* and SCD than men. The risk of arrhythmia differs based on sex, age, and genotype. Before puberty, boys with long QT type 1 (ie, *KNCQ1* variants) have an increased risk of arrhythmia than girls, but the risk of arrhythmia is similar between the sexes for individuals with long QT type 2 (*KCNH2*) or long QT type 3 (*SCN5A*). After puberty, the risk of experiencing arrhythmias in long QT type 1 reverses, with female patients being at higher risk than men. A difference also emerges in long QT type 2, with females being at higher risk of arrhythmias.[27] Brugada syndrome predominately affects males. As such, males also have a considerably higher risk of arrhythmic SCD in adult men than women.[28] A pooled analysis of 4140 Brugada syndrome patients (22% female) showed that symptomatic male patients have a significantly higher risk profile than asymptomatic male patients. This difference was not evident in the female population.[29] Studies about sex differences in the risk of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia are rare, include a limited number of patients, and the results differ.[30,31]

A study of all SCD in Denmark between 2000 and 2009 (32% female), the first to specifically investigate sex differences in SCD in the young, found the incidence rate of SCD in young men is twice that for women.[10] This incidence rate was not explained by a difference in risk profile between the sexes. Therefore, traditional risk factors may only play a minor role in young SCD, as many are lifestyle-related and manifest later in life. The age at death, the ratio of postmortem examination performed, and the causes of SCD were also mostly comparable between the sexes. SCD from potentially inherited cardiac conditions, while not statistically significant, was less prevalent in women than men (80% versus 86%). Female sex may therefore protect from arrhythmias, diminishing the risk of SCD in those with both primary cardiomyopathies and inherited arrhythmia syndromes. This protection may be explained by the presence of the endogenous hormone estrogen. The estrogen-effect has been well-described in CAD, where estrogen is considered to have both long-term and rapid effects. These effects occur via an atheroprotective effect on lipid serum concentrations and direct action on blood vessels.[32–37] Less is known about the role of estrogen in SCD. Studies investigating estrogen's role in the development of ventricular arrhythmias have found both proarrhythmic and antiarrhythmic effects in females or both sexes,[38–43] indicating a need for further investigation.

Coronary Artery Disease

The most common clinical finding associated with SCD at all ages, especially in older cohorts, is CAD (Figure 2).[19] The proportion of SCD due to CAD is lower in women

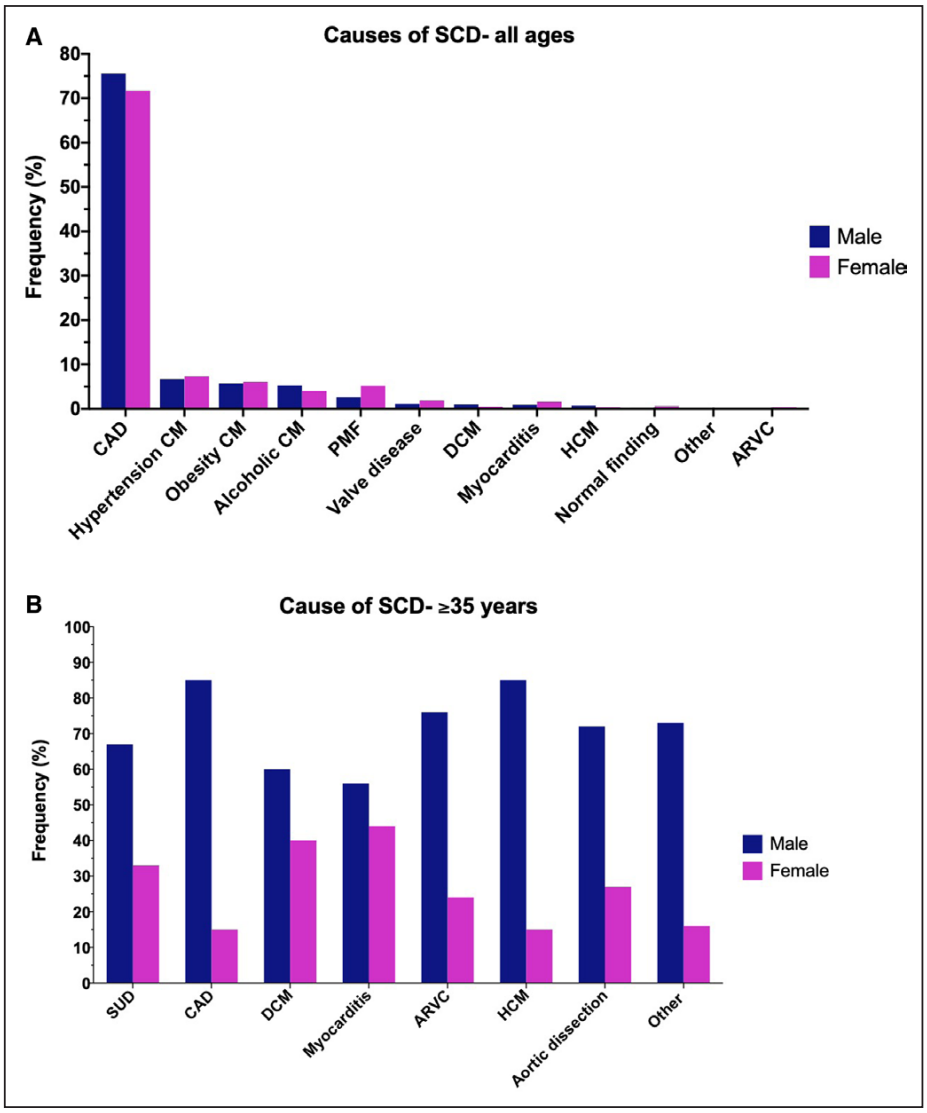

Figure 2. Causes of sudden cardiac death (SCD) by sex.
A, Cause of sudden cardiac death (SCD): all ages (modified from Haukilahti et al[11] with permission. Copyright ©2019. Wolters Kluwer Health, Inc.); **B**, Cause of SCD: <35 y (modified from Bagnall et al[9] with permission. Copyright ©2016. Massachusetts Medical Society). Reprinted with permission from Massachusetts Medical Society). ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; PMF, primary myocardial fibrosis; and SUD, sudden unexplained death.

(estimated at 45%–50% versus 80%–90% in men) and[44–46] women are also less likely to have an established diagnosis of cardiac disease before SCD.[4,6,7,12,46,47] In the Framingham study (29% female), 37% of women with SCD had prior cardiac disease compared with 56% of men.[4] Conversely, the Nurse's Health Cohort Study (100% female) found that 69% of women did not have a documented CAD event before SCD, with only 10% having symptoms of an acute coronary syndrome in the week preceding death.[12] As such, SCD is often the first indication of CAD among women, with women being more at risk of unrecognized myocardial infarction.[5,11]

Myocardial infarction (MI) with nonobstructive CAD (MINOCA) also leads to SCD. MINOCA is common among young, women, and Black patients.[48] The prevalence of MINOCA in SCD is unknown. An extensive multicenter registry of 322 523 patients presenting with MI (35% female) found that 6% (n=18 918) had MINOCA.[48] MINOCA was more common in women than men (n=11 763 (11%) versus n=7155 (3%); $P<0.0001$). This difference was not dependent on whether the patients present with ST-elevation MI (STEMI) or no-ST-elevation MI. Patients with MINOCA have fewer traditional risk factors for CAD and are

instead more likely to have end-stage renal disease, prior heart failure, atrial fibrillation or flutter, or chronic lung disease.[48] Patients with MINOCA are at a risk of mortality than MI with obstructive CAD.[48]

The underlying cause of SCD is heterogeneous in women. In the Fingesture population, Haukilahti et al[11] examined sex differences in autopsy findings and archived ECG available for a subset of patients (21% female). They concluded that women were less likely to have CAD than men (72% versus 76%, P=0.005), although the rate of CAD in women was much higher than previously reported. They found that SCD in women is more likely associated with a nonischemic cause of death when compared with men, with women more likely to have primary myocardial fibrosis, albeit not a common finding with limited clinical significance (5% versus 3%, P<0.001).

Mechanism

Sex differences have been identified in the prevalence of the presenting arrhythmia underlying sudden cardiac arrest. Irrespective of age, women are more likely than men to present in pulseless electric activity or asystole than ventricular tachycardia or ventricular fibrillation (VF).[6,49,50] This has implications as resuscitation rates are significantly lower in pulseless electric activity/asystole than ventricular tachycardia/VF (2% versus 25%).[51] Accordingly, female patients are less likely to survive to be discharged from hospital (6% versus 25%).[49] The observed difference in presenting cardiac arrhythmia is likely due to ventricular tachycardia/VF being the most commonly observed arrhythmias in CAD, which is significantly more prevalent in men.

A recent Danish case-control study of patients presenting with STEMI who underwent percutaneous coronary intervention found that while men are more likely to have a STEMI, they are even more likely to experience VF within the first 12 hours of symptoms of STEMI before percutaneous coronary intervention than women (86% versus 14% [P=0.004], respectively).[52] The higher prevalence of VF before percutaneous coronary intervention may explain results from the CONCORDANCE acute coronary syndrome registry, which recruited 2183 men and 715 women with STEMI in Australia and found that women are less likely to receive invasive management, revascularization, or preventative medication at discharge.[53]

Circumstances

The circumstances surrounding SCD events differ by sex. In both young and older cohorts, several studies have identified differences in the place of death, with women less likely to die in a public place than men.[10,11] This may be explained by variation in activity at the time of death. Men are more likely to experience their death during exercise than women, who are more likely to die in their sleep.[10,11] The difference in place of death has also been thought to reflect the higher frequency of witnessed deaths in men.[11,54,55] A recent study of individuals aged 1 to 35 years found the opposite, with women more likely to experience a witnessed death.[10,56] This disparity between age groups may be explained by differences in housing situation as older women may be more likely to live alone, thereby contributing to many unwitnessed events.[10] This further highlights issues of ascertainment biases.

Risk Factors

There is currently no consensus on sex-specific risk factors in SCD. This lack of unanimity is due to the inconsistent investigation of risk factors and a lack of sex-disaggregated evidence, resulting from study designs only including women with no comparison group, data not being presented stratified by sex, and risk statistics not being presented (Figure 3). As such, it is difficult to estimate the difference between men and women concerning risk factors. Investigation of risk factors is limited as it requires the individual to have been followed up in some way before their SCD. The few studies that have investigated symptoms before SCD have found that 50% to 70% of victims sought medical attention before their SCD.[57–60] The unexpected nature of SCD in previously healthy individuals means data about previous symptoms are often not available and has led to the reliance on large prospective observational cohorts of healthy individuals followed up over lengthy periods.

In investigating risk factors for SCD, many studies examine the same factors associated with CAD. Traditional CAD risk factors are somewhat predictive of SCD in women.[4,12–14,61] Diabetes and hypertension are substantial risk factors for SCD in both sexes. Smoking is also a significant risk factor, with higher cigarette use per day leading to increased risk of SCD.[4,12–14] Conversely, cessation of smoking seems to reduce this risk.[12] The Nurse's Health Study found that SCD risk linearly decreased over time after quitting in women and was equivalent to that of a never smoker after 20 years of cessation.[62] Depression has also been identified as a possible risk factor, although the reason for this is not well understood.[14] Antidepressants have been reported to increase the risk of SCD as they can promote arrhythmias.[47] The Nurse's Health Study found antidepressant use was associated with SCD in women independent of the level of depression as rated on the Mental Health Index-5 Score.[63]

ECG markers have been investigated, with females more likely to have a normal or near-normal ECG before death.[11] This suggests that ECG risk markers may not perform as well in women as in men. Prolonged QTc and

	Kannel et al. 1998[4] n=325		Albert et al. 2003[12] n=244			Bertoia et al. 2012[13] n=418		Mehta et al. 2017[14] n=904
	35-64 yrs	65- 94 yrs	Overall	≤60yrs	>60yrs	Without prior CHD	Overall	Overall
Previous MI	-	-	-	-	-	-	=4.71	-
Heart failure	-	-	-	-	-	-	=3.51	-
Hypertension	=1.9 =1.7	=2.2 =1.7	=2.49	=1.94	=3.07	=1.55	=1.46	-
Diabetes	=3.9 =1.5	=4.0 =1.3	=2.93	=2.56	=3.09	=2.20	=2.00	=2.69
High Cholesterol	=1.3 =1.4	=1.0 =1.4	=1.04	=1.35	=0.9	-	-	-
Obesity	-	-	=1.8	=1.31	=1.8	=1.12	=1.15	-
Depression	-	-	-	-	-	-	-	=2.28
Atrial fibrillation	-	-	-	-	-	=1.39	-	-
LVH by ECG	=1.0 =1.4	=2.6 =3.7	-	-	-	-	-	-
Smoking Ever	=1.0 =1.4	=0.9 =1.2	-	-	-	-	-	=3.01
Past	-	-	=1.49	=1.73	=1.38	-	-	-
Current	-	-	-	-	-	=3.12	=2.26	-
Current (1-14/day)	-	-	=2.83	=2.85	=2.85	-	-	-
Current (15-24/day)	-	-	=2.40	=1.94	=2.86	-	-	-
Current (≥25/day)	-	-	=4.13	=4.86	=3.31	-	-	-

Figure 3. Multiple-adjusted relative risks for risk factors of sudden unexplained death in studies where relative risk was reported.
MI indicates myocardial infarction; and LVH, left ventricular hypertrophy.

marked QTc were associated with an increased risk of SCD in both sexes, although the finding's prevalence was significantly higher in men. Left ventricular hypertrophy with repolarisation abnormalities was significantly more common in women than men (10.2% versus 4.6%, *P*=0.038). Supporting data from the Framingham study that found left ventricular hypertrophy on ECG was associated with a higher risk of SCD in women than men.[4] Multiple case-control studies have also found ECG early repolarization pattern to be associated with arrhythmic mortality and an increased risk of VF.[64,65] early repolarization is characterized as an elevation of the QRS-ST junction (J point), exhibited as QRS notching or slurring (J wave) in multiple inferior or lateral leads, with or without ST-segment elevation.[65] Patients with early repolarization are more likely to be male, have a history of either unexplained syncope or sudden cardiac arrest during sleep, and have a shorter QTc interval than those without ER.[64]

Prevention and Management

If we extrapolate from the cardiovascular disease literature, sex disparities exist in both prevention and management. Underpinning these differences is the misapprehension that men are more at risk of cardiovascular disease than women, although we know it is the leading cause of death and life years lost in women.[66] Factors contributing to these disparities include personal, community, and professional factors (Figure 1).

Personal factors

There appears to be little awareness and prioritization of cardiovascular disease by women and competing prioritization of family commitments.[67–69] A Canadian study that surveyed 1654 women found that women lack knowledge of heart disease symptoms and risk factors, and significant proportions are unaware of their own risk status.[67] Fewer than 50% knew the main symptoms of heart disease, with only 43% indicating chest pain and 38% dyspnea or difficulty breathing while exercising as cardiac symptoms. Pain radiating to the shoulder, neck, or arm was recognized by only 29%. Awareness of symptoms increased by education and age and was associated with knowing someone with heart disease. In terms of cardiovascular disease risk factors, <50% of surveyed women knew that smoking was a risk factor, and fewer than 25% named hypertension or high cholesterol as risk factors. Based on medical history, 62% of those at high risk rated their risk as low to moderate.

The National Heart Foundation HeartWatch Survey showed that in 2018, 55% of men, compared with just 39% of women aged >45 years in Australia, had undergone a heart risk assessment by a health professional within the preceding 2 years.[70] It has been suggested that women are less likely to visit their general practitioner for a regular check-up or even to have symptoms investigated, perhaps due to the significant role women play within the family structure, resulting in them putting their

own needs behind family and other commitments.[67,69] SCD is often the first presentation of symptoms. Increasing awareness of cardiovascular disease symptoms and risk factors among women can still be a powerful prevention and management tool, improving the health of women, their children, and families.

Community Factors

There are significant differences concerning the first response to a cardiac arrest. The prompt delivery of bystander cardiopulmonary resuscitation (BCPR) increases the chance of survival from out-of-hospital cardiac arrest. Despite this, numerous studies from several countries (Sweden, Denmark, The Netherlands, Japan, and the United States) have found that women who experience a cardiac arrest are less likely to receive BCPR than men.[54,55,71–75] This disparity appears to differ based on the location of the arrest. Blewer et al recently assessed the sex differences in receiving BCPR stratified by location of cardiac arrests in the US Resuscitation Outcomes Consortium (n=19 331, mean age 64 years) and found that men were more likely to receive BCPR in a public location than were women (44% versus 35%; OR, 1.27 [95% CI, 1.05–1.53]). This difference did not exist if the arrest occurred at home, where first responders were more likely to be family members.[72]

This finding was replicated in the All-Japan Utstein Registry of the Fire and Disaster Management Agency (n=84 734, median age 78 years), finding that in public locations, women aged 18 to 64 years were less likely to receive BCPR (OR, 0.86 [95% CI, 0.74–0.99]) and that when witnessed by a nonfamily member, women are less likely to receive BCPR regardless of age group.[73] The authors speculate that in Japan, BCPR on a woman can result in accusations of sexual assault and suggest that cultural factors specific to Japan may influence bystander attitudes toward patients of different sex.

Perman et al[76] recently examined the potential barriers and contributing factors to delivering BCPR to women in public in the general US population. Barriers to providing BCPR included misperceptions about women in medical distress, fear of causing harm due to the perceived frailty of women, and social norms about the touching or exposure of a women's chest, which could lead to accusations of sexual assault.[76] Underpinning this disparity is the use of male mannequins in cardiopulmonary resuscitation courses and focus on the physical technique of performing cardiopulmonary resuscitation rather than the psychosocial aspects of providing CPR.[74] Further research is required to determine if these results are consistent in other cultures and countries. Community awareness and training are vital to combating these perceptions and improving the rates of BCPR in females.

Professional Factors

Medical practitioners are prone to the misapprehension that men are more at risk of cardiovascular disease than women.[69] Physician bias contributes to less cardiovascular disease screening and reduced primary and secondary prevention in women than men.[77] An Australian study showed that women were 12% less likely to be screened for cardiovascular disease in general practice than men. Women were, therefore, less likely to have risk factors assessed and recorded to allow overall risk to be determined.[77]

Primary prevention of SCD continues to be a public health challenge since most deaths occur in those with no overt evidence of disease before death. Numerous studies have established the role of implantable cardioverter defibrillator (ICD) in the prevention of SCD. Women have been consistently underrepresented in clinical trials accounting for just 10% to 30% of cohorts, and many of these studies were underpowered to draw any conclusions on the benefit of ICD therapy in women.[78–85] Large meta-analyses of ICD trials has revealed either no benefit to women or a similar survival between the sexes.[86,87] Women are less likely to receive an ICD for primary prevention of SCD, even after adjustment for known clinical confounders such as age and comorbidities.[88,89] This may be due to women being less likely than men to have a clinical diagnosis of structural heart disease, including left ventricular dysfunction or CAD before SCD, both due to inadequate assessment and different risk factors based on sex. As a result, fewer women are eligible for prophylactic ICD placement based on current guidelines and therefore may not have equal opportunity for prevention.[6]

Symptoms of acute coronary syndrome are less likely to be identified in women than men, with women more likely to have an incorrect diagnosis on initial presentation resulting in poorer outcomes. Kim et al[50] showed that despite improving cardiac arrest trends over 10 years, women continued to have high in-hospital mortality compared with men. This is likely related to women being less likely to receive therapeutic procedures such as coronary angiography, percutaneous coronary interventions, and targeted temperature management after presenting with a cardiac arrest. Women are more likely to present with atypical symptoms before their cardiac arrest, leading to delayed presentation and under-recognition of ischemia as cardiac arrest cause. This further highlights the lack of sex-specific risk factors to apply effective prevention strategies (Figure 3).

SCD in Specific Groups

SCD in Athletes

SCD is the leading medical cause of death in athletes. Current estimates of the incidence of SCD in athletes

vary widely due to differing methodologies and populations. A recent review found an overall incidence of 1 in 50 000 to 80 000 young athletes to be a reasonable estimate.[90] In this subpopulation, male athletes are consistently found to be at greater risk, with competitive women athletes found to have a 10 times lower risk of SCD.[91,92] It was thought that this difference in risk was explained by the higher proportion of male athletes participating in competitive sports. However, the increasing number of women participating in competitive sports has not resulted in an increased incidence of SCD in female athletes.[92] In athletes <35 years of age, SCD is commonly due to inherited or congenital cardiac disorders. The most common cause is HCM, followed by anomalous coronary arteries.[93] In athletes >35 years, most SCD events are due to CAD.

Cardiomyopathies may be less prevalent in women athletes than men. Finocchiaro et al[94] showed that in a cohort of athletes (n=367 [8%]), 55% of females who died during exercise had a structurally normal heart, indicating an inherited arrhythmia syndrome rather than cardiomyopathy or CAD, perhaps due to hormonal differences. The higher concentrations of androgens in males may accelerate disease progression of cardiomyopathy or CAD, while women may be protected from ventricular arrhythmias due to the presence of estrogens.[95]

Another cause of SCD in athletes with no underlying cardiac disease is Commotio cordis.[96] Commotio cordis occurs overwhelmingly in adolescent boys and young men. The US Commotio cordis registry, which included 128 confirmed cases, found a mean age of 14 years and 95% were male.[97] It is usually caused by a projectile such as a baseball, football, or hockey puck but can also be caused by the blow of an elbow or other body part.[96] Being less developed, the thorax of an adolescent is likely more prone to this injury. The predominance of males is partially explained by more significant number of males involved in sports where commotio cordis is a risk. However, it has been speculated that there may also be some sex-related biological susceptibility to chest wall impact.[96]

Intense exercise training promotes cardiac physiological adaptation, which includes electrical, structural and, functional changes. Cardiac physiological adaptation is comparable between female and male athletes. Irrespective of sex, athletes generally show an increase in left ventricular wall thickness and size compared with controls. Large cardiac dimensions can sometimes overlap with those observed in patients with cardiomyopathy. These dimensions are more likely in male athletes, as female athletes generally exhibit smaller absolute cardiac dimensions due to their smaller body size.[92] As such, only 1% of females show dimensions consistent with dilated cardiomyopathy or HCM, compared with 14% of male athletes who have left ventricle dimensions consistent with dilated cardiomyopathy and 2% with left ventricular wall thickness consistent with HCM.[95]

Ethnicity may play a role in SCD in athletes, with black athletes more likely to experience SCD.[98] Unfortunately, sex differences within this subgroup have not yet been investigated. A recent multicenter prospective cohort study of Blacks (n=3832) and Whites (n=11 237) participating in the Atherosclerosis Risk in Communities Study found that the increased risk associated with race was more pronounced in women than in men.[99] Therefore, this warrants further investigation within the athlete subgroup.

SCD in Pregnancy

Approximately 1 in 30 000 pregnancies are complicated by maternal cardiac arrest.[100] However, the prevalence of SCD in pregnancy and the postpartum period is largely unknown. The most extensive autopsy series of maternal SCD referred to a specialized cardiac pathology center identified 80 cases of SCD that occurred during pregnancy or the postpartum period.[101] The mean age of the cohort was 30 years with a range of 16 to 43 years. A third of deaths occurred in women aged >35 years.[102]

The leading causes of SCD in pregnant women were unexplained (54%) and cardiomyopathies (14%). Other causes included dissection of the aorta or its branches (9%), valvular disease (4%), and congenital heart disease (3%). In long QT syndrome, women are at a decreased risk of cardiac events during pregnancy, particularly those with the long QT type 1 genotype. However, the risk of arrhythmic events in the 9-month postpartum period is elevated, especially among women with the long QT type 2 genotype.[103] Mothers with long QT syndrome are at twice the risk of miscarriage (fetal death at ≤20 weeks gestation; 16% versus 8%) and 8 times the risk of stillbirth (fetal death >20 weeks; 4% versus 0.5%).[104] Arrhythmic risk is not elevated during pregnancy or the postpartum period in Brugada syndrome or catecholaminergic polymorphic ventricular tachycardia.[105]

The contribution of cardiomyopathies to maternal death is well known, although the prevalence is likely over-estimated,[106] with dilated cardiomyopathy and peripartum cardiomyopathy well described. However, the above autopsy study also found HCM and arrhythmogenic cardiomyopathy to be implicated.[101] Further, obesity-related cardiomyopathy has been linked to an increased risk of SCD during pregnancy,[107] and subsequently autopsy data showed that 43% of women were obese (BMI, ≥30) and 16% overweight (BMI, 25–30).[101]

Lack of Prespecified Sex-Disaggregated Data

Underlying these differences is a lack of sex-disaggregated research. Women are thoroughly under-represented in most studies representing around 30% of

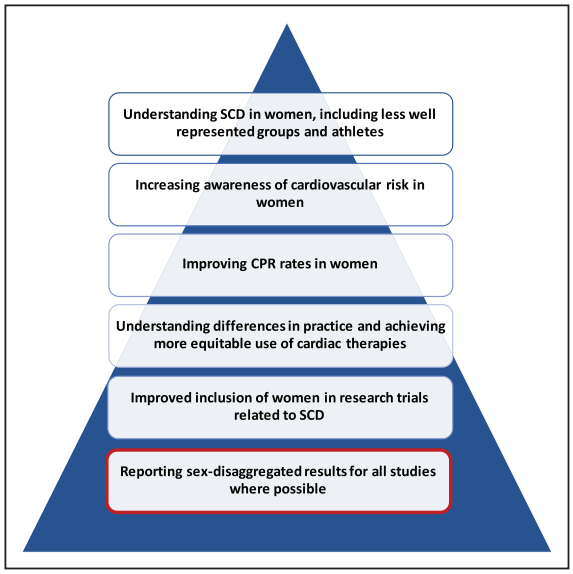

Figure 4. Key areas to be addressed in future sudden cardiac death (SCD) research.
CPR indicates cardiopulmonary resuscitation.

study cohorts (Table 1). While this is likely representative of disease incidence, ensuring a relatively equal number of males and females are included in studies is necessary to identify why these differences exist. Studies that include only females lack a comparison group, and as such, it is difficult to conclude if there is an association between female sex and the variables investigated. Therefore, it is crucial to report sex-disaggregated results for all studies on SCD, even if this is not the study's primary focus. These data have the potential to inform research and patient care to the benefit of both sexes.

CONCLUSIONS

Sex differences affect almost every aspect of SCD, from epidemiology, cause, risk factors, prevention, and outcomes. Adequate female representation with prespecified sex-disaggregated analysis is essential to elucidating the different pathology and risk factors contributing to this tragic event between the sexes. Further understanding of barriers to cardiopulmonary resuscitation and acute care in women will also be beneficial. Awareness campaigns at the community/physician level may also improve SCD understanding and outcomes (Figure 4).

ARTICLE INFORMATION

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Sources of Funding

Dr Semsarian is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (No. 1154992). Dr Ingles is the recipient of an NHMRC Career Development Fellowship (No. 1162929).

Disclosures

Dr Ingles receives research grant support from Myokardia, Inc.

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1.7 Racial, ethnic and ancestral differences among patients with genetic heart diseases

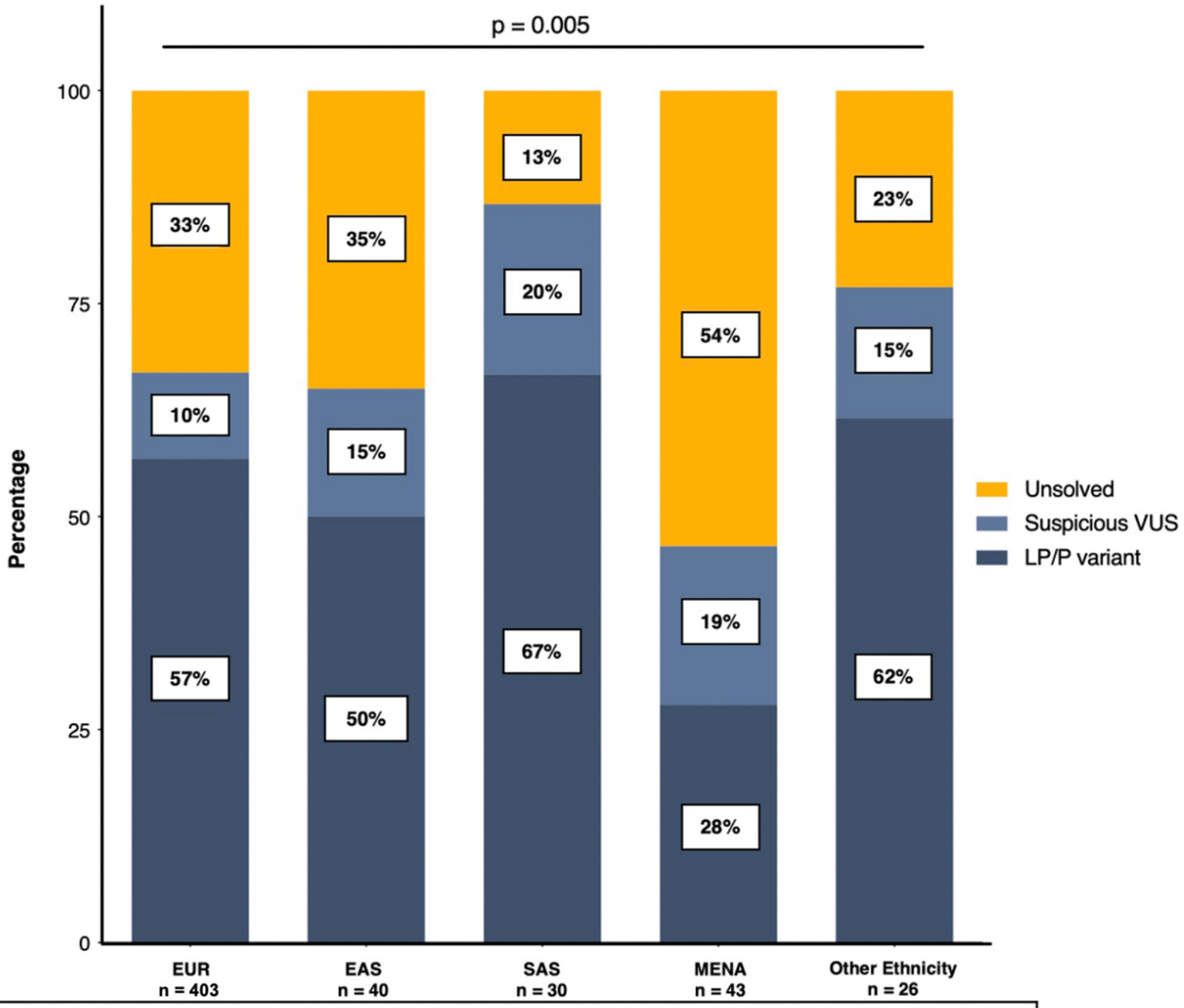
Most genomic research has predominantly centred around populations of European ancestry, thereby exhibiting a limited scope that fails to represent the diverse global population.[60] This narrow concentration on a fraction of the world's population has resulted in pronounced racial and ethnic disparities in cardiovascular disease and genomics.[6] As the field of precision medicine gains broader acceptance, these disparities are poised to intensify significantly.

Race and ethnicity are social constructs.[6,61] The definitions of different racial and ethnic categories are not fixed and instead reflect a combination of elements such as appearance, culture, religion, and language, which are influenced by evolving societal and political conventions.[6,61] In comparison, ancestry refers to information about the people an individual is biologically descended from, including their genetic relationships.[6,61] Self-reported race and ethnicity has been shown to correlate with genetic ancestry.[62]

Understanding racial, ethnic and ancestral differences in genetic heart diseases is crucial for several reasons. Firstly, genetic heart diseases can manifest differently in different populations, and certain genetic variants may be more prevalent in specific ethnic groups.[16,63–67] Secondly, the lack of diversity in genomic research has resulted in unequal access and outcomes from genetic testing.[68] Historically, research studies and reference databases have predominantly included individuals of European ancestry, leading to a limited understanding of genetic variations in other populations.[69–71] This lack of diversity hinders the accuracy and utility of genetic testing for individuals from non-European backgrounds, perpetuating health disparities and exacerbating the existing inequalities in

healthcare.[70] By understanding these differences, healthcare providers can tailor their approach to diagnosis and treatment, leading to better patient outcomes.

Several examples highlight the importance of ethnic diversity in genetic research on heart diseases. For instance, studies have shown higher rates of variants of uncertain significance in Middle Eastern, North African, and South Asian patients with HCM (Figure 1.3).[71] Similarly, another study found an excess of variants of uncertain significance in Singaporeans with HCM compared to Europeans. This study additionally showed that variants in specific HCM genes, *TNNI3* and *TNNT2*, were more prevalent Singaporean patients.[67] A greater yield of uncertain variants in diverse patient populations is due to historical poor representation in genomic research leading to a lack of reference population data for these populations.[68,70] Thus, it is difficult to ascertain if a variant is causative of disease or just a single nucleotide polymorphism.



Population (%)					
Cohort in Audit	75.5	7.4	5.5	7.9	4.8
Greater Sydney	67.9	14.8	6.4	6.0	4.9

Figure 1.3: The role of genetic testing in diagnosis and care of genetic heart conditions in a specialised multidisciplinary clinic
(Figure from work by our team that I contributed to[71])
Abbreviations: EUR, European; EAS, East Asian; SAS, South Asian; MENA, Middle Eastern and Northern African; VUS, variant of uncertain significance; LP/P, likely pathogenic or pathogenic.

Within specific regions, such as The Netherlands, Iceland, and South Africa, founder variants of HCM have been identified.[63–65] These founder variants refer to specific genetic variants that become prevalent in certain populations due to historical factors such as isolated populations or migration patterns.[72] Identifying founder variants adds another layer of complexity to the genetic landscape of HCM, emphasising the need for comprehensive genetic screening and personalised approaches to diagnosis and treatment for patients worldwide.[72] Founder variants offer unique insights into genotype-phenotype correlations and can have significant clinical implications for service delivery in those regions.

Differences in the clinical presentation of HCM have been reported, with self-reported Black race associated with a younger age at diagnosis, fewer sarcomere variants, and an increased burden of heart failure.[16,17] These findings highlight the impact of ethnicity on the clinical presentation and outcomes of genetic heart diseases, emphasising the need for ethnic diversity in research to improve diagnostic accuracy and develop targeted interventions.

Understanding ethnic differences in genetic heart diseases is crucial for accurate diagnosis, treatment, and improved outcomes for individuals from diverse backgrounds. The lack of diversity in genomic research has contributed to unequal access and outcomes from genetic testing. Including individuals from different ancestral backgrounds in research studies can enhance our understanding of the genetic basis of heart diseases, facilitate the identification of causal variants, and promote more equitable healthcare for all populations.

1.8 Socioeconomic status and genetic heart diseases

Socioeconomic status plays a crucial role in the development of CVD encompassing various economic and sociological factors such as education, income, occupation, and overall wealth.[7] Numerous studies have demonstrated the significant impact of lower socioeconomic status in a range of CVDs, including coronary heart disease,[73] heart failure,[74] stroke,[75] myocardial infarction and cardiovascular mortality.[76]

Considering the important impact of lower socioeconomic status on CVD, only a small number of studies have explored this in genetic heart diseases. Ingles et al. highlighted the impact of socioeconomic status on health service use and clinical outcomes in the context of HCM.[20] Socioeconomic Indexes for Areas were used to group patients by socioeconomic status (Index of Socioeconomic Advantage and Disadvantage), education and occupation (Index of Education and Occupation) and remoteness (Geographic remoteness areas), developed by the Australian Bureau of Statistics and based on an individual's residential postcode.[77] The findings revealed an overrepresentation of highly educated patients from advantaged and major metropolitan areas, indicating that the accessibility of specialty clinics played a vital role in determining the clinical course of HCM (Figure 1.4).

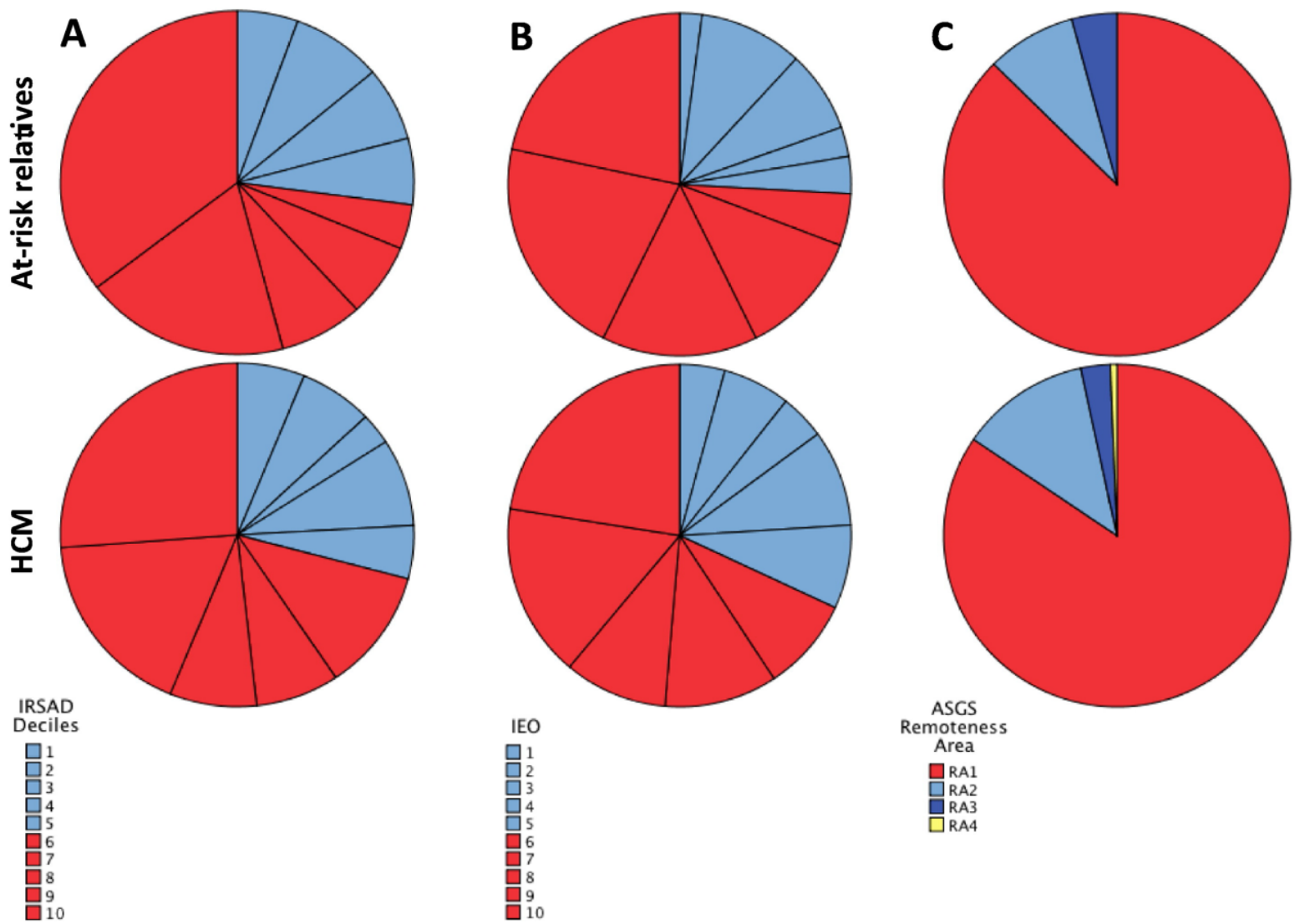


Figure 1.4: Distribution of (A) Index of Socioeconomic Advantage and Disadvantage (IRSAD), (B) Index of Education and Occupation (IEO) and (C) Geographic remoteness areas for consecutive patients attending a specialised clinic.[20]
Abbreviations: RA1, Major cities of Australia; RA2, Inner regional; RA3, Outer regional; RA4, Remote; and RA5, Extremely remote

A second study, also focusing on HCM, examined outcomes among HCM patients in the Yale New Haven Health System between June 2011 and December 2017.[21] Patients were assigned to lower or higher socioeconomic status groups based on their medical insurance status. In addition, patients were categorised depending on whether they received care at a specialty HCM clinic or general cardiology care. The study found that low socioeconomic status patients without access to specialised HCM care had significantly higher all-cause mortality than their high socioeconomic status counterparts. However, when patients were referred to a specialised HCM care team, no significant differences in the clinical course were observed between different socioeconomic statuses. This suggests that access to specialty care is crucial in mitigating the adverse effects of socioeconomic disparities in HCM.

These studies underscore the importance of considering socioeconomic factors in genetic heart diseases, particularly regarding access to specialty care. Addressing socioeconomic disparities and ensuring equitable access to specialised healthcare resources can potentially improve outcomes and reduce mortality rates among socioeconomically vulnerable individuals with genetic heart diseases like HCM.

1.9 Routinely collected data sources

Routinely collected health data are information collected for a non-research purpose and repurposed to examine real-world health trends in research studies.[78] These data allow investigation of common patterns of care for the whole population, including an individual's interactions with the healthcare system over time. Few studies use routinely collected healthcare data in genetic heart diseases research, and we have previously shown poor alignment with clinical diagnoses and available International Classification of Disease

diagnosis codes.[79] To overcome this issue, disease registry data may be linked to routinely collected data.

1.10 Hypothesis and aims

The underlying hypotheses of this PhD are:

1. Women with genetic heart diseases have a different clinical course and outcomes than men. A lack of pre-specified sex-disaggregated evidence and limited recruitment of women to studies means current management guidelines comprise data primarily derived from men.
2. Current evidence guiding management and care for genetic heart disease patients is derived primarily from European cohorts. More diverse patient populations will provide important genetic insights and are critically needed to ensure equitable, evidence-based care for all patients.
3. Reference population datasets primarily consist of participants of European ancestry. This over-representation limits our ability to classify variants in patients from poorly represented populations, giving rise to a lower diagnostic yield of confident disease-causing variants and risk of misclassification.
4. Routinely collected health data linked to a registry database could provide essential insights into real-world disparities in healthcare access for patients with genetic heart diseases.

Based on these hypotheses, the specific aims of my PhD studies (summarised in Figure 5) are to:

- **Aim 1:** Use sex-disaggregated analysis to examine sex-specific risk factors of outcomes in a consecutive cohort of hypertrophic cardiomyopathy (HCM) patients from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) (approx. 8000 patients).

- **Aim 2:** Explore the clinical profile and health disparities in a consecutive cohort of multi-ethnic patients with HCM who attended a specialised multidisciplinary clinic.
- **Aim 3:** Determine if *TNNT2*; NM_001001430.2: c.571-1G>A is a variant causative of inherited cardiomyopathies and sudden cardiac death, or a common single nucleotide polymorphism found in Polynesian populations.
- **Aim 4:** Describe health care utilisation and health disparities among patients enrolled in the Australian Genetic Heart Disease Registry using routinely collected health datasets (NSW Admitted Patient Data Collection, Emergency Department Data Collection and Registry of Births, Deaths and Marriages).

These hypotheses and aims collectively focus on equitably improving the overall management and health outcomes in individuals with genetic heart diseases.

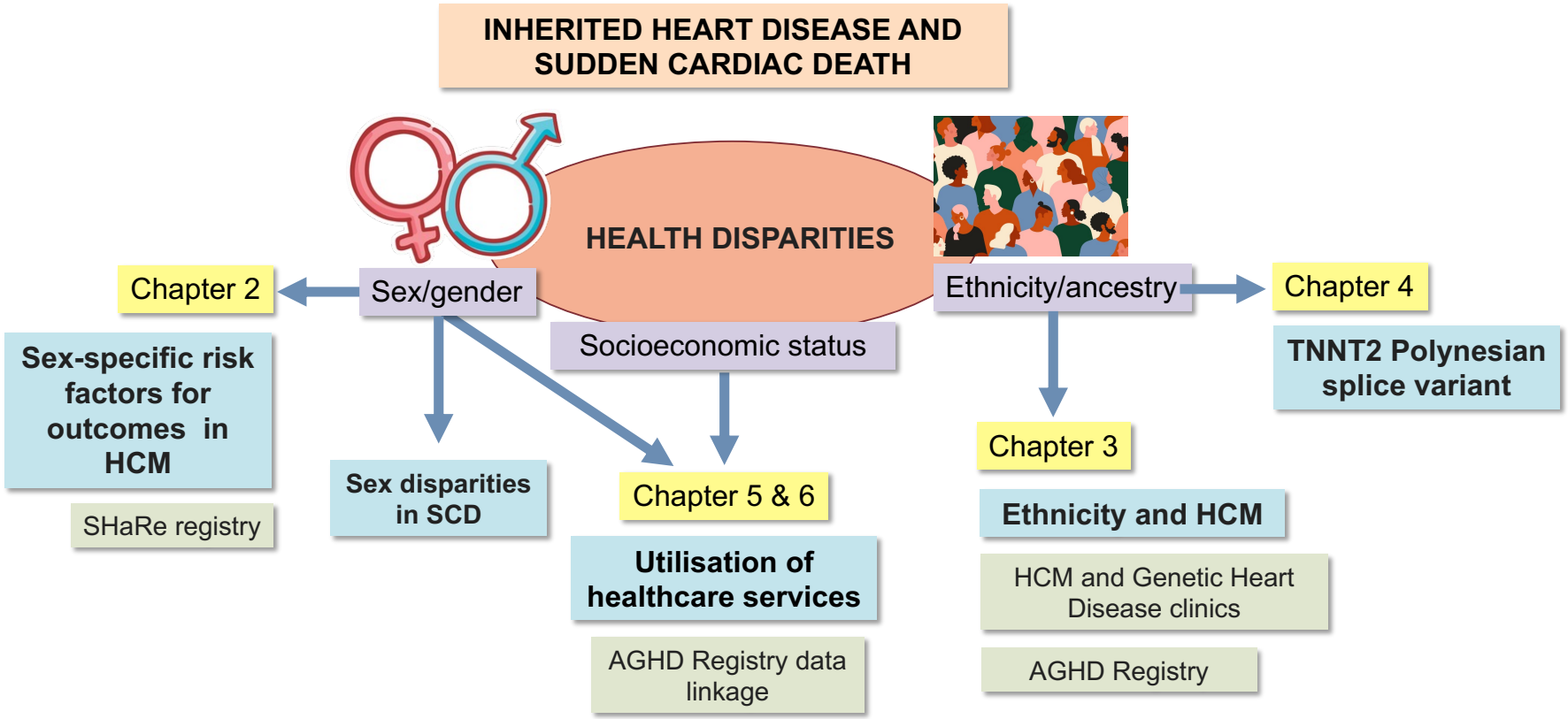


Figure 5: Overview of PhD studies. Abbreviations: HCM, hypertrophic cardiomyopathy; SHaRe, Sarcomeric Human Cardiomyopathy Registry; SCD, sudden cardiac death; AGHD, Australian Genetic Heart Disease.

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CHAPTER 2

SEX-SPECIFIC CLINICAL AND GENETIC FACTORS FOR ADVERSE OUTCOMES IN HYPERTROPHIC CARDIOMYOPATHY

2 CHAPTER 2: SEX-SPECIFIC CLINICAL AND GENETIC FACTORS FOR ADVERSE OUTCOMES IN HYPERTROPHIC CARDIOMYOPATHY

2.1 Preface to Chapter

Patient sex has been associated with differences in disease penetrance and clinical expression in HCM. Women present at a more advanced stage of disease, are older at diagnosis, have higher symptom burden, carry a greater risk for heart failure and are at greater risk of mortality than men. We believe understanding factors contributing to these sex differences are required to improve the care of both women and men with HCM. This chapter presents sex-disaggregated differences in risk factors for adverse outcomes in a large international HCM registry.

This chapter is currently published as a preprint and is under revision. Author contributions are outlined in the following author contribution statement.

Reference

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

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Task	**Role of co-author**
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Sources of funding

The Sarcomeric Human Cardiomyopathy Registry (SHaRe) is supported by unrestricted research grants from Bristol Myers Squibb, Pfizer, and Cytokinetics, including funds to individual sites for database support. No sponsor played a role in the design or conduct of this study nor participated in the article's preparation, review, or approval. A/Prof Ingles is the recipient of a National Health and Medical Research Council (NHMRC) Career Development Fellowship (#1162929). Prof Semsarian is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992) and a New South Wales Health Cardiovascular Disease Clinical Scientist Grant. This study was partly funded by a New South Wales (NSW) Health Cardiovascular Research Capacity Program early-mid career research grant.

Disclosures

A/Prof Ingles receives research grant support from Bristol Myers Squibb. Dr Joseph Rossano is a consultant for Bayer, Merk, Bristol Myers Squibb, Cytokinetics. Dr Arnott has received honoraria from Astra Zeneca and Amgen. Dr Lakdawala is a consultant for Bristol Myers Squibb, Cytokinetics, Pfizer, Tenaya and Sarepta and receives grant support from Pfizer. A/Prof Ho is a consultant for Bristol Myers Squibb, Cytokinetics, and Viz-AI and receives research support from Bristol Myers Squibb, Cytokinetics, and Pfizer. All remaining authors have nothing to disclose.

2.2 Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease affecting at least 1/500 in the general population.[1] HCM is a heterogeneous condition, with approximately half of cases due to likely pathogenic or pathogenic (LP/P) autosomal dominant variants in genes encoding sarcomere proteins (sarcomere-positive), which are critical for contractile function of cardiomyocytes. The two most common genes implicated are myosin-binding protein C (*MYBPC3*) and β-myosin heavy chain (*MYH7*), which account for ~75% of all HCM patients with causative variants [2]. Despite the inheritance pattern conveying 50% risk to first-degree relatives, incomplete penetrance is common, and not all carriers of causative variants will develop disease.[3, 4] There is increasing evidence that ~40% have a non-Mendelian subtype, where the underlying disease mechanism is likely due to a combination of polygenic risk and comorbidities (sarcomere-negative).[5–8]

Despite this being considered an autosomal dominant disease, published HCM cohorts are disproportionately male, with women accounting for only 30-45% of published study populations.[9] This might be explained by decreased disease penetrance in women, with male sex previously associated with three times the risk of developing HCM among individuals with sarcomere gene variants.[3] Additionally, differences in clinical recognition due to the lack of sex-specific diagnostic criteria in clinical guidelines[17] and unequal access to care also likely play a role.[10] Indeed, multiple studies have also shown that women have a higher risk of adverse events, including heart failure and death.[10–13] Despite the lower penetrance, women with HCM are more likely to have a LP/P sarcomere variant, while men are more likely to be sarcomere-negative.[5,10] Compared to men, women are older at diagnosis, present at an advanced stage of disease, have a higher prevalence of

obstruction, exhibit heart failure symptoms (New York Heart Association (NYHA) III-IV), and have worse exercise capacity and diastolic function.[10, 11]

We expand on previous work by evaluating sex-specific differences in risk factors for adverse outcomes in men and women with HCM. Early detection and management of cardiovascular risk factors remain vital for improving women's cardiovascular health.[14] We hypothesised that clinical and genetic factors contributing to adverse outcomes in HCM might be influenced differently by sex. Understanding the underlying factors contributing to these sex differences in outcomes of HCM is essential if we are to improve health outcomes and care for both men and women with HCM.

2.3 Methods

2.3.1 Study Design

Details of SHaRe have been previously described.[7] SHaRe is a consortium of patients from 12 international HCM referral centres. Each centre maintains longitudinal databases capturing clinical, genetic and outcomes data on HCM patients and their families. Site data are mapped to corresponding fields in the secure, centralised database to produce standardised SHaRe definitions and values. Outcome events that occurred before or after the initial visit were identified and recorded. De-identified site data are mapped to corresponding discrete fields in the database to yield standardised SHaRe definitions and values. Prospective data are captured via quarterly uploads from site databases. Each participating site has received ethical approval in accordance with local policies, as follows: Ethical approval requiring participant informed consent was granted by by each institutional review board for the following sites: Cincinnati Children's Hospital, United States of America (USA); Children's Hospital of Philadelphia, USA; Michigan Medical, USA; Yale Medical, USA; Royal Brompton Hospital, United Kingdom; Erasmus University Medical Center, The Netherlands; Florence Centre for Cardiomyopathies, Italy; and Sydney Local Health District, Royal Prince Alfred Hospital, Australia; InCor, Heart Institute, University of Sao Paulo, Brazil. Ethical approval with a waiver of consent was granted by each institutional review board for the following sites: Stanford School of Medicine, USA; Brigham and Women's Hospital, USA; Boston Children's Hospital, USA; Pennsylvania University Medical Center, USA; and Sydney Local Health District, Royal Prince Alfred Hospital, Australia. All individual-level data are pseudonymised prior to upload to SHaRe.

2.3.2 Study population

Patients were included if they had a site-designated diagnosis of HCM, defined as unexplained left ventricular (LV) hypertrophy with maximal wall thickness >13mm if positive genetic testing, or >15mm if negative genetic testing and negative family history, or equivalent z-score for paediatric patients. Only probands were included, i.e., the first affected family member to seek medical attention for HCM. All analysed metrics of cardiac dimensions and function were based on echocardiographic measurements.

2.3.3 Genetic testing

Genetic testing was performed at all sites using different tests available over time. Variants were classified as pathogenic (P), likely pathogenic (LP), unknown significance (VUS), or benign/likely benign by each site using contemporary criteria, concentrating on the eight sarcomere genes definitively associated with HCM (myosin binding protein C [*MYBPC3*], myosin heavy chain [*MYH7*], cardiac troponin T [*TNNT2*], cardiac troponin I [*TNNI3*], α-tropomyosin [*TPM1*], myosin essential and regulatory light chains [*MLY2, MYL3*], and actin [*ACTC1*]). [3]. Sarcomere variants with ambiguous classifications underwent additional systematic review by a subgroup of investigators to adjudicate and standardise classification (SD, JW, JI). Patients were excluded if they had potentially pathogenic variants in genocopy genes such as α-galactosidase (*GLA*) or lysosome-associated membrane protein (*LAMP2*), indicating the presence of a metabolic or storage disease, or diagnoses other than HCM. Genotyped patients were designated as sarcomere-positive (at least one LP/P variant in any of the above sarcomere genes), sarcomere-negative (no causative sarcomere variants identified), or VUS (variant of uncertain significance in a sarcomere gene).

2.3.4 Outcome definitions

The four primary adverse outcomes were heart failure composite, ventricular arrhythmia composite, atrial fibrillation (AF) and death. Outcomes were documented by site investigators during routine clinical encounters and captured directly into the database. Composite outcomes were defined as follows:

Heart failure composite: the first occurrence of cardiac transplantation, LV assist device implantation, or NYHA functional class III-IV symptoms.

Ventricular arrhythmia composite: the first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate ICD therapy.

2.3.5 Statistical analysis

Baseline characteristics for women and men are presented as number (percentage) for categorical variables, mean (standard deviation) for approximately symmetrical continuous variables, and median (interquartile range) for asymmetrical continuous variables. Continuous variables were compared using the unpaired t-test, and categorical variables using the χ^2 test. The incidence of adverse outcomes (heart failure composite, ventricular arrhythmia composite, AF, death) was estimated separately for women and men. Multivariable Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for adverse outcomes comparing women with men. Only incident outcomes were included in analyses. The time variable was from first evaluation at a SHaRe site to either development of the outcome, or last follow-up for those who had no events. All models were adjusted by age at the first encounter at a SHaRe center. Patients missing data on the occurrence or timing of events were not included in analyses of those outcomes. However, to maximise sample sizes across analyses, such patients were included in analyses of other outcomes where data were available.

The association between baseline risk factors and adverse outcomes was assessed using Cox regression models. Heterogeneity of associations was tested between women and men by adding an interaction term into the Cox regression model with no adjustment for multiplicity. Time was from first evaluation at a SHaRe site to either development of the outcome, or last follow-up for those who had no events. All models were adjusted by age at the first encounter at a SHaRe site, and echocardiographic models were adjusted for body surface area. Data were reported as HR with 95% CI for women versus men as the reference. A 2-sided p-value <0.05 was considered statistically significant. Multiple corrections were not applied as this is hypothesis generating research. Kaplan-Meier survival analysis with log-rank comparison was used to compare the age of heart failure composite and death separately for women and men by sarcomere status and genotype. The time variable was age (years) at first event or age at most recent follow-up where they were known to be free from events, ≤80 years. Longitudinal analysis of echocardiographic parameters was performed using linear mixed models. All analyses were conducted using R version 4.1.2.

2.4 Results

2.4.1 Demographic and clinical characteristics

There were 7315 patients with HCM seen between 1960-2020, and after excluding 768 family members, there were 6647 probands included in the study (Figure 2.1A). There were 2538 (38%) women, with an overall mean follow-up time from the first to the last encounter of 6.4 ± 7.1 years (Table 2.1). The cohort consisted of 667 pediatric patients (<18 years), of which 226 (33.9%) were female and 441 (66.1%) male.

Women were approximately 6.0 years older than men at diagnosis (47.5 ± 20.6 versus 41.6 ± 18.4; p<0.0001). At baseline, NYHA class III-IV symptoms were present in 455 (22.9%) of women, compared to only 337 (10.5%) of men; p<0.0001. Additionally, 895 (47%) women had LV outflow tract obstruction (LVOTO) (defined as LVOTO ≥30mmHg at rest or with provocation) compared to 1086 men (36%); p<0.0001. Subsequently, women also had significantly higher LV outflow tract gradient 37.1 ± 38.4 versus 26.9 ± 31.4; p<0.0001). LV ejection fraction was greater in women, although not clinically significant (65.6 ± 9.8 versus 64.4 ± 9.0; p<0.0001). After adjusting for body surface area, women had significantly greater absolute maximum LV wall thickness, LV cavity diameter, and left atrial (LA) diameter (Table 1).

Genetic testing was performed in 4182 (63%) probands, with a total of 2630 (64%) men and 1552 (61%) women undergoing genetic testing (p=0.019) (Table 2.1). Sarcomere status differed by sex; a total of 728 (52%) women and 1047 (46%) men were sarcomere-positive (p<0.0001). Among the sarcomere-positive group, most had *MYBPC3* variants, although men were proportionately even more likely to have *MYBPC3* variants (p=0.001).

Proportionately more women had variants in *MYH7* and other sarcomere genes compared to men (p=0.001; Figure 2.1B).

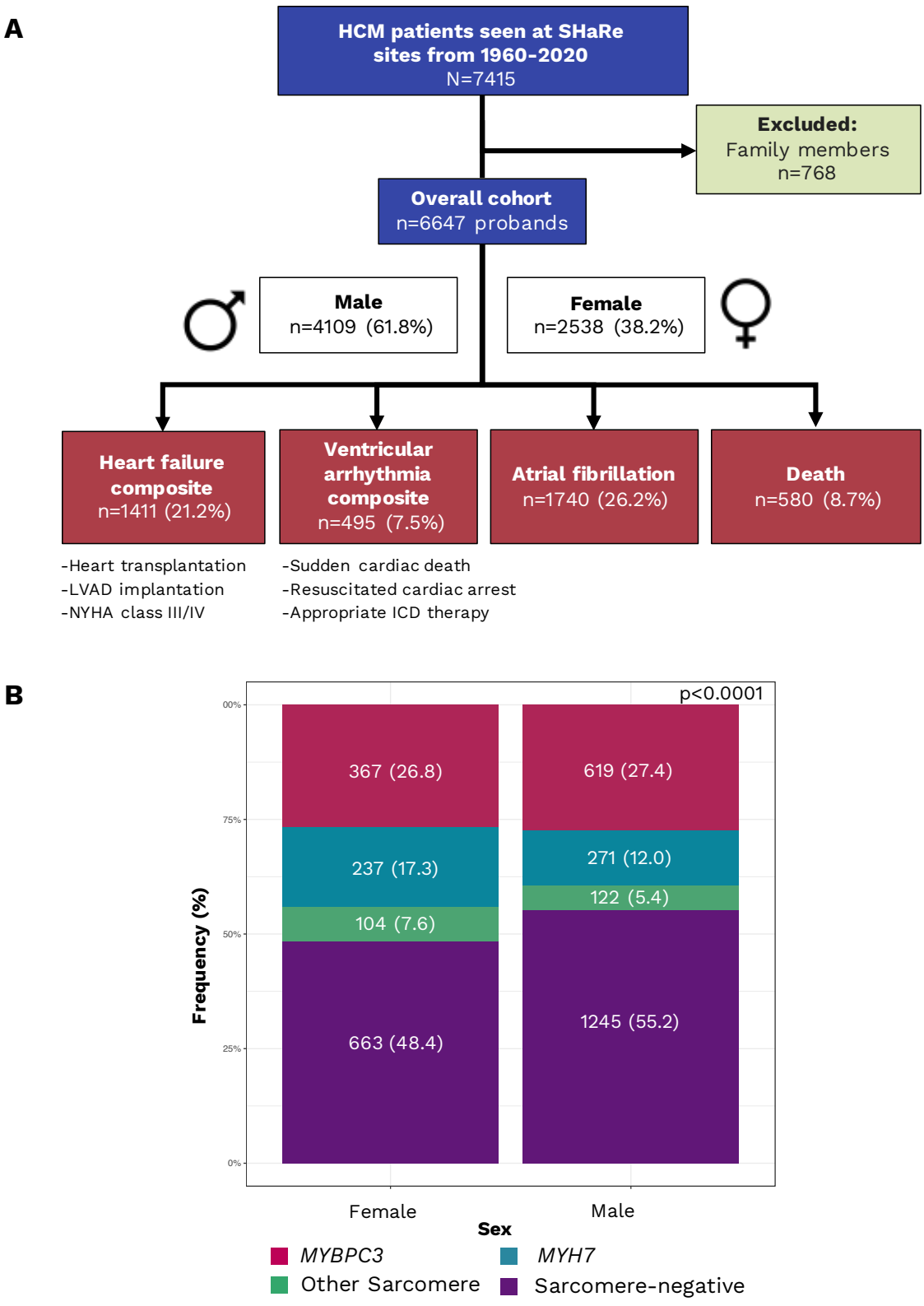

Figure 2.1: Study outcomes and genetic findings (A) Flow diagram of study participants **(B)** Sarcomere variant gene distribution including sarcomere-negative probands**.** Abbreviations: ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; NYHA, New York Heart Association

Table 2.1: Demographic and baseline characteristics of hypertrophic cardiomyopathy probands by sex

Characteristic		Total cohort	Female	Male	p-value
n		6647	2538 (38.2)	4109 (61.8)	
Age at diagnosis (years)		43.9 ± 19.5	47.5 ± 20.6	41.6 ± 18.4	<0.0001
Follow-up time (years)		6.4 ± 7.1	6.3 ± 6.8	6.5 ± 7.2	0.412
Race	White	5465 (91.8)	2114 (92.2)	3351 (91.6)	0.300
	Black	269 (4.5)	92 (4.0)	177 (4.8)	
	Asian	217 (3.7)	87 (3.8)	130 (3.6)	
Genetic testing		4182 (62.9)	1552 (61.2)	2630 (64.0)	0.019
Sarcomere status	Positive	1775 (48.2)	728 (52.3)	1047 (45.7)	<0.0001
	Negative	1908 (51.8)	663 (47.7)	1245 (54.3)	
Gene status	*MYBPC3*	986 (57.3)	367 (51.8)	619 (61.2)	0.001
	MYH7	508 (29.5)	237 (33.5)	271 (26.8)	
	Other sarcomere	226 (13.1)	104 (14.7)	122 (12.1)	
Hypertension		2690 (40.5)	1091 (43.0)	1599 (38.9)	0.001
Body mass index (kg/m^2)		27.5 ± 6.2	27.3 ± 7.0	27.7 ± 5.7	0.080
NYHA III-IV		792 (15.3)	455 (22.9)	337 (10.5)	<0.0001
Syncope		1008 (15.6)	432 (17.5)	576 (14.4)	0.001
ESC HCM Risk score	Low risk (<4%)	4220 (87.0)	1627 (89.2)	293 (85.7)	0.0002
	Moderate risk (4 to <6%)	415 (8.6)	117 (6.4)	298 (9.9)	
	High risk (≥6%)	216 (4.5)	81 (4.4)	135 (4.5)	
Echo characteristics					
Indexed Max LV wall thickness, mm[a]		9.9 ± 2.3	10.4 ± 4.3	9.5± 4.2	<0.0001
Indexed LV end diastolic diameter, mm[a]		23.6 ± 6.6	24.2 ± 6.7	23.2 ± 6.6	<0.0001
Indexed end systolic diameter, mm [a]		14.3 ± 5.2	14.5 ± 2.9	14.2 ± 5.4	0.071
LV ejection fraction (%)		64.9 ± 9.3	65.6 ± 9.8	64.5 ± 9.0	<0.0001
LV outflow tract obstruction		1981 (40.2)	895 (46.9)	1086 (36.0)	<0.0001
LV outflow tract gradient at rest (mmHg)		30.8 ± 34.6	37.1 ± 38.4	26.9 ± 31.4	<0.0001
Mitral regurgitation		3737 (64.6)	1527 (68.6)	2210 (62.2)	<0.0001
Indexed left atrial diameter, mm[a]		22.6 ± 6.2	23.9 ± 6.5	21.7 ± 5.8	<0.0001

Data shown as n (%) or mean ± SD.
Abbreviations: NYHA, New York Heart Association; LV, left ventricular; ESC, European Society of Cardiology.
[a]Adjusted for body surface area

2.4.2 Incident use of medications and interventions

Table 2.2 shows overall medication use and interventions in the cohort. Compared to men, women were more likely to be prescribed beta-blockers (1495 [62%] women versus 2294 [59%]; p=0.001), calcium channel blockers (529 [22%] versus 682 [18%]; p<0.0001), disopyramide (240 [11%] versus 236 [7%]; p<0.0001), and loop diuretics (157 [15%] versus 151 [8%]; p<0.0001), though noting data missingness for these variables (missing, 5%-14%), especially loop diuretics (55%). There was no sex difference in the prescription of anti-arrhythmic drugs (p=0.953). The prevalence of ICD insertion was similar between the sexes (p=0.386). In patients with obstruction, women were significantly more likely than men to undergo alcohol septal ablation (102/895 [11.4%] versus 80/1082 [7.4%] p=0.002); however, there was no sex difference for septal myectomy (331/895 [37.0%] versus 361/1086 [33.2%]; p=0.08).

Table 2.2: Incident medication use, interventions and outcomes by sex

	Total cohort	Women	Men	p-value
n	6647	2538 (38.2)	4109 (61.8)	
Medications				
Beta blocker	3789 (60.1)	1495 (62.2)	2294 (58.8)	0.001
Anti-arrhythmic	718 (13.7)	275 (13.8)	443 (13.7)	0.953
Calcium channel blocker	1211 (19.3)	529 (22.0)	682 (17.6)	<0.0001
Disopyramide	476 (8.4)	240 (11.0)	236 (6.7)	<0.0001
Loop diuretic	308 (10.4)	157 (14.7)	151 (7.9)	<0.0001
Interventions				
ICD implantation	1697 (25.5)	633 (24.9)	1064 (25.9)	0.386
Alcohol septal ablation	295 (4.5)	160 (6.3)	135 (3.3)	<0.0001
Septal myectomy	1124 (16.9)	505 (19.9)	619 (15.1)	<0.0001
Outcomes				
Heart failure composite	1411 (21.2)	729 (28.7)	682 (16.6)	-
Ventricular arrhythmia composite	495 (7.5)	175 (6.9)	320 (7.8)	-
Atrial fibrillation	1740 (26.2)	681 (26.8)	1059 (25.8)	-
Death	580 (8.7)	289 (11.4)	291 (7.1)	-

Data shown as n (%) or mean ± SD.
Abbreviations: ICD, implantable cardioverter defibrillator.
Heart failure composite: first occurrence of cardiac transplantation, left ventricular assist device implantation, or New York Heart Association functional class III-IV symptoms. Ventricular arrhythmia composite: first occurrence of sudden cardiac death, resuscitated cardiac arrest, or appropriate ICD therapy.

2.4.3 Adverse clinical outcomes

During the follow-up period, a total of 1411 heart failure composite events were recorded (729, 28.7% women), 495 ventricular arrhythmia composite events (175, 6.9% women), 1740 AF events (1740, 26.8% women), and 580 deaths (289, 11.4% women; Table 2.2). Multivariate Cox models were fit to test if sex was an independent predictor of key outcomes (Table 2.3). Women had a higher risk of heart failure (HR 1.51, CI 1.21-1.88; p=0.0003) in a model adjusted for age, sarcomere status, baseline LVEF<50%, baseline indexed LA size, baseline LVOTO, body mass index (BMI) and hypertension. However, female sex did not remain a significant predictor of death in a model adjusted for age, sarcomere status, baseline LVEF<50%, baseline indexed LA size and baseline LVOTO (HR 0.96, CI 0.66-1.41; p= 0.843). Additionally, women had a reduced risk of AF (HR 0.74 CI 0.59-0.93; p<0.0001) and ventricular arrhythmia (HR 0.60 CI 0.38-0.94; p=0.027) compared to men.

Table 2.3: Univariable and Multivariable analysis of outcomes in HCM

Covariate	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Heart failure composite				**Events n=353**		
Female sex	1.77	1.56-1.99	<0.0001	1.51	1.21-1.88	0.0003
Age	1.08	1.07-1.10	<0.0001	1.08	1.06-1.11	<0.0001
Sarcomere-positive	1.02	0.87-1.20	0.829	1.20	0.95-1.51	0.137
Indexed baseline max LV wall thickness (mm)	1.04	1.02-1.05	<0.0001			
Indexed LV end diastolic diameter (mm)	1.00	0.99-1.02	0.834			
Indexed LV end systolic diameter (mm)	1.03	1.01-1.05	0.009			
LV ejection fraction <50%	2.26	1.87-2.73	<0.0001	2.67	1.83-3.91	<0.0001
Indexed left atrial size (mm)	1.04	1.03-1.05	<0.0001	1.04	1.02-1.07	0.0001
LV outflow tract obstruction	1.90	1.65-2.19	<0.0001	1.73	1.38-2.17	<0.0001
Mild-severe mitral regurgitation	1.28	1.12-1.48	0.0004			
Hypertension	1.29	1.13-1.47	0.0002	1.14	0.90-1.45	0.276
Body mass index (kg/m^2)	1.05	1.03-1.06	<0.0001	1.05	1.03-1.07	<0.0001
Atrial fibrillation	1.55	1.37-1.75	<0.0001			
Death				**Events= 129**		
Female sex	1.22	1.03-1.45	0.020	0.96	0.66-1.41	0.843
Age	0.97	0.96-0.97	<0.0001	0.96	0.94-0.97	<0.0001
Sarcomere-positive	1.46	1.17-1.83	0.001	1.26	0.85-1.88	0.254
Indexed baseline max LV wall thickness (mm)	1.03	1.00-1.06	0.026			
Indexed LV end diastolic diameter (mm)	1.02	1.01-1.04	0.006			
Indexed LV end systolic diameter (mm)	1.03	1.02-1.05	0.0002			
LV ejection fraction <50%	2.80	2.22-3.54	<0.0001	2.04	1.14-3.65	0.0164
Indexed left atrial size (mm)	1.04	1.03-1.06	<0.0001	1.08	1.05-1.12	<0.0001
LV outflow tract obstruction	1.25	1.03-1.53	0.028	1.89	1.27-2.80	0.0017
Mild-severe mitral regurgitation	1.19	0.97-1.46	0.105			
Hypertension	0.60	0.51-0.72	<0.0001			
Body mass index (kg/m^2)	1.01	1.00-1.03	0.173			
Atrial fibrillation				**Events=360**		
Female sex	0.97	0.84-1.10	0.6	0.74	0.59-0.93	<0.0001
Age	1.01	1.00-1.02	0.008	1.00	0.99-1.02	0.608
Sarcomere-positive	1.30	1.10-1.54	0.002	1.48	1.17-1.86	0.0009
Indexed baseline max LV wall thickness (mm)	1.03	1.01-1.05	0.007			
Indexed LV end diastolic diameter (mm)	0.98	0.96-1.00	0.01			
Indexed LV end systolic diameter (mm)	0.99	0.97-1.01	0.3			
LV ejection fraction <50%	1.40	1.09-1.81	0.01			
Indexed left atrial size (mm)	1.05	1.04-1.06	<0.0001	1.06	1.04-1.09	<0.0001
LV outflow tract obstruction	1.49	1.28-1.73	<0.0001	1.63	1.31-2.03	<0.0001
Mild-severe mitral regurgitation	1.38	1.19-1.61	<0.0001			

Hypertension	1.15	1.00-1.33	0.05	1.07	0.95-1.35	0.557
Body mass index (kg/m^2)	1.04	1.03-1.05	<0.0001			
VA composite				**Events= 100**		
Female sex	0.85	0.65-1.12	0.244	0.60	0.38-0.94	0.027
Age	0.99	0.98-1.01	0.7	0.99	0.97-1.01	0.335
Sarcomere-positive	1.61	1.16-2.23	0.004	1.85	1.16-2.95	0.01
ESC family history SCD	1.59	1.08-2.34	0.03	1.52	0.88-2.64	0.136
Syncope	2.14	1.63-2.82	<0.0001	1.52	0.98-2.36	0.063
Indexed baseline max LV wall thickness (mm)	1.04	1.02-1.07	0.003			
Indexed LV end diastolic diameter (mm)	1.00	0.97-1.02	0.6			
Indexed LV end systolic diameter (mm)	1.00	0.97-1.03	0.966			
LV ejection fraction <50%	1.96	1.32-2.91	0.002			
Indexed left atrial size (mm)	1.02	0.99-1.04	0.174	1.02	0.98-1.06	0.421
LV outflow tract obstruction	1.23	0.91-1.66	0.175	1.44	0.95-2.18	0.088
Mild-severe mitral regurgitation	1.12	0.82-1.49	0.508			
Hypertension	0.76	0.57-1.02	0.0661			
Body mass index (kg/m^2)	1.03	1.01-1.05	0.00351			

Abbreviations: ESC, European Society of Cardiology; SCD, sudden cardiac death; LV, left ventricular.

2.4.4 Sex-specific clinical and genetic factors for heart failure composite

Sex differences existed for the associations between the heart failure composite and sarcomere-positive status, LP/P variants in *MYBPC3*, and baseline indexed LA diameter after adjusting for age at first encounter (Figure 2.2). In men, sarcomere-positive status was associated with an increased risk of the heart failure composite compared to sarcomere-negative patients (HR 1.34 [95% CI 1.06-1.69]), while for women, there was no significant change in risk by sarcomere status (HR 0.85 [95% CI 0.66-1.08]; p-heterogeneity=0.006). However, having an LP/P variant in *MYBPC3* was associated with a lower risk of the heart failure composite for women compared to sarcomere-negative HCM (HR 0.56 [95% CI 0.41-0.77]), with no significant change for men (HR 1.29 [95%CI 0.99-1.67]; p-heterogeneity <0.0001). Greater indexed LA diameter (per cm increase) was associated with an increased risk of the heart failure composite in both women and men, but slightly more so in men (HR 1.50 [95% CI 1.36-1.65] compared to women (HR 1.25 [1.13-1.39]; p-heterogeneity 0.007).

While Black race, LP/P variants in *MYH7*, larger baseline indexed maximum LV wall thickness, larger baseline indexed LV end-systolic diameter, baseline LV outflow tract obstruction, LV ejection fraction <50%, greater BMI, and AF all increased the risk of the heart failure composite in the cohort, there was no heterogeneity by sex for any of these associations (p-heterogeneity >0.05).

Risk Factor	Incident events	HR (95% CI)	p-heterogeneity
Black vs White			
Female	497	1.61 (1.07-2.44)	0.711
Male	474	1.82 (1.23-2.72)	
Asian vs White			
Female	497	0.35 (0.18-0.71)	0.272
Male	474	0.60 (0.32-1.13)	
Sarcomere+ vs Sarcomere-			
Female	315	0.85 (0.66-1.08)	**0.006**
Male	320	1.34 (1.06-1.69)	
***MYBPC3* vs Sarcomere-**			
Female	310	0.56 (0.41-0.77)	**<0.0001**
Male	316	1.29 (0.99-1.67)	
***MYH7* vs Sarcomere-**			
Female	310	1.39 (1.03-1.88)	0.632
Male	316	1.55 (1.10-2.19)	
Other vs Sarcomere-			
Female	310	1.05 (0.66-1.66)	0.583
Male	316	1.29 (0.79-2.09)	
Indexed maximum LV wall thickness/10mm[a]			
Female	464	1.49 (1.28-1.74)	0.214
Male	443	1.33 (1.16-1.53)	
Indexed LV end diastolic diameter/10mm[a]			
Female	416	1.07 (0.92-1.25)	0.930
Male	384	1.06 (0.90-1.25)	
Indexed LV end systolic diameter/10mm[a]			
Female	344	1.26 (1.06-1.49)	0.921
Male	341	1.24 (1.04-1.48)	
LV outflow tract obstruction[a]			
Female	378	1.47 (1.19-1.82)	0.110
Male	348	1.91 (1.54-2.36)	
Mild-severe mitral regurgitation[a]			
Female	439	1.14 (0.92-1.41)	0.128
Male	418	1.44 (1.17-1.77)	
Indexed left atrial size/10mm[a]			
Female	397	1.25 (1.13-1.39)	**0.007**
Male	385	1.50 (1.36-1.65)	
Hypertension			
Female	536	1.17 (0.97-1.41)	0.490
Male	524	1.23 (1.03-1.49)	
Body mass index/5kg/m^2			
Female	486	1.19 (1.11-1.27)	0.753
Male	460	1.22 (1.13-1.33)	
Atrial fibrillation			
Female	536	1.62 (1.36-1.93)	0.249
Male	524	1.79 (1.50-2.13)	

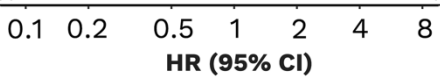

Figure 2.2: Sex-disaggregated analysis showing clinical and genetic features for heart failure

All models were adjusted for age at first evaluation. [a]Echocardiogram measurements adjusted for body surface area.

Abbreviations: CI; confidence interval; HR; hazard ratio; LV, left ventricular.

2.4.5 Sex-specific clinical and genetic factors for death

Sex differences existed for the associations between death and sarcomere-positive status, greater BMI, and the heart failure composite after adjusting for age at first encounter (Figure 2.3). Compared to sarcomere-negative HCM, sarcomere-positive status increased the risk of death in men (HR 1.48 [95% CI 1.08-2.04]) but not in women (HR 0.86 [95% CI 0.71-1.21]; p-heterogeneity=0.035). Greater BMI increased the risk of death in women (HR 1.18 [95% CI 1.05-1.31]) but not in men (HR 0.96 [95% CI 0.82-1.12]; p-heterogeneity 0.031). Heart failure increased the risk of death to a greater extent in men (HR 2.18 [95% CI 1.72-2.78]) than in women (HR 1.45 [95% CI 1.14-1.83]; p-heterogeneity=0.013).

The risk of death was increased for both sexes for the associations between baseline LV outflow tract obstruction, baseline indexed LA diameter, and ventricular arrhythmia composite. Hypertension was consistently associated with a lowered risk of death in both sexes (all p-heterogeneity >0.05).

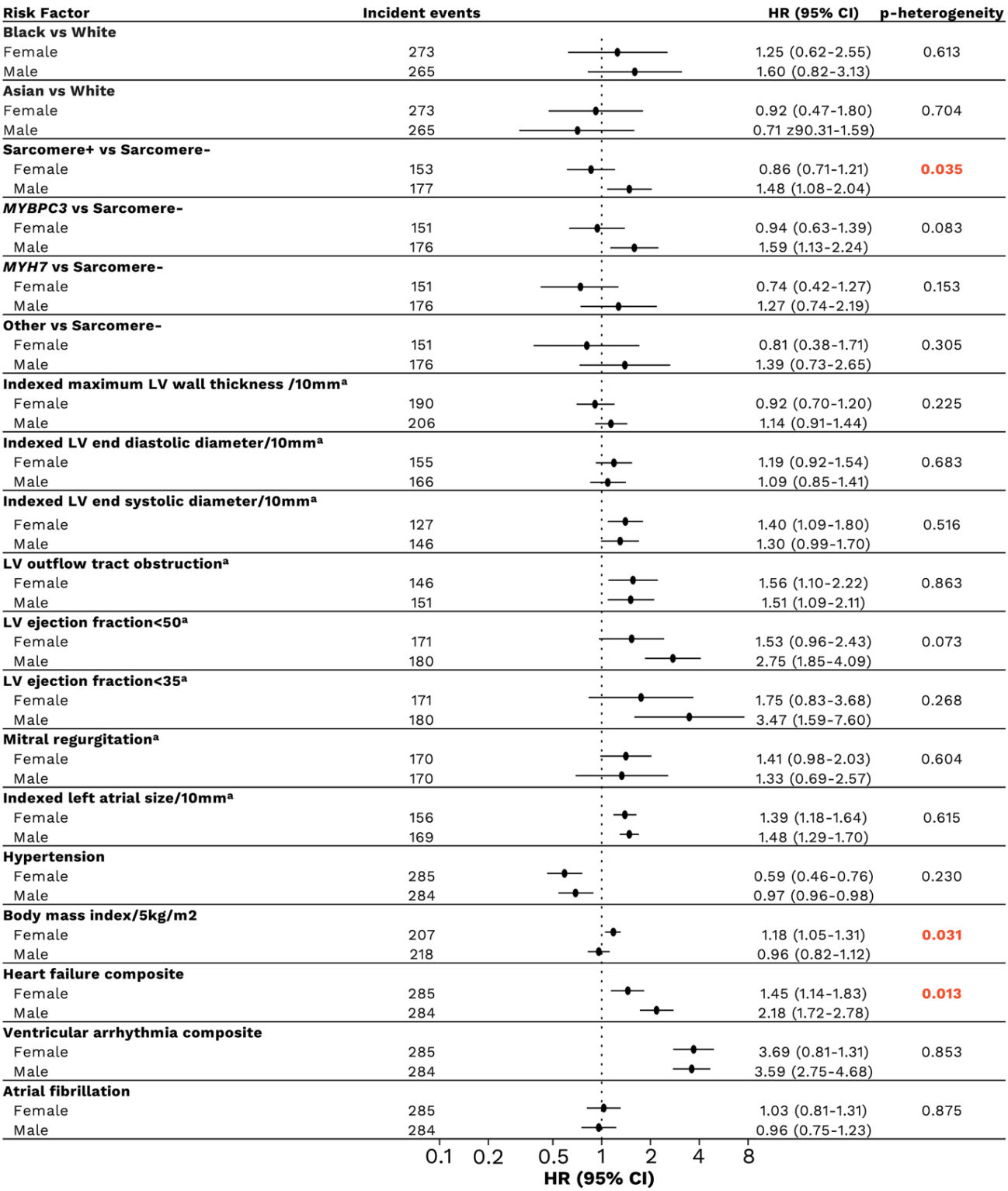

Figure 2.3: Sex-disaggregated analysis showing clinical and genetic features for death

All models were adjusted for age at first evaluation. [a]Echocardiogram measurements adjusted for body surface area.

Abbreviations: CI; confidence interval; HR; hazard ratio; LV, left ventricular.

2.4.6 Sex-specific clinical and genetic factors for atrial fibrillation (AF)

No heterogeneity by sex was observed in associations between risk factors and AF after adjusting for age at first encounter (Figure 2.4). Sarcomere-positive status, disease-causing variants in *MYH7*, larger baseline indexed maximum LV wall thickness, baseline LV outflow tract obstruction, mitral regurgitation, baseline indexed LA diameter and greater BMI were all associated with an increased risk of AF in both sexes (p-heterogeneity >0.05).

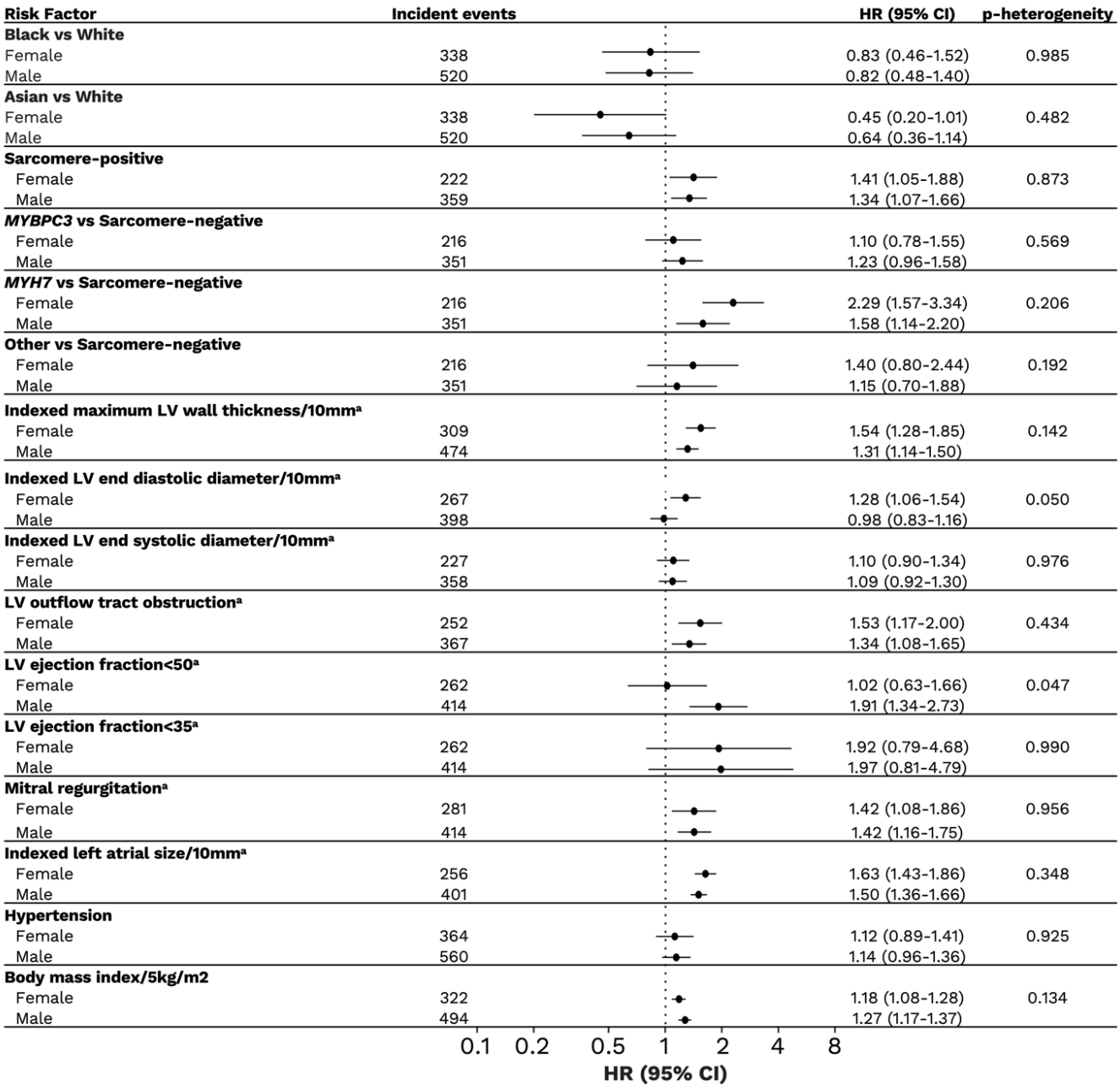

Figure 2.4: Sex-disaggregated analysis showing associations of clinical and genetic features with atrial fibrillation

[a]Echocardiogram measurements adjusted for body surface area

Abbreviations: CI; confidence interval; HR; hazard ratio; LV, left ventricular.

2.4.7 Sex-specific clinical and genetic factors for ventricular arrhythmia composite

Sex differences were identified for the associations between the ventricular arrhythmia composite and European Society of Cardiology (ESC) HCM risk score and greater baseline BMI after adjusting for age at first encounter (Figure 2.5). There was a sex difference in the association between moderate ESC HCM risk (4 to <6%) compared to low risk (<4%), with women at moderate risk more likely to experience ventricular arrhythmia (HR 3.57 [95% CI 1.70-7.49]), and this was not observed in men (HR 1.13 [95% CI 0.63-2.03]; p-heterogeneity=0.019). Men had a 1.3-fold increased risk of ventricular arrhythmia composite for every 5kg/m^2 increase in BMI above the mean (HR 1.29 [95% CI 1.14-1.48]) with no significant change for women (HR 1.04 [95% CI 0.87-1.24]; p-heterogeneity 0.030).

The risk of ventricular arrhythmia was increased for both sexes for the associations between high ESC HCM risk score (>6%), non-sustained ventricular tachycardia, and syncopal events with no heterogeneity by sex (p-heterogeneity >0.05).

Risk Factor	Incident events	HR (95% CI)	p-heterogeneity
Black vs White			
Female	78	1.38 (0.50-3.82)	0.931
Male	155	1.97 (1.00-3.89)	
Asian vs White			
Female	78	1.14 (0.36-3.64)	0.211
Male	155	1.08 (0.44-2.65)	
Sarcomere-positive			
Female	52	1.15 (0.63-2.10)	0.136
Male	119	1.94 (1.30-2.89)	
***MYBPC3* vs Sarcomere-negative**			
Female	51	1.21 (0.61-2.40)	0.118
Male	117	2.29 (1.50-3.48)	
***MYH7* vs Sarcomere-negative**			
Female	51	1.19 (0.55-2.56)	0.586
Male	117	0.87 (0.42-1.82)	
Other vs Sarcomere-negative			
Female	51	0.90 (0.26-3.12)	1.171
Male	117	2.34 (1.19-4.61)	
ESC family history SCD			
Female	76	1.07 (0.53-2.16)	0.170
Male	159	1.98 (1.25-3.14)	
Syncope			
Female	82	2.12 (1.33-3.37)	0.783
Male	161	2.21 (1.57-3.12)	
Non-sustained VT			
Female	76	2.00 (1.25-3.20)	0.921
Male	162	2.00 (1.46-2.75)	
ESC risk score 4% to <6% vs <4%			
Female	61	3.57 (1.70-7.49)	**0.019**
Male	130	1.13 (0.63-2.03)	
ESC risk score ≥6% vs <4%			
Female	61	4.88 (2.21-10.77)	0.856
Male	130	2.67 (1.48-4.82)	
Indexed maximum LV wall thickness/10mm[a]			
Female	68	1.41 (0.98-2.04)	0.719
Male	145	1.55 (1.24-1.93)	
Indexed LV end diastolic diameter/10mm[a]			
Female	56	1.02 (0.67-1.54)	0.964
Male	125	1.02 (0.76-1.37)	
Indexed LV end systolic diameter/10mm[a]			
Female	50	1.01 (0.64-1.59)	0.576
Male	114	1.25 (0.94-1.65)	
LV outflow tract obstruction[a]			
Female	58	1.82 (1.04-3.18)	0.210
Male	104	1.19 (0.79-1.78)	
Maximum LV outflow tract gradient/10mmHg[a]			
Female	42	1.09 (1.01-1.16)	0.084
Male	96	0.99 (0.93-1.06)	
LV ejection fraction <50[a]			
Female	56	1.29 (0.56-2.95)	0.180
Male	121	2.38 (1.43-3.96)	
Indexed left atrial size/10mm[a]			
Female	45	1.32 (0.96-1.82)	0.871
Male	123	1.27 (1.06-1.51)	
Hypertension			
Female	82	0.55 (0.33-0.94)	0.171
Male	164	0.88 (0.63-1.25)	
Body mass index/5kg/m^2			
Female	72	1.04 (0.87-1.24)	**0.030**
Male	147	1.29 (1.14-1.48)	

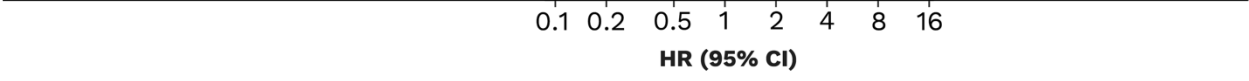

Figure 2.5: Sex-disaggregated analysis showing associations of clinical and genetic features with ventricular arrhythmia

[a]Echocardiogram measurements adjusted for body surface area

Abbreviations: HR; hazard ratio, CI; confidence interval; ESC, European Society of Cardiology; SCD, sudden cardiac death; LV, left ventricular.

2.4.8 Increased risk of events over time for sarcomere-negative women

To further explore why genotype is a sex-specific risk factor, Kaplan-Meier survival analysis with log-rank comparison was used to evaluate time to event for each sex descriptively. While sarcomere-negative men and women were initially less likely to develop heart failure compared with sarcomere-positive individuals, this difference diminished over time in women but persisted in men (Figure 2.6a). However, the risk remained higher in men and women with *MYH7* variants and men with *MYBPC3* variants (Figure 2.6b). Regarding death, for both sexes, those who are sarcomere-positive, on average, die at a younger age than sarcomere-negative individuals (Figure 2.6c). A comparison of the baseline characteristics, medications and interventions between sarcomere-positive and sarcomere-negative patients by sex can be found in Supplementary Table 2.4 & 2.5.

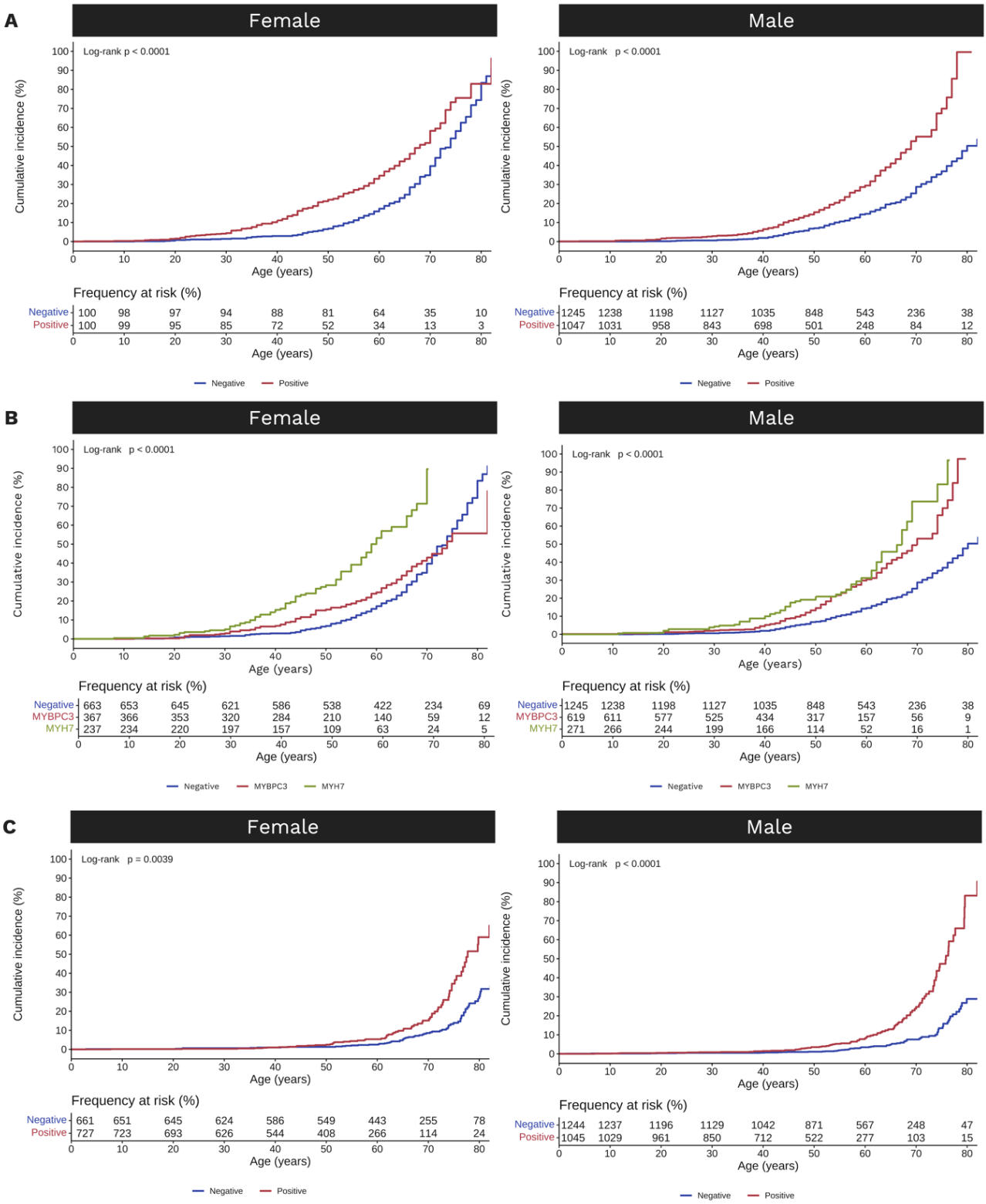

Figure 2.6: Kaplan-Meier survival analysis showing the difference in lifetime risk of **(A)** the heart failure composite for males and females by sarcomere status; **(B)** the heart failure composite for males and females by gene status; and **(C)** death by sarcomere status for females and males.

Table 2.4: Characteristics of hypertrophic cardiomyopathy probands at first encounter by sex and sarcomere status

	Sarcomere-negative		Sarcomere-positive	
	Female	***Male***	***Female***	***Male***
n	663	1245	728	1047
Age at diagnosis (years)	54.5 ± 18.4	46.9 ± 17.1	38.7 ± 18.5	35.1 ± 16.4
Follow-up time (years)	6.5 ± 6.1	6.6 ± 6.5	8.5 ± 7.7	9.1 ± 8.9
Hypertension	385 (58.1)	646 (51.9)	201 (27.6)	281 (26.6)
Body mass index (kg/m^2)	28.4 ± 6.7	28.8 ± 5.8	26.7 ± 6.6	26.6 ± 6.7
NYHA III-IV	135 (24.4)	99 (9.5)	101 (16.7)	87 (10.4)
Syncope	110 (16.7)	169 (13.9)	149 (20.7)	176 (17.3)
Echo characteristics				
Maximum LV wall thickness, mm	17.6 ± 5.7	18.1 ± 6.0	18.9 ± 6.5	20.3 ± 6.4
Indexed max LV wall thickness, mm[a]	9.9 ± 3.5	8.9 ± 3.7	11.0 ± 4.5	10.6 ± 4.4
LV end diastolic diameter, mm	42.0 ± 7.8	46.1 ± 6.6	41.8 ± 6.5	44.6 ± 7.2
Indexed LV end diastolic diameter, mm[a]	23.8 ± 5.9	22.7 ± 5.5	23.9 ± 5.0	22.9 ± 6.5
LV end systolic diameter, mm	25.0 ± 6.7	27.8 ± 6.3	25.6 ± 6.4	27.5 ± 6.9
Indexed end systolic diameter, mm[a]	14.0 ± 4.6	13.7 ± 4.3	14.6 ± 4.2	14.1 ± 5.6
LV ejection fraction (%)	66.3 ± 9.3	65.0 ± 8.4	64.4 ± 10.0	64.0 ± 9.8
LV ejection <50%	31 (5.3)	58 (5.3)	52 (8.7)	65 (7.3)
LV ejection fraction< 35%	5 (0.9)	9 (0.8)	10 (1.7)	16 (1.9)
LV outflow tract obstruction	305 (58.5)	399 (44.1)	183 (32.1)	212 (25.2)
LV outflow tract gradient at rest (mmHg)	44.1 ± 40.9	30.6 ± 32.5	27.2 ± 31.5	21.0 ± 25.8
Mild-severe mitral regurgitation	428 (71.5)	672 (61.7)	392 (65.2)	508 (60.2)
Left atrial diameter, mm	42.1 ± 10.2	43.3 ± 10.6	41.2 ± 10.4	43.6 ± 11.4
Indexed left atrial diameter, mm[a]	23.9 ± 6.5	21.2 ± 5.2	23.5 ± 5.8	22.3 ± 6.5

Data shown as n (%) or mean ± SD.
Abbreviations: NYHA, New York Heart Association; LV, left ventricular.
[a]Adjusted for body surface area.

Table 2.5: Incident medication use and interventions by sex and sarcomere status

	Sarcomere-negative		Sarcomere-positive	
	Female	***Male***	***Female***	***Male***
n	663	1245	728	1047
Medications				
Beta Blocker	452 (69.5)	758 (63.1)	425 (63.6)	624 (65.8)
Anti-arrhythmic	70 (13.7)	119 (12.3)	108 (19.7)	150 (20.1)
Calcium channel blocker	175 (26.9)	249 (20.8)	140 (21.0)	167 (17.7)
Disopyramide	72 (11.8)	84 (7.6)	56 (9.5)	57 (6.8)
Loop diuretic	52 (21.0)	53 (10.3)	56 (16.3)	46 (9.3)
Interventions				
ICD implantation	118 (17.8)	266 (21.4)	293 (40.3)	412 (39.4)
Alcohol septal ablation	53 (8.0)	46 (3.7)	37 (5.1)	35 (3.4)
Septal myectomy	157 (23.7)	233 (18.7)	149 (20.5)	152 (14.5)

Data shown as n (%).
Abbreviations: ICD, implantable cardioverter defibrillator.

2.4.9 Longitudinal analysis of echocardiography parameters over time by sex

Longitudinal analysis was conducted on echocardiography parameters (indexed maximum LV wall thickness and LA size) to investigate whether disease progression over time differentiate the sexes. We used linear mixed models (R package lme4 v1.1.29) to compare women and men over time after rank-normalizing the parameters of interest. The echocardiography variable of interest was used as the outcome variable, and we tested for interactions between sex and age (measured in years). Additionally, all models included a random effect to account for repeated observations from the same individuals over time and patient site, sarcomere status, obstruction and body surface area were included as fixed effects. We found no significant interaction for maximum LV wall thickness (anova comparison, $p>0.05$; Supplemental Figure 2.7A), but we did find a significant interaction for LA size (anova comparison, $p=0.018$). Further analysis of this result by age categories found a significant association for 20-29 years and 60-69 years (anova comparison, $p=0.010$ and $p=0.0003$, respectively; Supplemental Figure 2.7B). While we have shown a significant association, we are mindful of the weakness in using this dataset given the intra-test variability within individuals, which may not represent their underlying HCM. Better-controlled experiments would be necessary to confirm these results.

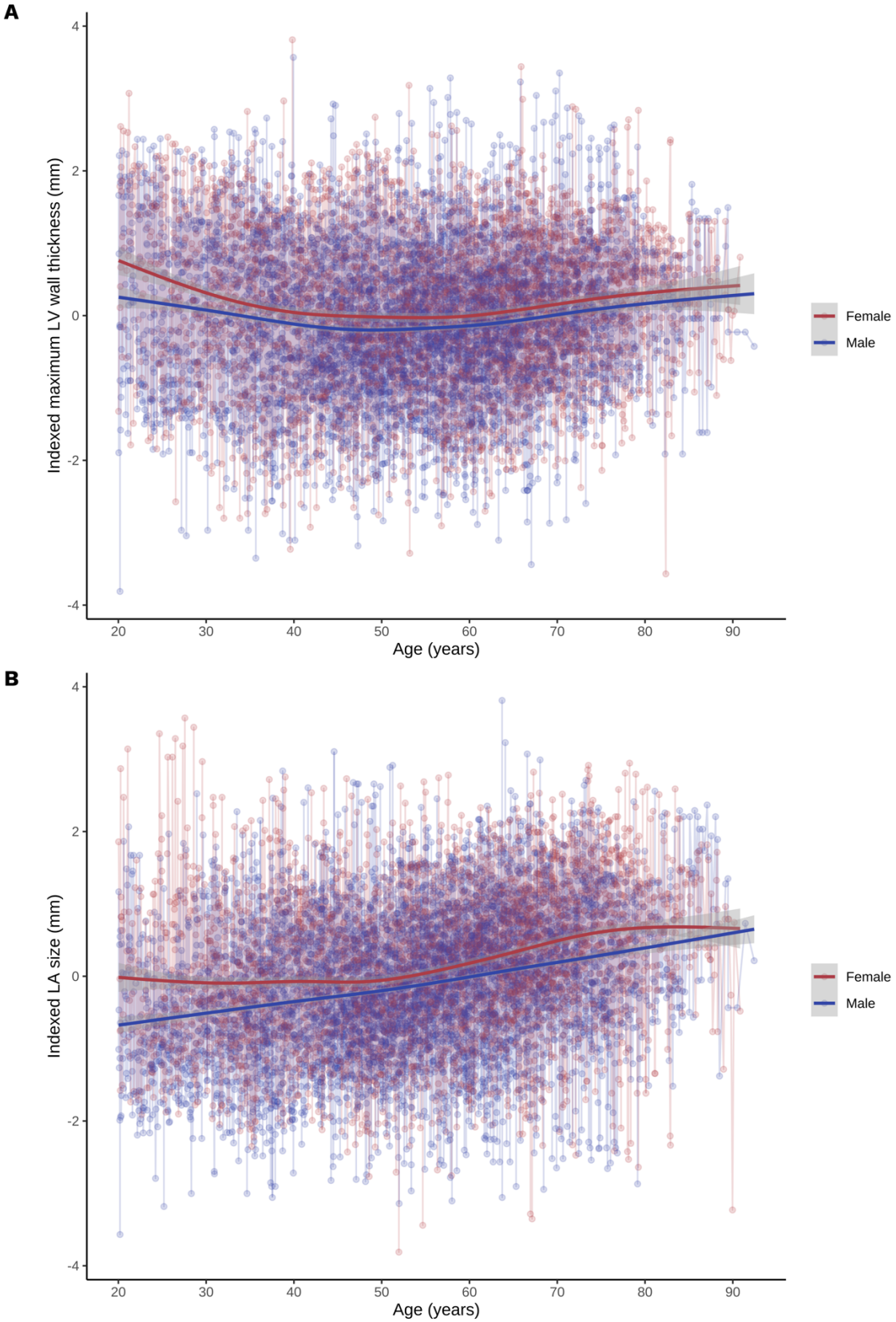

Figure 2.7: Longitudinal changes in echocardiographic parameters over time (years) by sex. A: Indexed maximum LV wall thickness B: Indexed LA size
Abbreviations: LA, left atrial; LV, left ventricular

2.5 Discussion

The majority of clinical evidence informing the management of HCM is predominantly based on studies involving men.[9, 15] It is therefore essential to gain a more comprehensive understanding of the social, clinical and biological factors that differentiate between sexes. A critical first step in addressing sex disparities is the reporting of sex-disaggregated statistics.[16] We show important sex differences in risk factors associated with heart failure, death and ventricular arrythmia in HCM, but not AF (Figure 2.8). Notably, we observed that although sarcomere-negative men and women were initially less susceptible to developing heart failure compared with sarcomere-positive individuals, sarcomere-negative women had an increased risk of heart failure later in life, similar to the heightened incidence observed in the general female population. Additionally, the presence of *MYBPC3* variants in women decreased the risk of heart failure in younger women, compared to men with *MYBPC3* variants, suggesting sex-based mechanistic differences. Importantly, the impact of AF, BMI, LV wall thickness and obstruction on heart failure, and to large extent, death, were similar by sex. We show sex differences in ESC HCM risk score in predicting risk of ventricular arrhythmia, whereby women with moderate ESC HCM risk had an increased risk of ventricular arrhythmia compared to women at low ESC HCM risk. No significant difference in risk was observed for men. As the risk score does not consider sex, this may indicate risk for women is not adequately predicted using this tool. Our findings underscore the need for pre-specified sex-disaggregated analyses to elucidate sex differences and suggest the potential value of sex-specific medical management recommendations that may improve outcomes. Further research, validation of our findings, and a better understanding of the role of genetics in predicting sex-based risk will inform a precision-based approach to care that benefits both men and women.

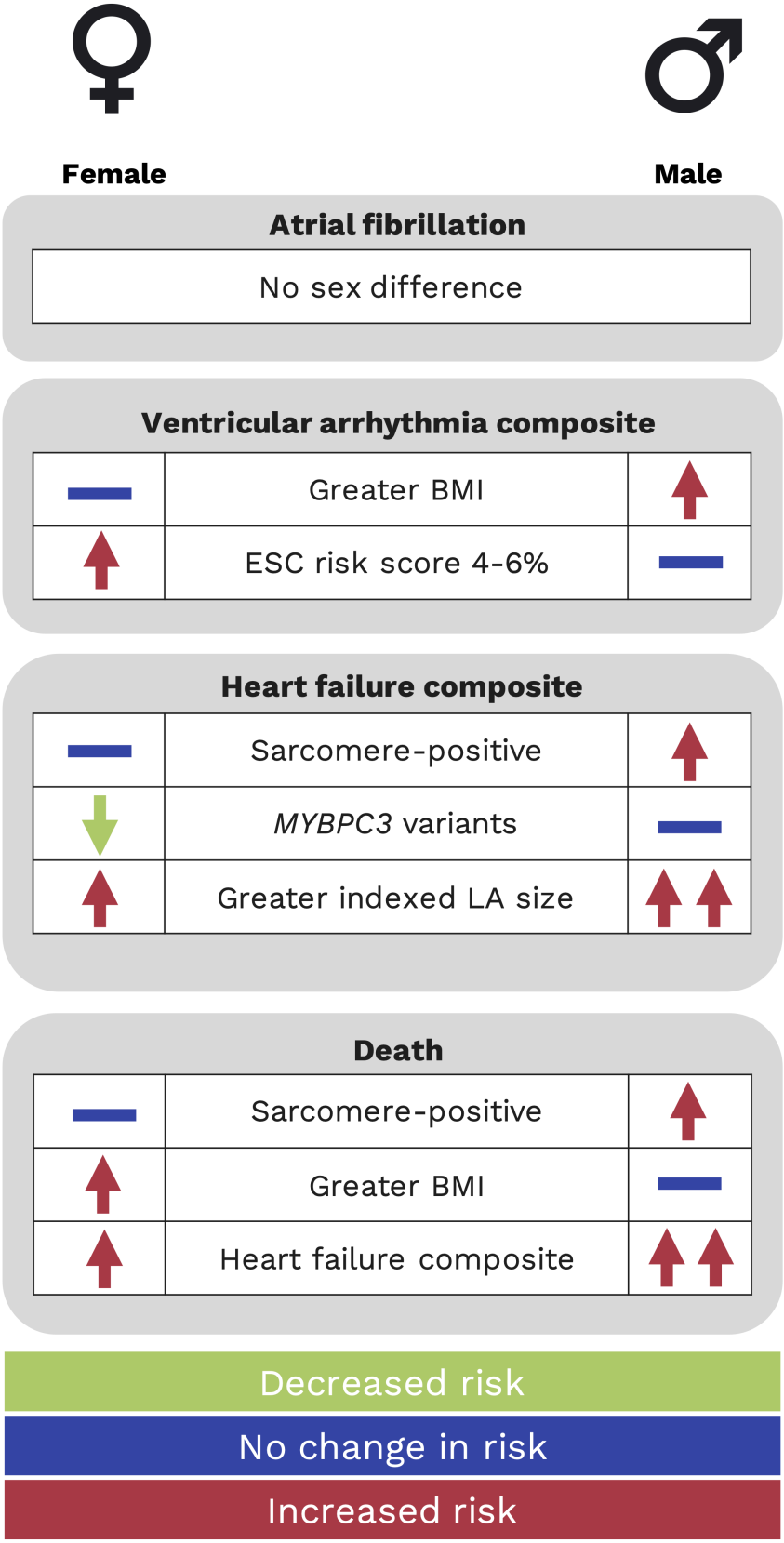

Figure 2.8: Sex-specific risk factors for adverse outcomes in hypertrophic cardiomyopathy. Abbreviations: BMI, body mass index; EF, ejection fraction; LA, left atrial.

The underlying genetic basis of HCM has a differential impact on adverse outcomes across the sexes. We demonstrated that LP/P variants in sarcomere genes increased the risk of heart failure and death for men but not women. Unlike sarcomere-negative men, sarcomere-negative women had an increased risk of heart failure and death in later life, likely mirroring the increasing risk of heart failure in women seen in the general population in later life.[17] In fact, the prevalence of heart failure increases with age for both sexes in the general population, but by the age of 79 more women than men have heart failure, with more associated comorbidities but better survival than men.[18–20] Sarcomere-negative men had a lower lifetime risk of both heart failure and death compared to sarcomere-positive men, consistent with previous reports in the general HCM literature suggesting a more benign clinical course compared to sarcomere-positive men with HCM.[5–7] Recent work to understand the underlying disease aetiology in this group has shown an important polygenic basis, and diastolic blood pressure has been demonstrated as an independent contributor to disease development in sarcomere-negative HCM.[21, 22] Interestingly, important sex differences exist for blood pressure in the general population, with men having a greater prevalence of hypertension overall but women experiencing steeper increases in measures earlier in life, hypothesised to contribute to cardiovascular disease risk in later life for women.[23, 24] The observed sex differences among sarcomere-negative patients in our study and known differences in modifiable risk factors such as hypertension signal a critical need for future studies to report sex-disaggregated data and consider clinical implications for each sex.

LP/P variants in *MYH7* and *MYBPC3* account for the majority of sarcomere-positive HCM, and we highlight important sex differences at the gene level. Men and women with *MYH7* variants had a greater risk of heart failure than those with sarcomere-negative HCM.

However, among women, LP/P variants in *MYBPC3* did not similarly increase risk. Although, subtle genotype-phenotype associations exist in HCM, such as LP/P variants in *MYH7* associated with a younger age at presentation[25] and greater risk of AF,[26, 27] the overall marked phenotypic and genetic heterogeneity in HCM limits the clinical utility of this information. Variants in *MYBPC3* are frequently truncations, with a proportion being founder variants.[28] Founder variants, which must withstand negative selection pressure to be inherited over generations, were initially considered to cause less penetrant or milder disease. However, more recent data suggest they do not confer a more benign prognosis[28, 29] with recent SHaRe data showing that the effects of founder truncating variants are identical to those of non-founder truncating variants.[29] Therefore, the significance of this finding in our study is unclear. Nevertheless, it raises interesting questions about the impact of the underlying biological cause of disease and its potential modification by sex.

Other adverse outcomes, including ventricular arrhythmia, AF and death were also evaluated in this study. We showed a sex-specific difference in risk of ventricular arrhythmia between women and men with a moderate ESC HCM risk score, compared to those with a low risk. Considering the key variables comprising the score, which do not include sex, this finding suggests the risk calculator might not adequately discriminate between those at high and low risk of sudden cardiac death in women. Men with greater BMI had an increased risk of the ventricular arrhythmia composite, while no difference was seen for women. Studies investigating sudden cardiac death in the general population have likewise reported this association previously, although there is disagreement on whether this is due to increased myocardial hypertrophy and fibrosis, which could potentially be a mechanism for ventricular arrhythmia.[30, 31] Comorbidities and other modifiable risk factors significantly contribute to cardiovascular disease risk in both men and women in the general

population.[14] Although these data were limited in our HCM dataset, a more extensive investigation of both traditional, sex-specific and non-traditional risk factors in HCM could provide even greater clarity on sex differences. Given the potential role of sex-specific hormones in modulating disease, gathering female-specific data, such as menarche, pregnancy and reproductive-associated variables, could be particularly important.

While the development of heart failure is a true finding, the fact that more women, have worse heart failure at initial visit, may be partly due to referral bias. Women are often sicker at presentation because they are not referred for evaluation, particularly to specialty centres, as early as men.[32–34] Women typically have smaller hearts than men and consequently, women require a more significant degree of hypertrophy to fulfil the diagnostic criteria of maximal wall thickness of at least 15mm (or 13mm in first-degree relatives). This underlying difference in biology has been postulated to contribute to the delay in diagnosis and the higher initial diagnosis of peak LV outflow gradient observed in women .[35] A general assumption that men are more at risk of cardiovascular disease, leading to reduced awareness and prioritisation among women must also be considered. The Heart Foundation of Australia reported that only 39% of women aged ≥45 years had undergone a heart risk assessment by a healthcare professional in the previous two years.[36] Indeed, physician bias contributes to reduced screening and prevention efforts for women compared to men.[37] Our results show equal access and utilisation of medical therapy and interventions by sex when treated in a SHaRe centre. Investigation of why women are referred to specialist centres later than men is warranted.

2.5.1 Limitations

Use of the heart failure composite outcome provides an incomplete measure of heart failure burden in HCM, including NYHA class III-IV symptoms which could be attributed to other causes such as LV obstruction. We had incomplete and limited information about comorbidities and could not interrogate the impact of menarche, pregnancy or reproductive history. Further research is necessary to determine the effects of these factors on adverse outcomes in HCM. Finally, all patients come from specialised HCM clinics that have been to lack ancestral diversity.[38]

2.6 Conclusion

Sex-specific differences in risk factors for poor outcomes in HCM mostly relate to heart failure or death. Although sarcomere-negative HCM patients tend to have a milder course, sarcomere-negative women have an increased risk of heart failure later in life, similar to the general female population. Further, women with *MYBPC3* variants have lower risk of heart failure than men with similar variants, the mechanism for which is currently unclear. Additionally, we show sex-specific differences in the performance of the ESC HCM risk score. Further work to explore sex differences in risk of heart failure and death in HCM include collection of female-specific variables such as menarche, pregnancy and menopause, and more detailed comorbidity data. Reporting of sex-disaggregated data are a critical first step in addressing sex disparities and informing sex-specific management strategies.

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CHAPTER 3

CLINICAL PROFILE AND HEALTH DISPARITIES IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY IN A MULTI-ETHNIC COHORT

3 CHAPTER 3: CLINICAL PROFILE AND HEALTH DISPARITIES IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY IN A MULTI-ETHNIC COHORT

3.1 Preface to Chapter

The clinical characteristics and management of hypertrophic cardiomyopathy (HCM) are well-described in Caucasian cohorts. However, less is known about other ethnic groups. Australia has a multicultural population, with 1 in 3 people born overseas. Common non-Caucasian countries of birth, such as China, India and Lebanon represent different minority ethnic groups to those found in North America and Europe. We believe drawing attention to these differences in pathophysiology, but also in socio-cultural factors that influence management and care is needed. Moving towards precision-medicine based care, the inequity gap will widen for under-represented groups. This chapter presents the clinical profile and health disparities in patients with HCM in a multi-ethnic Australian cohort.

The published paper forms this chapter. Author contributions are outlined in the following author contribution statement.

Reference

Butters A*,[1,2] Semsarian CR*,[3] Bagnall RD,[2,3] Yeates L,[1-4] Stafford F,[1] Burns C,[2-4] Semsarian C,[2-4] Ingles J.[1,2,4] Clinical Profile and Health Disparities in a Multiethnic Cohort of Patients with Hypertrophic Cardiomyopathy. Circ Heart Fail. 2021 Mar;14(3): e007537. doi: 10.1161/CIRCHEARTFAILURE.120.007537. Epub 2021 Mar 16. PMID: 33724884.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the first two authors equally contributed to the study and are both first authors.

The individual roles of co-authors are listed below:

Task	Role of co-author
Developing the concept of the study	AB, CRS, JI
Literature search	AB, CRS
Data analysis	AB
Drafting the manuscript	AB, CRS
Review and critical comments on manuscript	All authors
Responding to reviewer comments	AB, JI
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Sources of funding
Ms Yeates is the recipient of a co-funded National Heart Foundation of Australia/ National Health and Medical Research Council (NHMRC) PhD scholarship (no. 102568 and no. 191351). Prof Semsarian is the recipient of an NHMRC Practitioner Fellowship (no. 1154992). A/Prof Ingles is the recipient of an NHMRC Career Development Fellowship (no. 1162929). This study is funded in part by NSW Health Early-Mid Career Researcher Cardiovascular Grant.

Disclosures
A/Prof Ingles receives research grant support from Myokardia, Inc. The other authors report no conflicts

Circulation: Heart Failure

ORIGINAL ARTICLE

Clinical Profile and Health Disparities in a Multiethnic Cohort of Patients With Hypertrophic Cardiomyopathy

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BACKGROUND: Clinical studies of hypertrophic cardiomyopathy are over-represented by individuals of European ethnicity, with less known about other ethnic groups. We investigated differences between patients in a multiethnic Australian hypertrophic cardiomyopathy population.

METHODS: We performed a retrospective cohort study of 836 unrelated hypertrophic cardiomyopathy probands attending a specialized clinic between 2002 and 2020. Major ethnic groups were European (n=611), East Asian (n=75), South Asian (n=58), and Middle Eastern and North African (n=68). The minor ethnicity groups were Oceanian (n=9), People of the Americas (n=7), and African (n=8). One-way ANOVA with Dunnett post hoc test and Bonferroni adjustment were performed.

RESULTS: Mean age of the major ethnic groups was 54.9±16.9 years, and 527 (65%) were male. Using the European group as the control, East Asian patients had a lower body mass index (29 versus 25 kg/m^2, P<0.0001). South Asians had a lower prevalence of atrial fibrillation (10% versus 31%, P=0.024). East Asians were more likely to have apical hypertrophy (23% versus 6%, P<0.0001) and Middle Eastern and North African patients more likely to present with left ventricular outflow tract obstruction (46% versus 34%, P=0.0003). East Asians were less likely to undergo genetic testing (55% versus 85%, P<0.0001) or have an implantable cardioverter-defibrillator implanted (19% versus 36%, P=0.037). East Asians were more likely to have a causative variant in a gene other than *MYBPC3* or *MYH7*, whereas Middle Eastern and North African and South Asians had the highest rates of variants of uncertain significance (27% and 21%, P<0.0001).

CONCLUSIONS: There are few clinical differences based on ethnicity, but importantly, we identify health disparities relating to access to genetic testing and implantable cardioverter-defibrillator use. Unless addressed, these gaps will likely widen as we move towards precision-medicine–based care of individuals with hypertrophic cardiomyopathy.

Key Words: atrial fibrillation ■ ethnic group ■ genetic testing ■ healthcare disparities ■ hypertrophy ■ hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease with diverse phenotype expression. It is one of the most common inherited heart diseases, affecting at least 1 in 500 of the general population.[1] Over the past five decades, research efforts have focused on characterizing the natural history and genetic architecture of HCM, although this is largely based on European cohorts in North America and Western Europe. Although HCM is a global disease,[2] to date, study participants are over-represented by Europeans. Australia comprises a multiethnic population with 29% of individuals born overseas.[3] Common non-European countries of birth, such as China and India, represent different minority ethnic groups to those found in North American and European cohorts.[4–6] Australian patients hence

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.120.007537.
For Sources of Funding and Disclosures, see page 381.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Clinical characteristics are largely the same across different ethnic groups; however, health disparities are evident.
- Among patients with hypertrophic cardiomyopathy, East Asian patients are less likely to undergo genetic testing or implantable cardioverter-defibrillator insertion.
- Patients of Middle Eastern and North African and South Asian ethnicity have higher rate of variants of uncertain significance.
- East Asian patients more likely to have causative variant in sarcomere genes other than *MYBPC3* or *MYH7*.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Health disparities in under-represented ethnic groups are likely to increase as we move towards precision-based management of patients with hypertrophic cardiomyopathy.
- Greater diversity within population databases is essential to reduce the risk of misclassification and variants of uncertain significance.

Nonstandard Abbreviations And Acronyms

AF	atrial fibrillation
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
LP/P	likely pathogenic or pathogenic
LV	left ventricular
LVOTO	left ventricular outflow tract obstruction
SCD	sudden cardiac death
VT	ventricular tachycardia

comprise an ideal population to explore ethnic differences and health disparities in HCM.

Previous studies have shown ethnic differences in HCM include an increased prevalence of apical hypertrophy in Asian[7] and African American[5,6] populations. Recently, African American patients were shown to be diagnosed younger, have fewer sarcomere variants, and more symptoms than a white population.[4] A 25 bp intronic deletion in the gene encoding myosin-binding protein C (*MYBPC3*), occurring in 1% of the South Asian population, was until recently considered pathogenic[8–10]; however, more recent work has refuted this by showing this variant is often linked to a pathogenic intronic variant c.1224-52G>A.[9] Furthermore, different ethnic groups possess varying susceptibilities to risk factors that may alter the course and severity of HCM. These include metabolic and cardiovascular comorbidities, such as diabetes, coronary artery disease, and hypertension, which are each more prevalent in various Asian populations.[11]

Health disparities are preventable difference in the burden of disease based on socioeconomic disadvantage.[12] Perceived ethnic differences in medicine are now often considered to relate to health disparities, rather than underlying genetic differences.[13] Geographic disparities in implantable cardioverter-defibrillator (ICD) insertion rates have been observed in the United States,[14] United Kingdom,[15] and South Africa.[16] Furthermore, ICD implantation rates in the United States are lower among ethnic minorities and female patients.[17,18] In Australia, males are also more likely to receive an ICD.[19] It is currently not known whether ethnicity, which is considered a social construct, influences access to health care including attendance at specialized HCM clinics or HCM genetic testing options. Here, we compare clinical features, management, and investigate health disparities within a multiethnic HCM cohort.

METHODS

Consecutive Patient Series

This was a retrospective study of consecutive unrelated adult patients seen in a specialized HCM clinic in Sydney, Australia, between 2002 and 2020. All patients had a definite clinical diagnosis of HCM. A clinical diagnosis was made based on maximal left ventricular (LV) wall thickness ≥15 mm in adults in the absence of a loading condition.[20,21] The proband was defined as the first affected family member who sought medical advice for HCM in our clinic. Ethnicity was self-reported or derived using principal component analysis of ancestry informative markers. Ethnic groups were created based on the Australian Standard Classification of Cultural and Ethnic Groups (Figure 1A; https://mapchart.net/).[22] Patients were excluded if ethnicity was unknown or if a baseline echocardiogram report was unavailable. The study was approved by the local human research ethics committee. Data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

Demographic, clinical, genetic, and management data were collected from the medical record or the Australian Genetic Heart Disease Registry.[23] Presence of comorbidities, age, and presentation at diagnosis, New York Heart Association class, syncope, nonsustained ventricular tachycardia (VT), sudden cardiac death (SCD) events, interventions (septal myectomy, alcohol septal ablation, ICD, and permanent pacemaker) were adjudicated based on the consulting physician report. Nonsustained VT was defined as ≥3 consecutive beats of VT at a rate of ≥120 beats per minute, from Holter monitoring or ICD interrogation. SCD events were defined as SCD, resuscitated cardiac arrest, or appropriate ICD shocks following VT or ventricular fibrillation. Socioeconomic status was determined from postcodes using the Index of Relative Socio-Economic Advantage and Disadvantage, which is 1 of 4 indexes of the Australian

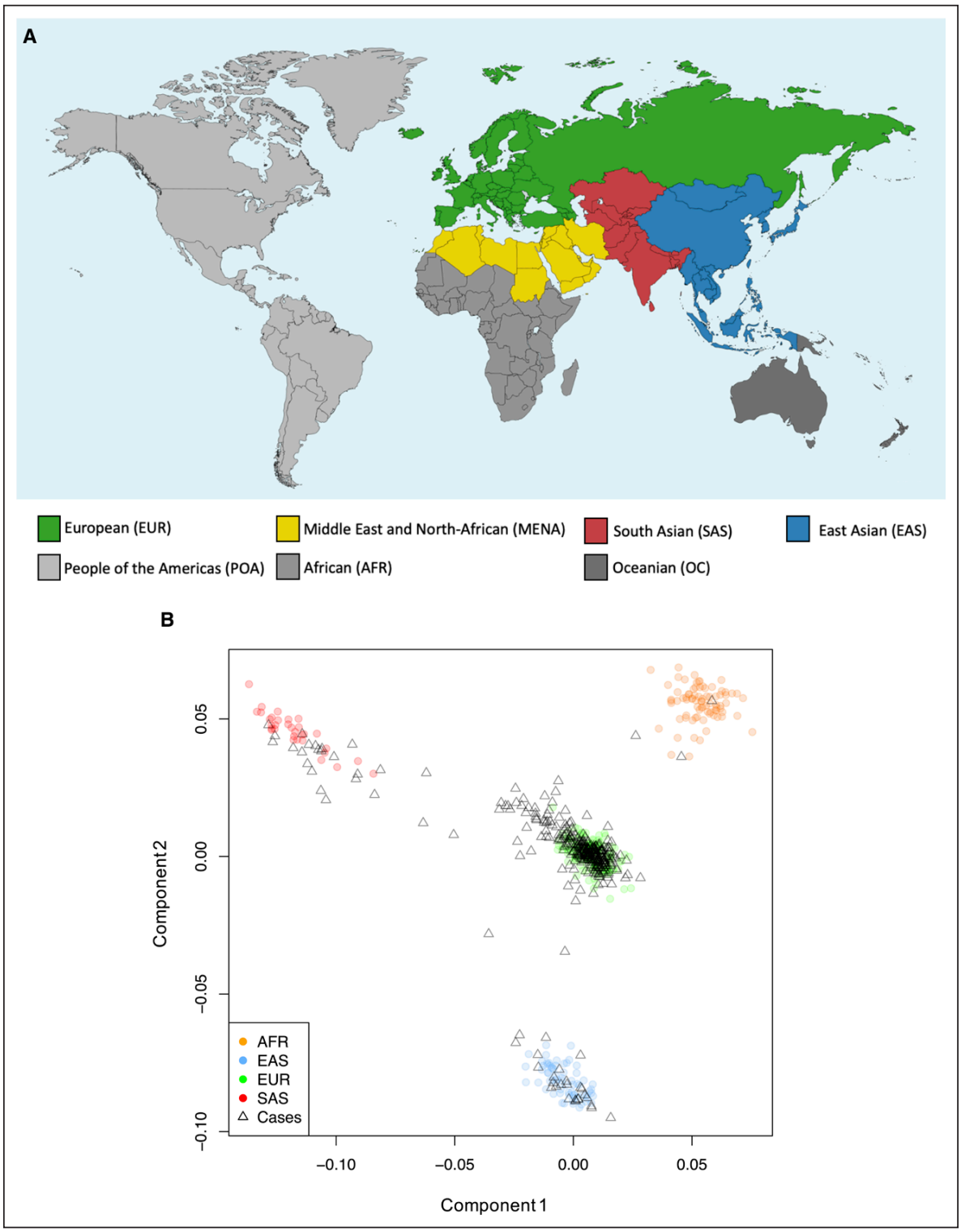

Figure 1. Ethnic groupings of a multiethnic hypertrophic cardiomyopathy cohort.
Ethnic groupings by (**A**) Australian Standard Classification of Cultural and Ethnic Groups and (**B**) principal component analysis using exome sequence data of 323 participants of the 1000 Genomes Sequencing Project at 5758 ancestry informative single-nucleotide variants. AFR indicates African; EAS, East Asian; EUR, European; MENA, Middle Eastern and North African; OC, Oceanian; POA, People of the Americas; and SAS, South Asian. https://mapchart.net/.

Bureau of Statistics Socio-Economic Indexes for Areas providing measures of socioeconomic conditions by geographic area. A high percentile reflects relative advantage and a low percentile reflects relative disadvantage (ie, the highest-scoring 1% of areas are given a percentile of 100 and the lowest-scoring 1% of areas a percentile of 1).[24] Baseline echocardiographic measurements were included, as previously described.[25] LV outflow tract obstruction (LVOTO) was defined as a gradient of ≥30 mm Hg at rest. Septal morphology was defined as asymmetrical (ie, reverse curvature),[26] apical, or other (eg, concentric). The European Society of Cardiology HCM risk-SCD estimate was calculated for patients with ICD. As previously described, these patients were categorised into low, intermediate, and high-risk groups.

Outcome Definitions

To maximize statistical power, composite outcome measures were developed as per Ho et al[27] and included (1) heart failure composite: heart failure, previous heart transplantation, LV ejection fraction <40%, New York Heart Association classification III or IV; (2) ventricular arrhythmia composite: history of SCD, resuscitated cardiac arrest, appropriate ICD shock (for fast VT or ventricular fibrillation); and (3) overall composite: inclusion in either ventricular arrhythmia or heart failure composite, atrial fibrillation (AF), or all-cause mortality. Prevalent and incident outcomes were included.

Ethnicities Determined by Exome or Genome Sequencing

We derived ethnicity for HCM probands with sequencing data available using principal component analysis of ancestry informative markers. From the 826 with self-reported ethnicities, we compared HCM probands who had undergone research-based exome sequencing (n=280) or genome sequencing (n=51) to exome sequence data of 323 participants of the 1000 Genomes Sequencing Project at 5758 ancestry informative single-nucleotide variants who were classified as European, South Asian, East Asian, or African. Individuals were assigned to one of these major ethnic groups based on the presence of ethnic-specific single-nucleotide variants and self-reported ethnicities were compared against these (Figure 1B).

Genetic Analyses and Variant Classification

Outcomes of genetic testing, performed either commercially or on a research basis, were recorded. Recent *MYH7* modified American College of Medical Genetics and Genomics and Association of Molecular Pathologists criteria were used to classify variants as per routine clinical practice in our center.[28] Rare variants with a minor allele frequency of ≤0.004% in the Genome Aggregation Database (http://gnomAD.broadinstitute.org/) and in an established HCM gene (*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL2, MYL3, ACTC1*) were considered.[29] Probands with causative variants in phenocopy genes (*PRKAG2, LAMP2, GLA*) and atypical HCM phenotypes (*ACTN2, PLN*)[30] were excluded from further analysis. Those variants classified as likely pathogenic or pathogenic (LP/P) were considered causative. Given current approaches to classification are known to be overly conservative,[31] suspicious variants of uncertain significant (VUS) were those variants considered to have a high likelihood of causation, that is, sufficiently rare and in a key sarcomere gene but lacking evidence for LP/P classification.

Statistical Analysis

Statistical analyses were performed using SAS Studio (SAS Institute, Inc, Cary, NC) and Prism version 8.0 (GraphPad Software, Inc, La Jolla, CA). Continuous data are expressed as mean and SD, and categorical data as number and percent. Differences between means for continuous variables were analyzed using 1-way ANOVA. Comparison of categorical variables, expressed as proportions, was performed using χ^2 test. For variables with expected counts <5 (New York Heart Association III–IV, heart transplant, alcohol septal ablation, and septal myectomy), Fisher exact test was used to compare European and non-European cohorts. A $P<0.05$ was considered statistically significant. If a statistically significant result was observed, post hoc analysis was performed to identify which groups differed. To maintain the significance level at 0.05 and limit multiple comparisons, Dunnett test was used for continuous variables. As such, the East Asian, South Asian, and Middle Eastern North African groups were each compared with the European group, which acted as the control. Conversely, Bonferroni correction was used for categorical variables, with the significance cutoff at α/n (number of comparisons), which resulted in an adjusted significance level of 0.05/3=0.02 for the post hoc analyses.

RESULTS

Patient Characteristics

Of 1025 consecutive HCM probands, 836 were included in the analysis (Figure 2). Self-reported ethnicity was known for 826 probands, whereas a further 10 had their ethnicity derived from principal component analysis only. There were 812 patients representing 4 major ethnic groups: European (n=611), East Asian (n=75), South Asian (n=58), and Middle Eastern and North African (n=68). The remaining 24 patients represented 3 minor but diverse ethnicity groups: Oceanian (n=9), People of the Americas (n=8), and African (n=8; Table I through VI in the Data Supplement). There were 189 patients excluded from further analysis due to their ethnicity being unknown (n=124) or where no echocardiogram data were available (n=65). The overall mean age of the major cohort was 54.9±16.9 years and 527 (64.9%) were male (Table 1).

Single-Nucleotide Variant–Derived Ethnicities

Principal component analysis identified ancestral ethnicity in 269 individuals: 219 European, 26 East Asian, 21 South Asian, and 3 African (Figure 1B). Individuals that were either not from these groups or of mixed race did not cluster with other samples and therefore ethnicity was unable to be derived (inconclusive n=62). Self-reported ethnicities were 97.3% congruent with ancestral ethnicities as determined by principal component analysis from exome or genome sequencing.

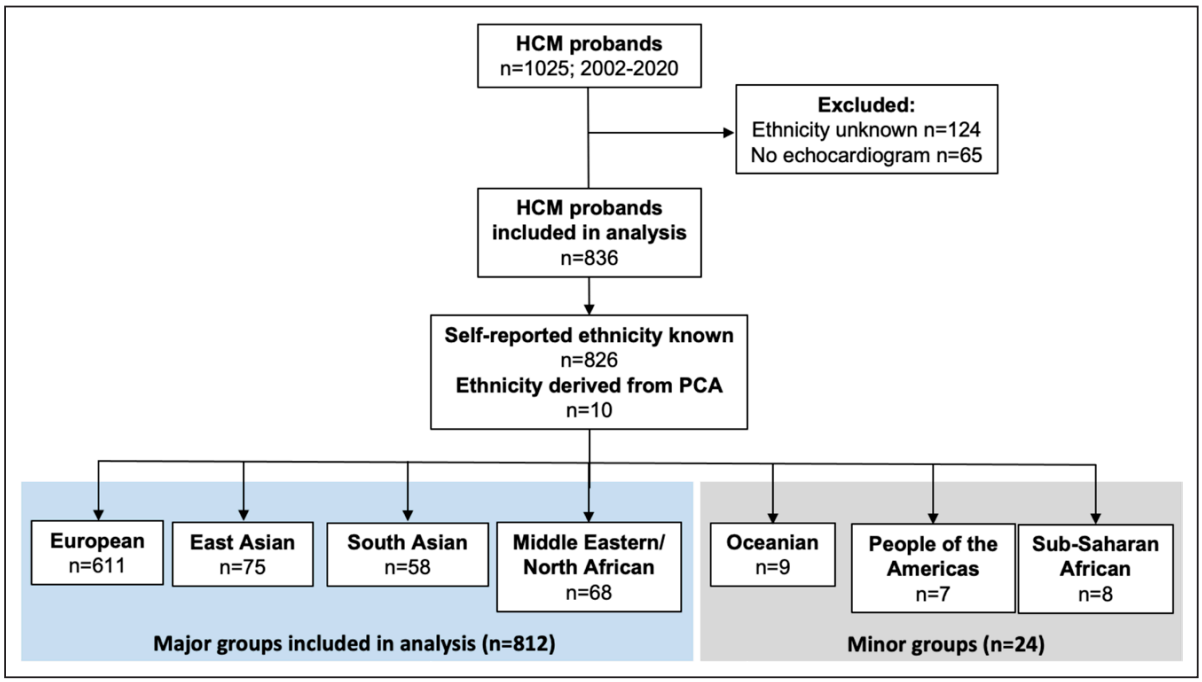

Figure 2. Flow diagram of study participants.
HCM indicates hypertrophic cardiomyopathy; and PCA, principal component analysis.

Clinical Differences Between Major Ethnic Groups

The key clinical differences between the major ethnic groups are shown in Table 1. The ethnic groups differed in age (52–56 years, P=0.028), although post hoc analysis did not identify a difference between either of the 3 ethnicity groups compared with Europeans. Body mass index (kg/m^2) differed between groups (25–29 kg/m^2, P<0.001), with East Asian patients having a significantly lower body mass index compared with Europeans (P<0.05). Only 10% of South Asian probands had AF, compared with 31% of European, 30% East Asian, and 26% Middle Eastern and North African groups (P=0.024), and post hoc analysis identified South Asian patients were significantly less likely to experience AF than Europeans (P<0.02). Although there were no significant differences in sex or presence of diabetes, 80% of South Asian patients were male, compared with 59% to 69% in the other groups, and 21% of East Asian patients had diabetes compared with only 7% to 12% in the other groups. There were no differences regarding socioeconomic advantage and disadvantage (Index of Relative Socio-Economic Advantage and Disadvantage percentile), age at diagnosis, presentation, prevalence of hypertension, prevalence of high cholesterol, New York Heart Association class, syncope, nonsustained VT, and family history of disease and SCD.

Echocardiographic Differences

Several baseline echocardiographic features differed significantly between the ethnic groups. As shown in Table 2, mean maximum LV wall thickness (19–21 mm, P=0.013) and mean LV posterior wall thickness (17–20 mm, P=0.023) differed between the groups. Post hoc analysis identified a subtle but significant difference in maximum LV wall thickness between Middle Eastern and Northern Africans and Europeans (20.9±5.9 mm versus 19.3±5.0 mm, P<0.05). LV end-systolic (24–27 mm, P=0.021) and diastolic (42–45 mm, P=0.003) diameter were significantly different between the ethnic groups, with South Asians having a significantly lower LV systolic (24.2±5.7 mm versus 26.9±7.1 mm, P<0.05) and diastolic diameter (41.7±6.4 mm versus 44.6±7.1 mm, P<0.05), whereas Middle Eastern and Northern African patients had a significantly lower diastolic diameter only (42.2±7.3 mm versus 44.6±7.1 mm, P<0.05). After controlling for body surface area, the significant differences in LV wall thickness did not persist; however, LV cavity size remained significantly different. Differences in hypertrophy pattern were seen, with 23% of East Asian patients having apical hypertrophy compared with 5% to 11% in the other groups (P<0.0001), post hoc analysis for East Asian and European patients remained significantly different (16 [23%] versus 33 [6%], P<0.02). The presence of systolic anterior motion of the mitral valve was most prevalent in Middle Eastern and North African probands (64%) followed by South Asian (51%), European (48%), and East Asian (27%; P=0.0002). Post hoc analysis showed greater prevalence than Europeans in the Middle Eastern and Northern African group (41 [64%] versus 265 [48%], P<0.02) and a lower prevalence in the

Table 1. Demographic and Clinical Features of HCM Probands From the Major Ethnic Groups Represented in a Multiethnic Cohort

	Total cohort	EUR	EAS	SAS	MENA	*P* value
N	812	611	75	58	68	
Age, y	54.9±16.9	55.8±17.1	53.1±15.2	50.5±14.5	51.7±18.0	0.028
Male sex	527 (64.9)	390 (63.8)	44 (58.7)	46 (79.3)	47 (69.1)	0.06
Follow-up time, median (IQR)	4.4 (1.0–9.8)	5.2 (1.4–10.4)	1.8 (1.0–5.4)*	1.2 (1.0–9.4)*	4.2 (1.4–8.7)	<.0001
IRSAD percentile	66.8±30.0	66.9±30.1	71.5±26.7	69.0±28.8	58.5±32.0	0.07
Age at diagnosis, y	44.4±17.6	45.0±17.8	44.8±15.8	42.7±15.3	39.2±18.7	0.08
Symptomatic presentation	411 (55.0)	306 (53.3)	37 (59.7)	33 (66.0)	35 (56.5)	0.30
BMI, kg/m^2	28.2±5.7	28.6±5.8	25.1±4.3*	27.5±5.3	28.8±6.0	<.0001
Hypertension	269 (34.5)	205 (34.6)	26 (37.7)	19 (34.6)	19 (30.2)	0.84
Diabetes	74 (10.7)	51 (9.8)	12 (20.7)	4 (7.3)	7 (11.9)	0.06
High cholesterol	123 (17.8)	84 (16.2)	15 (25.4)	14 (25.9)	10 (17.0)	0.13
Atrial fibrillation	215 (29.2)	176 (31.1)	18 (29.5)	5 (10.4)†	16 (26.2)	0.024
NYHA class (III–IV) ever‡	35 (4.9)	25 (4.6)	5 (7.9)	2 (3.9)	3 (5.1)	0.70
Syncope	148 (22.2)	121 (23.7)	9 (18.4)	9 (19.6)	9 (15.0)	0.40
NSVT	156 (20.9)	125 (21.9)	7 (11.1)	10 (18.9)	14 (23.3)	0.23
Family history of HCM	260 (33.0)	210 (35.2)	18 (25.4)	15 (27.8)	17 (35.2)	0.15
Family history of SCD	104 (13.2)	88 (14.7)	4 (5.6)	5 (9.3)	7 (10.8)	0.11

Data shown as n (%) or mean±SD. BMI indicates body mass index; EAS, East Asian; EUR, European; HCM, hypertrophic cardiomyopathy; IRSAD, Index of Relative Socio-Economic Advantage and Disadvantage; MENA, Middle Eastern and North African; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SAS, South Asian; and SCD, sudden cardiac death.

*P<0.05 Dunnett test compared with European group (control).

†P<0.02 Bonferroni adjustment compared with European group (control).

‡Fisher exact test did not find a significant difference in rates of NYHA class III–IV (EUR: 4.6% vs non-EUR: 5.8%, P=0.542).

East Asian group (18 [27%] versus 265 [48%], P<0.02). LVOTO (defined as LVOTO ≥30 mm Hg at rest; 18%–44%, P=0.009) also differed between the groups. However, post hoc analysis only showed Middle Eastern and Northern African patients were significantly more likely to have LVOTO than Europeans (29 [44%] versus 171 [29%], P<0.02). All analyses were repeated removing those with apical pattern of hypertrophy and the results remained unchanged.

Access to Genetic Testing

Genetic testing was performed in 669 (82%) patients. A result was available in 629 out of 669 patients at time of analysis. The uptake of genetic testing varied significantly between the ethnic groups with only 57% of East Asian patients undertaking genetic testing compared with 86% European, 78% South Asian, and 78% Middle Eastern and Northern African (<0.0001). As such, post hoc analysis showed East Asian patients were significantly less likely to undergo genetic testing than Europeans (521 (85%) versus 41 (55%), P<0.02). To further investigate why this disparity may be occurring, use of genetic testing in patients with asymmetrical HCM only was examined; however, disparate rates of genetic testing persisted (European 421 [85%]; East Asian 27 [55%]; South Asian 38 [79%]; Middle Eastern (44 [77%], P<0.0001).

Of 629 probands where a classification was made, a total of 247 (39%) patients received an LP/P result, 68 (11%) suspicious VUS, and 314 (50%) were indeterminate. The yield of genetic testing differed between the major ethnic groups, with 42% of Europeans receiving an LP/P result compared with 35% South Asian, 30% East Asian, and 19% Middle Eastern (P<0.0001). Predictably, rates of suspicious VUS were highest in the Middle Eastern and North African group (27%), followed by South Asian (21%), East Asian (15%), and European (8%) patients. Indeterminate results occurred in 55% of East Asian, 54% Middle Eastern and Northern African, 50% European, and 44% South Asian (Figure 3A). Post hoc analysis showed the genetic yield of LP/P variants significantly differed between Middle Eastern and Northern African and European patients (10 [19%] versus 210 [43%], P<0.02).

Among those with LP/P variants, the distribution of disease genes varied significantly between the ethnic groups (P=0.0003). Variants in *MYBPC3* accounted for 59% of patients and were most common in South Asian patients (67%) followed by European (61%), Middle Eastern and North African (50%), and East Asian (25%). Variants in *MYH7* were most common in Middle Eastern and Northern African (40%) followed by South Asian (33%), European (28%), and East Asian (17%). Other sarcomere variants *(TNNT2, TNNI3, TPM1, MYL2, MYL3,* and *ACTC1)* were overwhelmingly more common

Table 2. Baseline Echocardiographic Features of HCM Probands From the Major Ethnic Groups Represented in a Multiethnic Cohort

	Total cohort	EUR	EAS	SAS	MENA	*P* value
N	812	611	75	58	68	
Maximum LV wall thickness, mm	19.4±5.3	19.3±5.0	18.5±4.5	20.5±6.9	20.9±5.9*	0.013
LV posterior wall, mm	11.3±2.9	11.3±2.9	10.6±2.4	11.3±2.9	12.1±3.3	0.023
Hypertrophy pattern			†			<0.0001
ASH	649 (84.6)	495 (86.1)	49 (70.0)	48 (85.7)	57 (86.4)	
Apical	58 (7.6)	33 (5.7)	16 (22.9)	6 (10.7)	3 (4.6)	
Concentric	60 (7.8)	47 (8.2)	5 (7.1)	2 (3.6)	6 (9.1)	
LV end-diastolic diameter, mm	44.1±7.1	44.6±7.1	43.7±7.1	41.7±6.4*	42.2±7.3*	0.003
LV end-systolic diameter, mm	26.5±6.7	26.9±7.1	25.9±5.5	24.2±5.7*	25.5±5.3	0.021
LV ejection fraction %	65.2±10.9	65.1±10.8	63.1±11.7	64.9±9.3	68.4±11.1	0.32
SAM	352 (47.5)	265 (47.8)	18 (26.5)	28 (50.9)†	41 (64.1)†	0.0002
LA size, mm	42.8±8.2	42.8±7.8	42.3±9.1	41.7±8.9	44.3±10.5	0.61
LVOT obstruction (≥30 mm Hg)	232 (29.6)	171 (29.0)	13 (18.1)	19 (33.3)	29 (43.9)†	0.009
LVOT max gradient at rest, mm Hg	55.1±44.2	53.0±44.6	60.5±58.6	64.2±37.0	62.9±35.5	0.48

Data shown as n (%) or mean±SD. ASH indicates asymmetrical hypertrophy; EAS, East Asian; EUR, European; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract; MENA, Middle Eastern and North African; SAM, systolic anterior motion of the mitral valve; and SAS, South Asian.

*P<0.05 Dunnett test compared with European group (control)

†P<0.02 Bonferroni adjustment compared with European group (control)

in East Asian patients, identified in 58% of patients compared with 11% of European, 10% of Middle Eastern and Northern African, and 0% of South Asian patients (Figure 3B through 3E). The only significant difference observed in the distribution of disease genes on post hoc analysis was between East Asian and European patients (P<0.02). Of the 7 East Asian patients with variants in other sarcomere genes, 3 variants were in *TNNT2,* and 4 were in *TNNI3*.

To determine whether differences persisted in those with sarcomere positive HCM only, clinical characteristics and outcomes by ethnicity for the subset of patients with an LP/P sarcomere variant were investigated (Table II in the Data Supplement). There were n=247 included total, with small subgroups for non-European patients (10–15 patients per group). There were fewer statistical differences, though this may be due to the limited sample size.

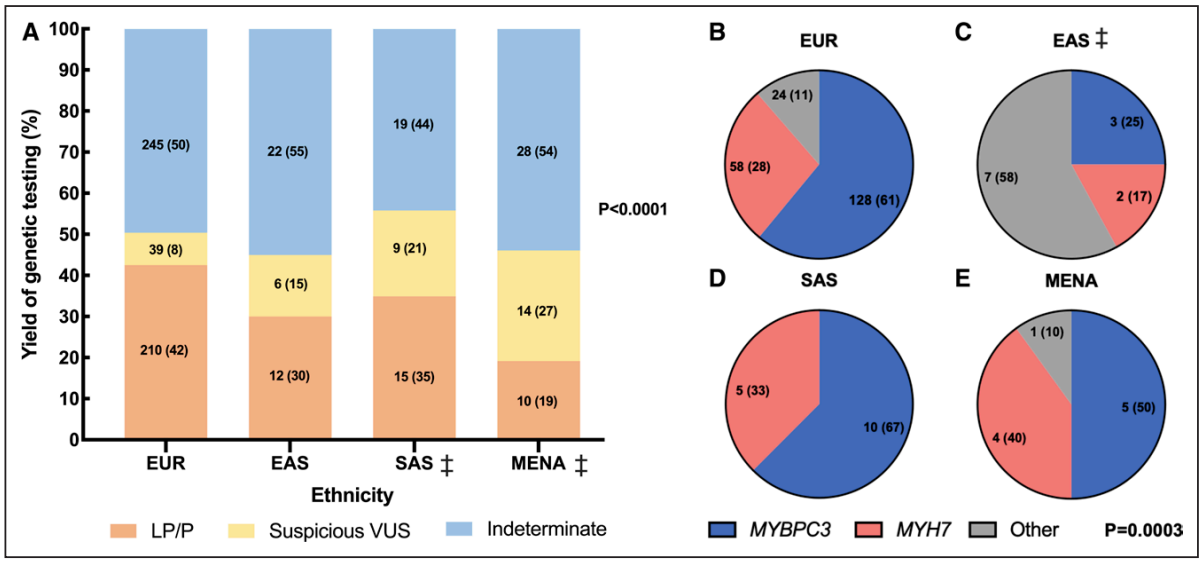

Figure 3. Yield of genetic testing in hypertrophic cardiomyopathy probands from the major ethnic groups represented in a multiethnic cohort.

Yield of (**A**) Genetic classifications and (**B**–**E**) Likely pathogenic or pathogenic (LP/P) genes. Data shown are n (%). EAS indicates East Asian; EUR, European; MENA, Middle Eastern and Northern African; SAS, South Asian; and VUS, variant of uncertain significance. ‡P<0.02 Bonferroni adjustment compared with European group (control).

Management and Outcomes

A comparison of the management and clinical outcomes of HCM probands for each ethnic group is shown in Table 3. Only 19% of patients of East Asian ethnicity underwent ICD implantation, a significantly lower proportion than the other ethnic groups (36%–30%, *P*=0.037; post hoc analysis 12 [19%] versus 212 [36%], *P*<0.02). Among those who received an ICD, there was no difference in European Society of Cardiology HCM Risk-SCD category (low, intermediate, or high) between the groups, indicating ICD implantation differences may indeed reflect health disparities. This subgroup analysis was limited by sample size and should be interpreted with caution. Furthermore, ICD indication and sex of those with an ICD implanted showed no differences between the groups for any of these variables. No differences were found in rates of alcohol septal ablation, septal myectomy, and heart transplant.

The prevalence of heart failure and ventricular arrhythmia composite outcomes did not differ between the major ethnic groups (Figure 4). The heart failure composite outcome was reached by 10 out of 74 (14%) East Asian, 8 out of 68 (12%) Middle Eastern and North African, 57 out of 608 (9%) European, and 5 out of 58 (9%) South Asian patients, *P*=0.650. The ventricular arrhythmia composite was reached by 48 out of 584 (8%) European, 4 out of 61 (7%) Middle Eastern and North African, 4 out of 64 (6%) East Asian, and 3 out of 57 (5%) of South Asian patients, *P*=0.802. The overall composite outcome did differ between the groups. We found 11 out of 58 (19%) South Asian patients had the outcome, compared with 21 out of 68 (31%) Middle Eastern and Northern African, 26 out of 74 (35%) East Asian, and 239 out of 611 (39%) European patients. Consequently, post hoc analysis identified that South Asian patients were significantly less likely to develop the overall composite outcome compared with Europeans (11 [19%] versus 239 [39%], *P*<0.02). The difference appears to be driven by the lower prevalence of AF in the South Asian group.

Table 3. Service Use and Management of HCM Probands From the Major Ethnic Groups Represented in a Multiethnic Cohort

	Total cohort	EUR	EAS	SAS	MENA	*P* value
N	812	611	75	58	68	
Genetic testing performed	669 (82.4)	528 (86.4)	43 (57.3)*	45 (77.6)	53 (77.9)	<0.0001
Genetic testing result				*	*	<0.0001
LP/P	247 (39.3)	210 (42.5)	12 (30.0)	15 (34.9)	10 (19.2)	
Suspicious VUS	68 (10.8)	39 (7.9)	6 (15.0)	9 (20.9)	14 (26.9)	
Indeterminate	314 (49.9)	245 (49.6)	22 (55.0)	19 (44.2)	28 (53.9)	
LP/P gene			*			0.0003
MYBPC3	146 (59.0)	128 (61.0)	3 (25.0)	10 (66.7)	5 (50.0)	
MYH7	69 (27.9)	58 (27.6)	2 (16.7)	5 (33.3)	4 (40.0)	
Other	32 (13.0)	24 (11.4)	7 (58.3)	0 (0)	1 (10.0)	
Heart transplant†	12 (1.6)	8 (1.4)	1 (1.5)	1 (1.9)	2 (3.2)	0.75
Alcohol septal ablation†	35 (4.6)	27 (4.6)	0 (0)	2 (3.7)	6 (9.5)	0.080
Septal myectomy†	51 (6.6)	44 (7.5)	2 (3.0)	2 (3.7)	3 (4.8)	0.36
Pacemaker	130 (16.9)	105 (17.9)	9 (13.9)	8 (14.8)	8 (12.5)	0.60
ICD	261 (33.7)	212 (35.9)	12 (18.5)*	16 (29.6)	21 (32.3)	0.037
ICD indication						0.20
Primary	238 (91.2)	195 (92.0)	9 (75.0)	14 (87.5)	20 (95.2)	
Secondary	23 (1.8)	17 (8.0)	3 (25.0)	2 (12.5)	1 (4.8)	
ICD implantation						0.20
Male	182 (69.7)	147 (69.3)	6 (50.0)	14 (87.5)	15 (71.4)	
Female	79 (30.3)	65 (30.7)	6 (50.0)	2 (12.5)	6 (28.6)	
ESC risk score						0.34
<4%	82 (48.0)	71 (51.1)	2 (40.0)	4 (36.4)	5 (31.3)	
4-6%	45 (26.3)	33 (23.7)	3 (60.0)	3 (27.3)	6 (37.5)	
>6%	44 (25.7)	35 (25.2)	0 (0)	4 (36.4)	5 (31.3)	

Data shown as n (%) or mean±SD. EAS indicates East Asian; ESC, European Society of Cardiology; EUR, European; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LP/P, likely pathogenic/pathogenic; MENA, Middle Eastern and North African; SAS, South Asian; and VUS, variant of unknown significance.

*P<0.02 Bonferroni adjustment compared with European group (control).

†Fisher exact test did not find and significant difference in rates of alcohol septal ablation (EUR: 4.6% vs non-EUR: 4.4%, *P*=0.894), septal myectomy (EUR: 7.5% vs 3.8%, *P*=0.080) or heart transplants (EUR: 1.4% vs non-EUR: 2.2%, *P*=0.434).

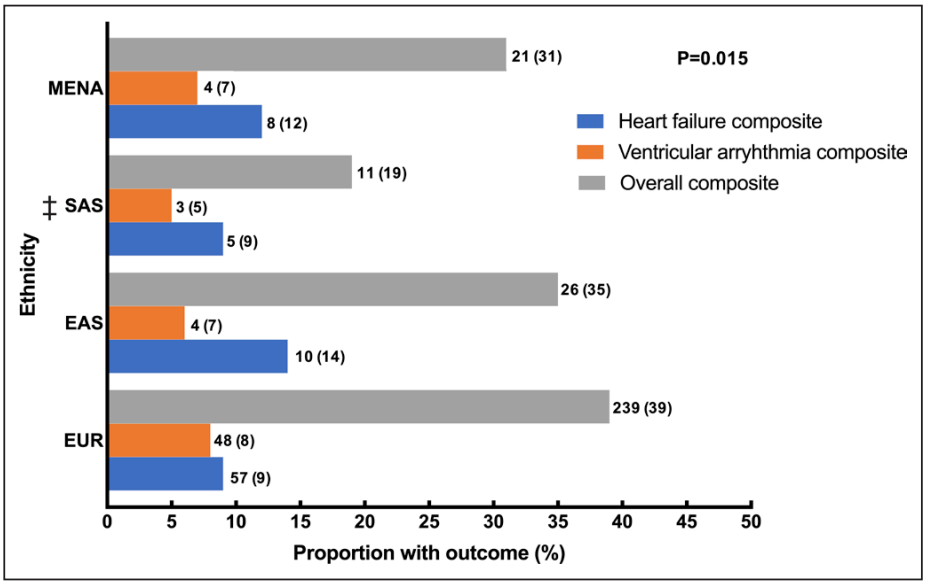

Figure 4. Proportion of patients meeting the composite outcomes by major ethnicity group.
Data shown are n (%). EAS indicates East Asian; EUR, European; MENA, Middle Eastern and Northern African; and SAS, South Asian.
‡*P*<0.02 Bonferroni adjustment compared with European group (control).

DISCUSSION

Current evidence guiding management and care of HCM patients is derived primarily from cohorts of European ethnicity. We report our experience of HCM in the ethnically diverse Australian population. We show there are overall very few physiological differences, however yield of genetic testing and distribution of genes across the groups were different. Differences were seen in the uptake of genetic testing and use of ICDs, suggesting social disparities across these ethnic groups. Our findings contribute to a greater understanding of HCM among different ethnic groups and point to current inequities in access to care. As health care moves towards precision-based management, it is important to recognize that the health disparity gap is likely to widen for some populations, particularly those that are currently not well represented in the scientific literature and disease registries. These are key issues to be addressed in the interest of providing tailored and evidence-based care to all individuals with HCM regardless of their ethnic background.

In the general population, East Asian and South Asian individuals overall have greater visceral adiposity and comorbid metabolic and cardiovascular risk factors at lower body mass index values than their European counterparts, though there is clinical heterogeneity within these groups.[32] Higher rates of type 2 diabetes among Asian individuals, particularly in South-East Asia are also well-documented and may be related to the increasing prevalence of prediabetes caused by adipocyte phenotype and rapidly changing food environments.[32] We show that only 10% of South Asian patients developed AF, which is consistent with data suggesting South Asian patients are at a decreased risk of AF, despite having higher frequencies of established risk factors.[33] Our findings support existing data showing higher rates of apical pattern of hypertrophy in non-European populations.[5–7] Furthermore, it is currently estimated that LVOTO is present in ≈30% of HCM patients at rest[34]; however, we show 44% of Middle Eastern and North African patients, and only 18% of East Asian patients, experienced LVOTO which likely relate to the frequency of apical hypertrophy pattern.

We observed lower uptake of genetic testing within the East Asian group. Studies investigating uptake of genetic testing in cancer and prenatal screening likewise report lower uptake, but the reasons why are not understood.[35] Our center offers primarily research-based HCM genetic testing to anyone with a confirmed diagnosis of HCM at no cost to the patient. Although we found no significant difference in socioeconomic advantage and disadvantage (Index of Relative Socio-Economic Advantage and Disadvantage) between ethnic groups, we hypothesize that genetic testing is underutilized in the East Asian population due to referral reasons and cultural differences. As this is a specialized center, a significant proportion of East Asian patients are referred for discussion of a management issue rather than for genetic testing, after which the patient returns to the care of their regular cardiologist. Lower uptake may be a cultural preference, differences in attitudes to genetic testing, or a decision impacted by language barriers. For example, the comparable uptake of genetic testing in South Asians and Europeans could be a result of English being more frequently spoken in these countries. We do provide

interpreters for those unable to speak English and aim to offer culturally sensitive genetic counseling; however, this may still be a barrier to the uptake of genetic testing. We need to better understand this issue, with implications for genetic counseling practice that acknowledges and support access to genetic testing for those who perceive more barriers.

Ability to interpret the genetic variants is challenging in poorly represented ethnic groups, resulting in greater risk of misclassification or more VUS.[36] In our population, Middle Eastern and North African and South Asian patients had the highest rates of VUS following HCM genetic testing. The need for greater diversity in population databases is well described[37] and greater efforts to understand ethnic-specific genetic variation is exemplified by the recent finding that the 25 bp deletion in *MYBPC3* found in 4% to 8% of South Asian populations does not directly confer increased risk of HCM but acts as a proxy marker for the rare intronic variant, *MYBPC3* c.1224-52G>A.[8,9] This variant is one of the most frequently reported HCM variants and potentially impacts 100 million individuals of South Asian ethnicity who carry the 25 bp deletion, who would have previously been considered at increased risk of HCM. Furthermore, we describe differences in the distribution of sarcomere gene involvement based on ethnicity with East Asian patients being more likely to have causative variants in *TNNI3* and *TNNT2.* Patients with variants in thin filament genes have been previously shown to have less LV hypertrophy, greater likelihood of nonasymmetrical pattern of hypertrophy, and less LVOTO.[38] The greater prevalence of *TNNT2* and *TNNI3* have recently been observed in Singaporeans with HCM, albeit with a modest prevalence of LP/P genes.[39]

The differential rate of ICD implantation among ethnic groups, despite similar clinical features, symptoms, reason for implant, and sex-distribution aligns with global trends. Previous studies show that men are more likely to receive ICD therapy in the United States[17,18,40] and Australia.[19] However, in the context of HCM, equal distribution of ICD devices has been shown in Italian[41] and Japanese[42] cohorts. Higher rates of ICD implantation in males shown across ethnic groups may be driven by sociocultural factors in the Australian health care system. In the United States, African American and Hispanic patients were less likely to receive ICD counseling and implantation than their white counterparts.[17] Our findings suggest similar underutilisation of ICD intervention, particularly among East Asian patients, although barriers to access should be further investigated.

Potential limitations of our study include the underrepresentation of Aboriginal and Torres Strait Islander patients who were part of the Oceanian group and together accounted for only a small percentage of patients.[43] Poor health care outcomes and greater barriers to accessing care are well described, and although genetic reference data for Indigenous Australians are beginning to emerge,[44] there is a long way to go to address health inequities in this population. Clinical evaluation across the cohort was not standardized, with investigations directed by the attending clinician and reflective of the evolving diagnostic landscape over the 18-year study period. Due to the retrospective nature of the study, complete datasets were not available for all patients despite our best efforts to collect all relevant clinical and genetic information. Finally, it is inherently difficult to categorize people into broad ethnic categories as these groups likely comprise numerous diverse ethnic subgroups. Caution in attributing physiological differences based on ethnic group is advised, and as we show are likely the result of important health disparities.

CONCLUSIONS

We demonstrate few differences in clinical characteristics, but important health disparities, including access to genetic testing and therapies among the major ethnic groups in a multiethnic HCM cohort. Health disparities in these under-represented groups are likely to increase as we move towards precision-based management approaches unless efforts are made to better understand and address these issues.

ARTICLE INFORMATION

Received June 19, 2020; accepted January 21, 2021.

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Sources of Funding

L. Yeates is recipient of a cofunded National Heart Foundation of Australia/National Health and Medical Research Council (NHMRC) PhD scholarship (no. 102568 and no. 191351). Dr Semsarian is the recipient of an NHMRC Practitioner Fellowship (no. 1154992). Dr Ingles is the recipient of an NHMRC Career Development Fellowship (no. 1162929). This study is funded in part by NSW Health Early-Mid Career Researcher Cardiovascular Grant.

Disclosures

Dr Ingles receives research grant support from Myokardia, Inc. The other authors report no conflicts.

Supplemental Material

Tables I–VI

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3.8 Data supplement

SUPPLEMENTARY TABLE I: Clinical and echocardiographic features of HCM probands from the minor ethnic groups represented in multi-ethnic cohort.

	OC	POA	AFR
n	9	7	8
Age (years)	51.0 ± 12.6	34.8 ± 9.8	50.6 ± 11.1
Male sex	5 (55.6)	6 (85.7)	5 (62.5)
Follow-up time, median (IQR)	5.9 (1.9-8.8)	2.8 (1.5-8.2)	4.7 (2.2-8.9)
IRSAD percentile	50.6 ± 32.2	70.3 ± 37.7	66.4 ± 33.6
Age at diagnosis (years)	41.1 ±15.4	24.7 ± 6.9	43.7 ± 15.7
Symptomatic presentation	7 (77.8)	4 (57.1)	6 (75.0)
BMI (kg/m2)	28.5 ± 9.1	26.9 ± 2.4	26.8 ± 5.4
Hypertension	3 (33.3)	0 (0)	4 (50.0)
Diabetes	2 (22.2)	1 (25.0)	0 (0)
High cholesterol	1 (11.1)	1 (25.0)	0 (0)
Atrial fibrillation	2 (22.2)	2 (28.6)	0 (0)
NYHA class (III-IV) ever*	3 (33.3)	1 (16.7)	0 (0)
Syncope	2 (25.0)	1 (16.7)	3 (37.5)
NSVT	1 (11.1)	0 (0)	1 (12.5)
Family history of HCM	3 (37.5)	2 (28.6)	2 (25.0)
Family history of SCD	1 (12.5)	1 (14.3)	1 (12.5)

Data shown as n (%) or mean ± SD. OC=Oceanian, POA= People of the Americas, AFR= Sub-Saharan African, HCM=hypertrophic cardiomyopathy, IRSAD = Index of Relative Socio-Economic Advantage and Disadvantage, BMI = body mass index, NSVT = non-sustained ventricular tachycardia, NYHA = New York Heart Association, SCD = sudden cardiac death.

SUPPLEMENTARY TABLE II: Echocardiographic features of HCM probands from the minor ethnic groups represented in multi-ethnic cohort.

	OC	POA	AFR
n	9	7	8
Maximum LVWT (mm)	18.7 ± 8.3	26.1 ± 7.6	17.4 ± 4.7
LVPW (mm)	11.2 ± 3.2	10.3 ± 2.0	11.3 ± 2.1
Hypertrophy pattern ASH Apical Concentric	 7 (87.5) 1 (12.5) 0 (0)	 6 (85.7) 1 (14.3) 0 (0)	 4 (57.1) 1 (14.3) 2 (28.6)
LVEDD (mm)	41.8 ± 7.1	40.7 ± 4.4	39.9 ± 4.1
LVESD (mm)	24.6 ± 6.1	24.7 ± 4.5	24.8 ± 5.4
LVEF %	70.2 ± 10.3	69.4 ± 9.4	65.3 ± 1.5
SAM	6 (66.7)	2 (33.3)	3 (37.5)
LA size, mm	42.2 ± 9.9	45.0 ± 22.3	45.5 ± 5.0
Obstructive physiology (≥30mmHg)	2 (22.2)	1 (14.3)	3 (37.5)

Data shown as n (%) or mean ± SD. OC=Oceanian, POA= People of the Americas, AFR= Sub-Saharan African, HCM=hypertrophic cardiomyopathy, LVWT= left ventricular wall thickness, LVPW= left ventricular posterior wall, ASH= asymmetrical hypertrophy, LVEDD= left ventricular end diastolic diameter, LVESD= left ventricular end systolic diameter, LVEF= left ventricular ejection fraction, SAM= systolic anterior motion of the mitral valve, LVOTO= left ventricular outflow tract obstruction, EF= ejection fraction.

SUPPLEMENTARY TABLE III: Service use and management of HCM probands from the minor ethnic groups represented in multi-ethnic cohort

	OC	POA	AFR
n	9	7	8
Genetic testing performed	8 (88.9)	6 (85.7)	4 (50.0)
Genetic testing result LP/P Suspicious VUS Indeterminate	 4 (50.0) 1 (12.5) 3 (37.5)	 3 (50.0) 2 (33.3) 1 (16.7)	 1 (25.0) 1 (25.0) 2 (50.0)
LP/P gene MYBPC3 MYH7 Other	 1 (25.0) 3 (75.0) 0 (0)	 3 (100) 0 (0) 0 (0)	 1 (100) 0 (0) 0 (0)
Heart transplant	1 (11.1)	0 (0)	0 (0)
Alcohol septal ablation	0 (0)	0 (0)	0 (0)
Septal myectomy	0 (0)	0 (0)	1 (12.5)
Pacemaker	0 (0)	1 (14.3)	3 (37.5)
ICD	1 (11.1)	2 (28.6)	4 (50.0)

Data shown as n (%) or mean ± SD. Oceanian, POA= People of the Americas, AFR= Sub-Saharan African, HCM=hypertrophic cardiomyopathy, LP/P = likely pathogenic/pathogenic, VUS = variant of unknown significance, ICD = implantable cardioverter defibrillator

SUPPLEMENTARY TABLE IV: Demographic and clinical features of sarcomere-positive HCM probands from the major ethnic groups represented in multi-ethnic cohort

	Total cohort	EUR	EAS	SAS	MENA	p-value
n	247	210	12	15	10	
Age (years)	48.7 ± 16.7	49.6 ± 16.7	52.8 ± 17.6	40.5 ± 11.4	38.6 ± 16.6	0.034
Male sex	146 (59.1)	122 (58.1)	5 (41.7)	12 (80.0)	7 (70.0)	0.187
Follow-up time, median (IQR)		8.2 (2.7-12.0)	6.0 (2.6-11.1)	2.3 (1.0-9.0)	4.8 (2.0-11.8)	0.0012
IRSAD percentile	64.5 ± 31.3	64.4 ± 31.7	83.1 ± 16.4	57.7 ± 31.4	54.0 ± 29.1	0.113
Age at diagnosis (years)	36.0 ± 16.4	36.5 ± 16.7	34.9 ± 17.3	33.3 ± 14.5	31.1 ± 14.3	0.692
Symptomatic presentation	116 (48.5)	94 (46.1)	8 (72.7)	9 (64.3)	5 (50.0)	0.215
BMI (kg/m2)	27.3 ± 5.8	27.6 ± 5.7	22.0 ± 2.3	25.8 ± 5.1	28.5 ± 9.0	0.011
Hypertension	55 (22.7)	50 (24.1)	2 (18.2)	1 (7.1)	2 (20.0)	0.503
Diabetes	18 (8.1)	15 (7.9)	2 (20.0)	1 (7.7)	0 (0)	0.436
High cholesterol	35 (15.8)	29 (15.3)	2 (20.0)	3 (23.1)	1 (11.1)	0.843
Atrial fibrillation	60 (25.6)	51 (25.6)	3 (25.0)	3 (21.6)	3 (33.3)	0.938
NYHA class (III-IV) ever*	14 (6.4)	11 (6.0)	0 (0)	1 (7.7)	2 (20.0)	0.268
Syncope	61 (26.9)	51 (26.6)	3 (27.3)	6 (40.0)	1 (11.1)	0.482
NSVT	64 (27.5)	59 (29.8)	0 (0)	4 (28.6)	1 (10.0)	0.100
Family history of HCM	150 (61.0)	129 (61.7)	6 (50.0)	9 (60.0)	6 (60.0)	0.881
Family history of SCD	62 (25.4)	58 (27.9)	1 (8.3)	3 (21.4)	0 (0)	0.110
Composites						
Heart failure composite	32 (13.0)	24 (11.5)	3 (25.0)	2 (13.3)	3 (30.0)	0.212
Ventricular arrhythmia composite	31 (12.9)	26 (12.7)	2 (18.2)	2 (13.3)	1 (10.0)	0.948
Overall composite	99 (40.1)	83 (39.5)	5 (41.7)	6 (40.0)	5 (50.0)	0.930

Data shown as n (%) or mean ± SD. EUR= European, EAS= East Asian, SAS= South Asian, MENA= Middle Eastern and North-African, IRSAD = Index of Relative Socio-Economic Advantage and Disadvantage, BMI = body mass index, NSVT = non-sustained ventricular tachycardia, NYHA = New York Heart Association, SCD = sudden cardiac death.

SUPPLEMENTARY TABLE V: Echocardiographic features of sarcomere-positive HCM probands from the major ethnic groups represented in multi-ethnic cohort

	Total cohort	EUR	EAS	SAS	MENA	p-value
n	247	210	12	15	10	
Maximum LVWT (mm)	20.9 ± 6.1	20.8 ± 5.9	17.3 ± 3.6	24.7 ± 8.2	21.1 ± 7.9	0.016
LVPW (mm)	10.7 ± 2.5	10.7 ± 2.5	9.8 ± 2.7	11.2 ± 2.8	11.2 ± 2.0	0.520
Hypertrophy pattern ASH Apical Concentric	 221 (93.6) 4 (1.7) 11 (4.7)	 188 (94.0) 3 (1.5) 9 (4.5)	 10 (90.9) 1 (9.1) 0 (0)	 14 (93.3) 0 (0) 1 (6.7)	 9 (90.0) 0 (0) 1 (10.0)	0.505
LVEDD (mm)	43.3 ± 6.4	43.6 ± 6.5	42.8 ± 6.5	42.3 ± 4.8	40.7 ± 6.2	0.504
LVESD (mm)	25.8 ± 7.0	25.9 ± 7.2	27.0 ± 6.5	24.6 ± 6.2	23.1 ± 4.8	0.535
LVEF %	65.3 ± 12.0	64.9 ± 12.0	54.8 ± 11.4	66.3 ± 7.4	74.7 ± 9.2	0.054
SAM	111 (50.7)	95 (51.1)	0 (0)	9 (64.3)	7 (77.8)	0.003
LA size, mm	42.5 ± 8.0	42.0 ± 7.3	45.9 ± 8.5	44.9 ± 9.6	45.0 ± 21.0)	0.398
Obstructive physiology (≥30mmHg)	59 (24.5)	49 (24.0)	0 (0)	5 (33.3)	5 (50.0)	0.045
LVOT max gradient at rest, mmHg	41.6 ± 36.0	41.0 ± 35.5	8.3 ± 5.8	56.0 ± 20.4	75.4 ± 53.6	0.030

Data shown as n (%) or mean ± SD. EUR= European, EAS= East Asian, SAS= South Asian, MENA= Middle Eastern and North-African, LVWT= left ventricular wall thickness, LVPW= left ventricular posterior wall, ASH= asymmetrical hypertrophy, LVEDD= left ventricular end diastolic diameter, LVESD= left ventricular end systolic diameter, LVEF= left ventricular ejection fraction, SAM= systolic anterior motion of the mitral valve, LVOTO= left ventricular outflow tract obstruction, EF= ejection fraction.

SUPPLEMENTARY TABLE VI: Service use and management of sarcomere-positive HCM probands from the major ethnic groups represented in multi-ethnic cohort

	Total cohort	EUR	EAS	SAS	MENA	p-value
n	247	210	12	15	10	
Heart transplant	7 (2.9)	5 (2.5)	1 (9.1)	0 (0)	1 (10.0)	0.280
Alcohol septal ablation	10 (4.2)	9 (4.4)	0 (0)	0 (0)	1 (10.0)	0.570
Septal myectomy	17 (7.1)	16 (7.8)	0 (0)	0 (0)	1 (10.0)	0.514
Pacemaker	51 (21.3)	39 (19.1)	3 (27.3)	6 (40.0)	3 (30.0)	0.221
ICD	131 (53.0)	113 (53.8)	4 (33.3)	9 (60.0)	5 (50.0)	0.599
ICD indication Primary Secondary	 120 (91.6) 11 (8.4)	 106 (93.8) 7 (6.2)	 2 (50.0) 2 (50.0)	 8 (88.9) 1 (11.1)	 4 (80.0) 1 (20.0)	0.014
ICD implantation Male Female	 81 (61.8) 50 (38.2)	 70 (62.0) 43 (38.1)	 1 (25.0) 3 (75.0)	 7 (77.8) 2 (22.2)	 3 (60.0) 2 (40.0)	0.351
ESC risk score <4% 4-6% >6%	 43 (45.3) 24 (25.3) 28 (29.5)	 37 (45.1) 19 (23.2) 26 (31.7)	 1 (33.3) 2 (66.7) 0 (0)	 2 (33.3) 2 (33.3) 2 (33.3)	 3 (75.0) 1 (25.0) 0 (0)	0.466

Data shown as n (%) or mean ± SD. EUR= European, EAS= East Asian, SAS= South Asian, MENA= Middle Eastern and North-African, LP/P = likely pathogenic/pathogenic, VUS = variant of unknown significance, ICD = implantable cardioverter defibrillator

CHAPTER 4

A RARE SPLICE-SITE VARIANT IN TNNT2: THE NEED FOR POPULATION-SPECIFIC GENOMIC REFERENCE DATASETS

4 CHAPTER 4: A RARE SPLICE-SITE VARIANT IN *TNNT2*: THE NEED FOR POPULATION-SPECIFIC GENOMIC REFERENCE DATASETS

4.1 Preface to Chapter

This chapter presents an analysis of *TNNT2*; c.571-1G>A, a variant we have identified is common among Pacific and Oceanian populations, emphasising the critical need for openly accessible large and diverse genomic reference databases to ensure accurate interpretation of genetic variants. This chapter will be submitted for publication. Author contributions are outlined in the author contribution statement.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the study	AB JI
Data Curation	AB, RB, JI
Formal analysis	AB, JI
Drafting the manuscript	AB, JI
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Sources of funding

Dr Semsarian is the recipient of a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (#1154992). A/Prof Ingles is the recipient of an NHMRC Career Development Fellowship (#1162929). This study uses data from the Pacific Islands Rheumatic Heart Disease Genetics Network. Funding for the project was provided by the British Heart Foundation (PG/14/26/30509; www.bhf.org.uk), the Medical Research Council UK (Fellowship G1100449; www.mrc.ac.uk), and the British Medical Association (Josephine Lansdell Grant; www.bma.org.uk).

Disclosures

A/Prof Ingles receives research grant support from Bristol Myers Squibb. All other authors report no conflicts of interest.

4.2 Introduction

Inherited cardiomyopathies such as hypertrophic (HCM), dilated (DCM) and restrictive cardiomyopathy (RCM) cumulatively affect at least 1 in 500 in the general population.[1] Most are inherited in an autosomal dominant pattern with marked clinical and genetic heterogeneity. Patients may report mild symptoms or more severe outcomes such as heart failure or sudden cardiac death (SCD). Genetic testing of genes with established clinical validity can identify the underlying genetic cause of disease and is part of mainstream clinical management.[2] Variants in genes encoding the cardiac sarcomere are an important cause of HCM and DCM.[2, 3]

Interpreting rare genetic variants is challenging among individuals from poorly represented ancestry groups. As a result, the yield of variants of uncertain significance (VUS) is higher compared to European patients.[4,5] Variant curation involves evaluating evidence to support a variant as a confident cause of a genetic disease. The American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) standards for variant interpretation and classification provide a framework for this taking into account population frequency, among other considerations.[6] Historic lack of ancestral diversity of participants included in large genomic reference databases limits our ability to understand whether genetic variants are truly rare.

Here we report a rare variant, *TNNT2*; NM_001001430.2: c.571-1G>A, identified in two patients with cardiac phenotypes and Pacific ancestry and highlight the challenges with variant classification among patients with diverse ancestry.[7,8] The Pacific Islands are within Oceania and include >1000 islands comprising Polynesia, Micronesia and Melanesia. Pacific Islanders originated from two vastly divergent ancestral populations. The first arrived

in South-East Asia more than 40,000 years ago, contributing to the ancestry of Aboriginal Australians, Papuans and some Pacific Island populations.[9,10] The second closely relates to mainland East Asians, specifically Indigenous Taiwanese, who populated remote Polynesia ~3000 years ago.[7, 8]

Given the lack of diversity in reference population datasets, including poor representation of those with Pacific ancestry, we hypothesised that this variant might be a common population single nucleotide variant. We aimed to determine if *TNNT2*:c.571-1G>A is a definite cause of inherited cardiomyopathy.

4.3 Methods

Variant curation was performed using the *MYH7*-modified ACMG/AMP criteria.[4] *TNNT2* encodes cardiac troponin T, an integral protein in the cardiac sarcomere. The troponin complex and calcium regulate the binding of actin and myosin.

Gene curation has shown *TNNT2* to be definitively associated with HCM and DCM.[11, 12] While causative variants in *TNNT2* have been reported in cases of RCM, the RCM gene-disease association has not been formally curated. Literature and ClinVar reports were sought, and clinical laboratories and research groups were contacted for additional information. Research groups with ancestry-matched participants with non-cardiac diseases and available genomic data were contacted.

4.4 Results

4.4.1 *TNNT2* rare variant

A rare variant in cardiac troponin T (*TNNT2*; NM_001001430.2: c.571-1G>A) was identified via research-based whole exome sequencing in two unrelated probands (Royal Prince Alfred Hospital Sydney Local Health District Human Research Ethics Committee X15-0089). The patients included a man of Pacific ancestry aged 20-25 years who suffered an SCD with no cause identified following a comprehensive postmortem investigation; and a 0-3 year old child of Pacific ancestry with RCM who died from rapidly progressive heart failure, with another pathogenic variant in TNNI3 also identified in this individual. This variant is located in the intron 11 canonical splice acceptor site, predicted to lead to an in-frame deletion of one amino acid in a three amino acid exon. Functionally, RNA studies have shown that the variant alters the splicing of exon 12, resulting in an in-frame deletion of one amino acid.[11]

4.4.2 Case data

We queried ClinVar and the literature to establish if the variant had been reported previously. There were 12 ClinVar entries for this variant, updated between December 2014 to April 2023. Ten entries classify this variant as uncertain, one likely pathogenic and one unknown. Of the 12 submitters, 10 are diagnostic genetic laboratories. Including ClinVar entries (where additional data were sought directly from the laboratory) and literature reports, a total of 25 cases were identified. Of these, 23 had a cardiac phenotype reported, including 14 with HCM (two diagnosed post-mortem following SCD), five with DCM (two presented at less than three years of age),[12] three with sudden unexplained death, while one case displayed high premature ventricular contractions, syncope, palpitations, and a family history of SCD. One case lacked a specific diagnosis but had a family history of

SCD, and in another case the diagnosis was unknown. Overall, four probands reported a family history of SCD in a close relative. The variant was shown to segregate to two affected individuals in one family. There were four probands with an additional pathogenic variant that would explain their cardiac phenotype. A total of 18 probands were reported as having Pacific ancestry, including Aotearoa New Zealand Māori, Samoan, Tongan, Aboriginal and Torres Strait Islander and Hawaiian (Figure 4.1).

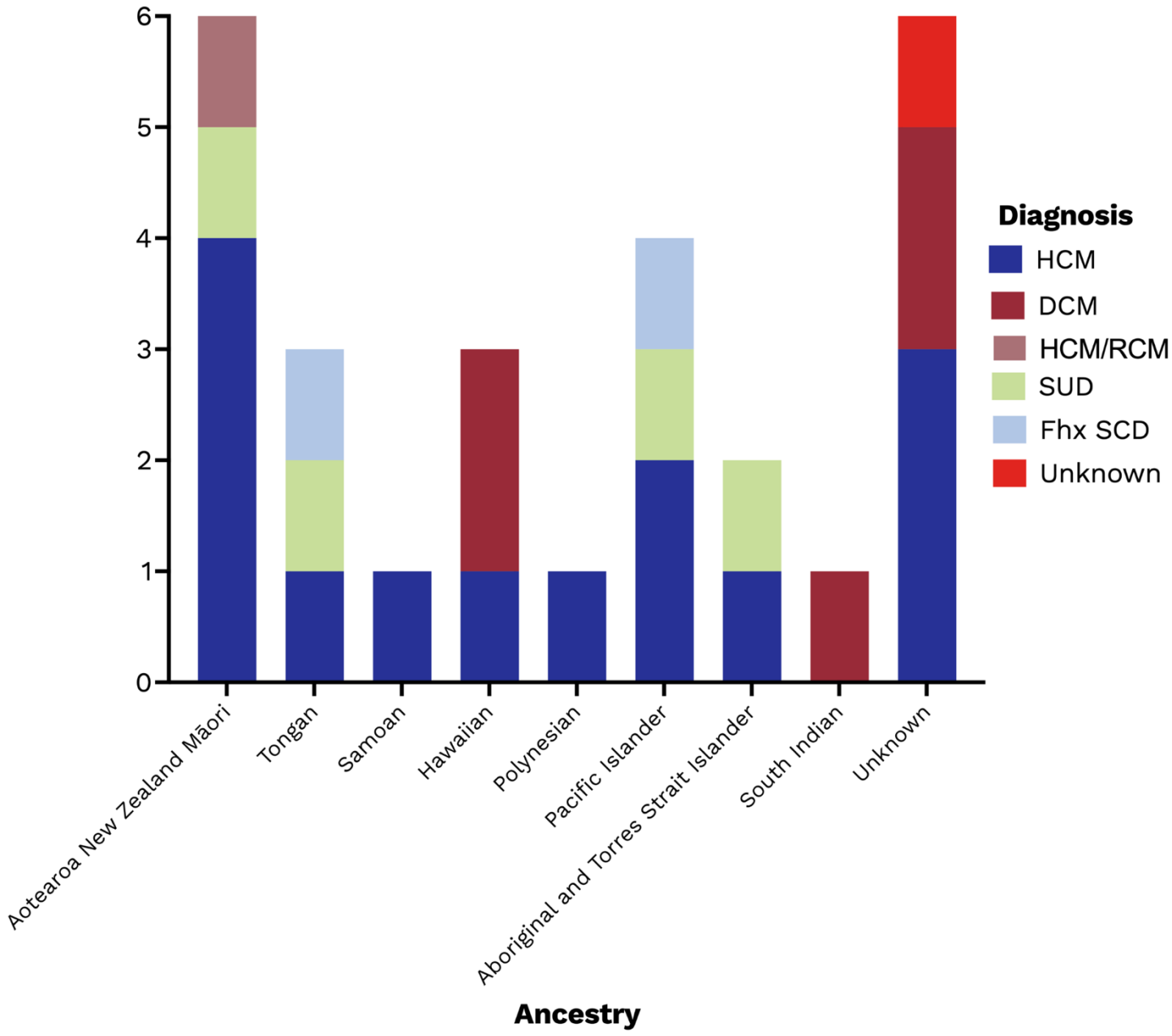

Figure 4.1: Probands with the *TNNT2* c.571-1G>A splice-site variant by self-reported ancestry and disease phenotype
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; SUD, sudden unexplained death; Fhx, family history; SCD, sudden cardiac death.

4.4.3 Rarity in population databases

Among publicly available databases, *TNNT2*:c.571-1G>A was present in the Genome Aggregation Database (gnomAD) in 5/249,022 (0.002%) alleles, with the highest sub-population frequency in South Asian alleles (5/30,444; 0.02%).[13] Within Genome Asia 100K Project, the variant was present in 6/148 (4.1%) alleles in the Oceanian population, with a frequency of 2/4 (50%) in Australian alleles (including one homozygote), and 4/140 (2.9%) in Papuan alleles.[14]

We approached groups with potentially ancestry-relevant population sequencing data, not in the public domain. The variant was absent in the Taiwanese Biobank (WGS), though this does not include any Indigenous Taiwanese individuals and primarily comprises Han Chinese (n=1517) participants.[15] The allele frequency of the variant in the Pacific Islands Rheumatic Heart Disease Genetics Network was sought, which includes participants from Vanuatu, New Caledonia, Fiji, Tonga, Samoa, Cook Islands, and French Polynesia. This dataset consists of low-coverage genomes and SNP arrays with imputation.[16] Specifically, for a Polynesian sub-group, the variant was present at a frequency of 0.088 (8.8%), while across the wider group, which included Melanesians and South Asians, the frequency was 0.035 (3.5%). In addition, we investigated the allele frequency in a sequence dataset of controls from Māori and Pacific populations of Aotearoa New Zealand (low-pass sequencing followed by imputation).[17] An allele frequency of 3.96% was observed in East Polynesian individuals (n=139), and 3.64% was observed among West Polynesian individuals only (n=55) (Figure 4.2A & B). Based on these allele frequencies, we classify *TNNT2*:c.571-1G>A as a benign variant.[18] This classification aligns with the ACMG/AMP variant pathogenicity recommendations, specifically the stand-alone rule BA1, which states that a variant with a minor allele frequency greater than 0.05 is considered benign.

4.4.4 Presence in archaic genomes

The variant was present in two archaic genomes (Vindija and Altai Neanderthal), but not the Altai Denisovan,[19–21] suggesting it might have arisen 130-145 thousand years ago when those populations diverged.[20] Of note, Indigenous Papuans and Australians derive greater than 3% of their DNA from Neanderthals[20], which is higher than that of Eurasian populations,[22] and likely explains the increased frequency of *TNNT2*:c.571-1G>A in these populations.

A

Reference Population	Data availability	Allele count	Allele Frequency	%
gnomAD	Public	5/249,022	0.00002	0.002
South Asian		5/30,444	0.0002	0.02
Genome Asia 100K (Oceania) n=73	Public	6/148	0.041	4.1
Australia (includes 1 homozygote) n=2		2/4	0.5	50
Papua New Guinean n=70		4/140	0.029	2.9
Taiwan Biobank (primarily Han Chinese) n=1517	Research	0/3032	0.0	0.0
Pacific Islands Rheumatic Heart Disease Genetics Network	Research			
Polynesian subgroup		-	0.088	8.8
Broader (including Melanesian)		-	0.035	3.5
Māori and Pacific populations of Aotearoa New Zealand n=194 controls	Research			
East Polynesian subgroup (n=139)		-	0.039	4.0
West Polynesian subgroup (n=55)		-	0.036	3.6

B

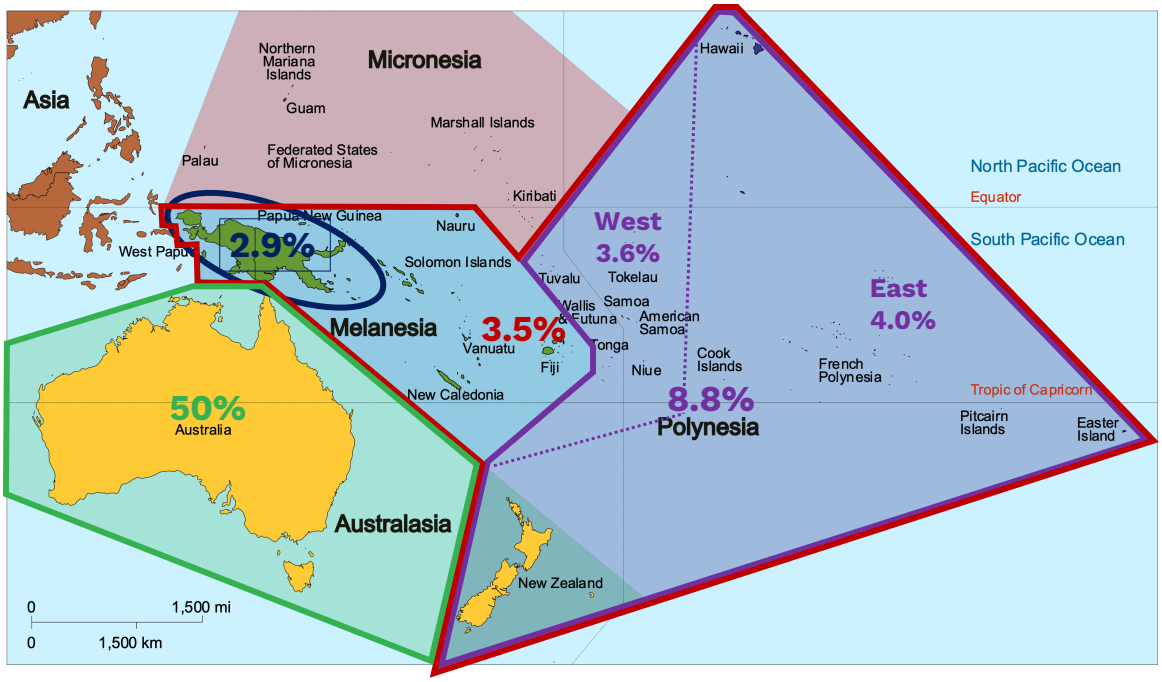

Figure 4.2: A: Frequency of *TNNT2*; NM_001001430.2: c.571-1G>A in population databases B: Oceanic regions of Polynesia, Micronesia and Melanesia with population-specific frequencies This work is licensed under Attribution-ShareAlike 3.0 Unported (CC BY-SA 3.0). The original can be found here: https://commons.wikimedia.org/wiki/File:Oceania_UN_Geoscheme_-_Map_with_Zones.svg#/media/File:Oceania_UN_Geoscheme_Regions.

4.5 Discussion

The historic lack of ancestral diversity in research studies and genomic reference datasets has limited our ability to classify and interpret genetic variants identified in the population. It is well-described that patients whose ancestry is not White/European have a 2-3 times greater risk of having an uncertain variant identified following genetic testing,[23, 24] limiting the utility of genetic testing and increasing the risk of variant misclassification.[25] We demonstrate the importance of publicly accessible ancestry-matched control populations in enabling accurate variant interpretation, avoiding potential harms that would disproportionately impact ancestrally diverse individuals. In this example, the genetic variant has been frequently identified as a potential disease-causing variant globally.

Contemporary variant curation includes evaluating other reported cases with the *TNNT2* c.571-1G>A variant. Our experience highlights the need for the patient's ancestry to be a key data field in these assertions so that the overrepresentation of a specific group becomes apparent. In the absence of ancestry-matched reference data, our only path forward was to identify and personally contact laboratories and research groups with sequencing data from Pacific peoples which determined the variant was present at a frequency of 0.9-8.8% and highest in the Polynesian sub-group. As a result, despite some evidence that might support pathogenicity (PS4: prevalence of the variant in affected individuals is significantly increased compared to controls, PM4: protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants, PP3: multiple line of computation evidence supports deleterious effect), the ancestry-matched allele frequency indicates this as a benign variant. Given there are 10 ClinVar assertions from clinical diagnostic laboratories reporting this as a VUS, this classification downgrade will have a clinically meaningful impact. While we cannot exclude a potential modifier role in

disease, this variant is not considered a monogenic cause of HCM or SCD but a common single nucleotide variant within Pacific populations.

The lack of representation of ancestrally diverse individuals in genomic reference databases limits the utility of genomic data for the population equally.[4] Efforts to improve representation in genomic databases, heavily reliant on effective community engagement and partnerships with underrepresented groups, are essential.[26] Further, efforts to enable open sharing of these data that comply with participant wishes and ethical approval ensures that all researchers can access this information and enable a more accurate understanding of the genetic basis of health and disease.[27] Open access to large and diverse genomic reference databases is crucial for advancing genomics research and improving health equity for all populations.

Our findings provide a cautionary tale for those who undertake genetic testing and variant curation in patient populations that have historically been poorly represented in research and reference databases. While there are important considerations when asking patients to disclose their ancestry, in the setting of genetic testing and variant interpretation, these data are critical for avoiding misclassification. Multiple studies have demonstrated the increased risk of uncertain findings in underrepresented ancestral populations with genetic heart disease.[23, 24] Such findings can limit the value of genetic testing, create anxiety in patients and lead to unnecessary medical interventions.[28] The significance of ancestry in interpreting variants underscores the need for increased diversity in genomic research and the adoption of more nuanced approaches to genetic testing and variant classification.

4.6 Conclusion

We highlight the challenges of identifying and interpreting rare variants causing monogenic disease in individuals from poorly represented ancestry groups. Our analysis of *TNNT2*; c.571-1G>A, a common single nucleotide variant within Pacific populations, emphasises the critical need for openly accessible large and diverse genomic reference databases to ensure accurate interpretation of variants and the value of genetic testing. While achieving ancestral diversity will require significant time, commitment, and resources, including deep community engagement and addressing existing barriers to research participation and mistrust,[29] it is a necessary step if we are to ensure the entire population can benefit equally from genomic medicine.

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CHAPTER 5

THE AUSTRALIAN GENETIC HEART DISEASE REGISTRY: DATA LINKAGE STUDY PROTOCOL

5 CHAPTER 5: THE AUSTRALIAN GENETIC HEART DISEASE REGISTRY: DATA LINKAGE STUDY PROTOCOL

5.1 Preface to Chapter

This chapter presents the protocol for the establishment of a comprehensive clinical dataset linking the Australian Genetic Heart Disease (AGHD) Registry with NSW state-wide routinely collected hospital admissions, emergency department episodes, and mortality registries. This chapter is published as a preprint and is currently under review. Author contributions are outlined in the following author contribution statement.

Reference

Butters A[1-3], Blanch B[4], Kemp-Casey A[5], Do J,[1-2] Yeates L,[1-4,6] Leslie F,[1-2] Semsarian C,[3,4,6] Nedkoff L,[7,8] Briffa T,[7] Ingles J,[1,2,6] Sweeting J.[1,2] The Australian Genetic Heart Disease Registry: Data Linkage Study Protocol. JMIR Preprints. 01/05/2023:48636

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the study	AB, JS, JI
Literature search	AB
Drafting the manuscript	AB
Review and critical comments on draft manuscript	All authors
Coordination of journal submission	AB, JS

As the candidate for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Candidate Name: Alexandra Butters

Signature: Date: 29/06/2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the

authorship attribution statements above are correct.

Supervisor Name: A/Prof Jodie Ingles

Signature: Date: 29/06/2023

Sources of funding
JI acknowledges a National Heart Foundation of Australia Future Leader Fellowship (#106732). This work was supported in part by New South Wales Health Early Mid-Career Research Cardiovascular Grant. LY is a recipient of a co-funded National Heart Foundation of Australia / National Health and Medical Research Council (NHMRC) PhD scholarship (#102568/ #191351). CS is supported by an NHMRC Investigator Grant (#2016822) and an NSW Health Cardiovascular Disease Clinician Scientist Grant. LN is supported by a National Heart Foundation Future Leader Fellowship (#105038).

Disclosures
JI receives research grant support from Bristol Myers Squibb. All remaining authors have nothing to disclose.

5.2 Introduction

Genetic heart diseases are a significant cause of cardiac morbidity and mortality in the young and are characterised by distinct variability in the onset and severity of symptoms.[1] The most prevalent is hypertrophic cardiomyopathy (HCM) which affects up to 1 in 500 people.[2] They are generally inherited as autosomal dominant traits, conferring a 50% risk to first-degree relatives. A diagnosis relies on clinical investigations with a cardiologist and in some cases, genetic testing, which is ideally conducted in a multidisciplinary clinic.[3]

Disease symptoms can be variable ranging from asymptomatic to episodes of unexplained syncope, palpitations and chest pain to the most serious outcomes of heart failure and sudden cardiac death (SCD).[4–6] Accordingly, some individuals with a genetic heart disease require life-saving medical intervention via emergency department presentation and hospitalisation.[7] Treatment options may include prescription medication, cardioversion and/or surgeries such as implantable cardioverter defibrillator insertion, pacemaker insertion, septal reduction therapies (e.g. alcohol septal ablation, septal myectomy) or heart transplant.[4–6] The implantable cardioverter defibrillator is the only proven therapy to prevent SCD in individuals with a genetic heart disease.[8] The frequency with which these individuals interact with the healthcare system is unknown, including for non-cardiac reasons.[7]

Routinely collected health data are data collected for purposes other than research or without specific a priori research questions developed before collection.[9] These data provide both population- and person-based information, meaning we can examine common patterns of healthcare for the population.[10, 11] In jurisdictions with universal healthcare such as Australia, we can observe an individual's interaction with hospitals and emergency

departments over time and link them to mortality data. Studies that have used routinely collected data to investigate genetic heart diseases, or their consequences such as SCD, focus predominantly on mortality data and may restrict to specific subpopulations such as infants or children.[12–14] There are limitations in correctly identifying individuals with a genetic heart disease in these data collections due to insufficient international classifications of diseases (ICD) codes,[7] inadequate recognition of these diseases outside of specialised settings and infrequent interaction with health facilities for many patients who remain largely well and are generally managed via outpatient clinics.

Here we report a protocol for the linkage of AGHD Registry participants[15, 16] with state-wide hospitalisation, emergency department and mortality registries, and the national mortality registry to establish a rich and comprehensive data resource to examine the healthcare utilisation of individuals with a genetic heart disease and their families for the first time.

5.3 Methods

5.3.1 Study setting, design and population

This is a retrospective cohort study of people in NSW, Australia, enrolled in the AGHD Registry from 2007-2019. The AGHD Registry operates nationally and has actively recruited participants since 2007.[15, 16] The goal of the AGHD Registry is to enrol every individual in Australia with a genetic heart disease and their at-risk relatives to understand and improve diagnosis, prevention and treatment options. Eligibility criteria include a confirmed diagnosis of any inherited cardiomyopathy (hypertrophic [HCM], dilated [DCM], arrhythmogenic [ACM] and restrictive cardiomyopathy [RCM] left ventricular non-compaction [LVNC], or primary arrhythmia syndromes (long QT Syndrome [LQTS],

Brugada syndrome [BrS] or catecholaminergic polymorphic ventricular tachycardia [CPVT]; Table 5.1) or at-risk relatives of those with a confirmed diagnosis.

Table 5.1: Classification and description of genetic heart diseases included in the AGHD Registry

Genetic heart disease type	Specific condition	Definition	Diagnostic tests
Inherited cardiomyopathies	Hypertrophic cardiomyopathy (HCM)	Abnormal thickening of the heart muscle on either the left or right ventricle.	Electrocardiogram; echocardiogram; cardiac magnetic resonance imaging (MRI); Holter monitor.
	Dilated cardiomyopathy (DCM)	Enlargement of the left ventricle of the heart affects the ability of the heart to pump blood effectively.	Electrocardiogram; echocardiogram; cardiac MRI; Holter monitor.
	Arrhythmogenic cardiomyopathy (ACM)	A disease of the heart muscle where the normal heart muscle cells on either the left or right ventricle are replaced by fat and scar tissue. This change can lead to heart rhythm abnormalities or the affected ventricle may become enlarged and not pump blood effectively.	Electrocardiogram; echocardiogram; cardiac MRI; Holter monitor
	Left ventricular noncompaction (LVNC)	Characterised by deep trabeculations (finger-like projections) in the heart muscle wall of predominantly the left ventricle, but may also appear in the right ventricle.	Electrocardiogram; echocardiogram; cardiac MRI.
Primary arrhythmia syndromes	Long QT syndrome (LQTS)	Characterised by abnormal electrical activity in the heart that often presents in children and teenagers.	Electrocardiogram; echocardiogram; exercise/stress test.
	Catecholaminergic polymorphic ventricular tachycardia (CPVT)	CPVT is a rare condition often present in children and teenagers. A cardiac event can occur during	Electrocardiogram; echocardiogram; exercise/stress test; Holter monitor.

		periods of high emotion or exercise as these situations cause the body to release adrenalin/noradrenalin. These persons have an abnormal response to adrenaline, which causes the heart to beat fast and irregularly.	
	Brugada syndrome (BrS)	A rhythm disorder that causes the ventricles to beat abnormally fast, affecting the ability of the heart to pump blood effectively.	Electrocardiogram; echocardiogram; drug infusion study.

Participant demographic, clinical and genetic information (provided by the AGHD Registry data custodian) were linked with whole-population routinely collected health data, specifically hospital admissions (NSW Admitted Patient Data Collection), emergency department presentations (NSW Emergency Department Data Collection) and in the event of death, mortality registry data (NSW Registry of Births, Death and Marriages; Australian Coordinating Registry (ACR) Cause of Death Unit Record File) (Table 5.2).

Table 5.2: Datasets included in AGHD Registry data linkage study

Dataset	Purpose	Description	Variables
Australian Genetic Heart Disease (AGHD) Registry	Cohort Definition and linked data	National registry collecting clinical and genetic data of genetic heart disease patients and their families	Demographics ● Sex ● Birth date (mm/yyyy) ● Ethnicity (based on the Australian Standard Classification of Cultural and Ethnic Groups[17]) ● Vital status (alive/deceased) ● Postcode ● Disease status (definite, possible, at-risk) ● Smoker status Clinical history ● Clinical diagnosis ● Age at diagnosis ● Reason for diagnosis ● Genetic status (Likely pathogenic/pathogenic variant identified/not identified) ● Sudden cardiac events ever ● Heart failure ever ● Syncope ever ● Non-sustained ventricular tachycardia ever ● Atrial fibrillation ever ● Left ventricular outflow tract obstruction ever ● Interventions (Implantable cardioverter defibrillator, pacemaker, ablations, myectomy, heart transplant) ● Family history Investigations ● Echocardiography parameters ● Electrocardiography parameters

NSW Admitted Patient Data Collection	Linked data	Records all admitted patient services provided by NSW public hospitals, private hospitals and private day procedure centres	Demographics ● Sex ● Birth date (mm/yyyy) ● Country of birth ● Residential statistical local area (SLA) at admission ● Health insurance on admission Episode of care ● Episode start date ● Episode end date ● Condition onset flag ● Diagnosis codes ICD-AM (up to 50) ● Australian Refined Diagnosis-Related Group (AR-DRG) ● Hours in ICU ● Hours on mechanical ventilation ● Mode of separation ● Procedure codes ICD-AM (up to 50) ● Procedure date ● Service-related group (SRG) Facility information ● Hospital type ● Local health district (LHD) ● Facility identifier ● Facility transferred to ● Facility transferred from
NSW Emergency Department Data Collection	Linked data	Provides information about patient presentations to the emergency departments of public hospitals in NSW	Demographics ● Sex ● Birth date (mm/yyyy) ● Country of birth ● Residential statistical local area (SLA) at admission

			● Health insurance on admission Episode of care ● Episode start date and time ● Episode end date and time ● Diagnosis code ICD-AM (up to 50) ● Type of visit ● Mode of separation ● Referred to on departure Facility information ● Local health district (LHD) ● Facility identifier
NSW Registry of Births, Deaths and Marriages	Linked data	Includes death registrations	● Birth date (mm/yyyy) ● Death date (mm/yyyy) ● Local health district (LHD) at death
Australian Coordinating Registry Cause of Death Unit Record File	Linked data	Includes death registrations	● Death date (mm/yyyy) ● Death age ● Place at birth ● State/Territory of usual of residence ● Sex ● Place of occurrence for external cause of death ● Underlying cause of death ICD code ● Contributing cause of death ICD codes (up to 20 comorbidity codes)

5.3.2 Aims

Our objective is to characterise AGHD Registry participants using routinely collected whole-population health datasets to investigate the healthcare utilisation of individuals with a genetic heart disease and their at-risk relatives. We will also examine the concordance between data sources to see whether diagnoses, interventions and outcomes match those recorded in the AGHD Registry. In our analyses, we will determine if patterns of care vary according to patient demographics such as age, sex, level of residential and relative socioeconomic disadvantage of patient residence (Figure 5.1). We will evaluate episodes of care for any medical condition or reason.

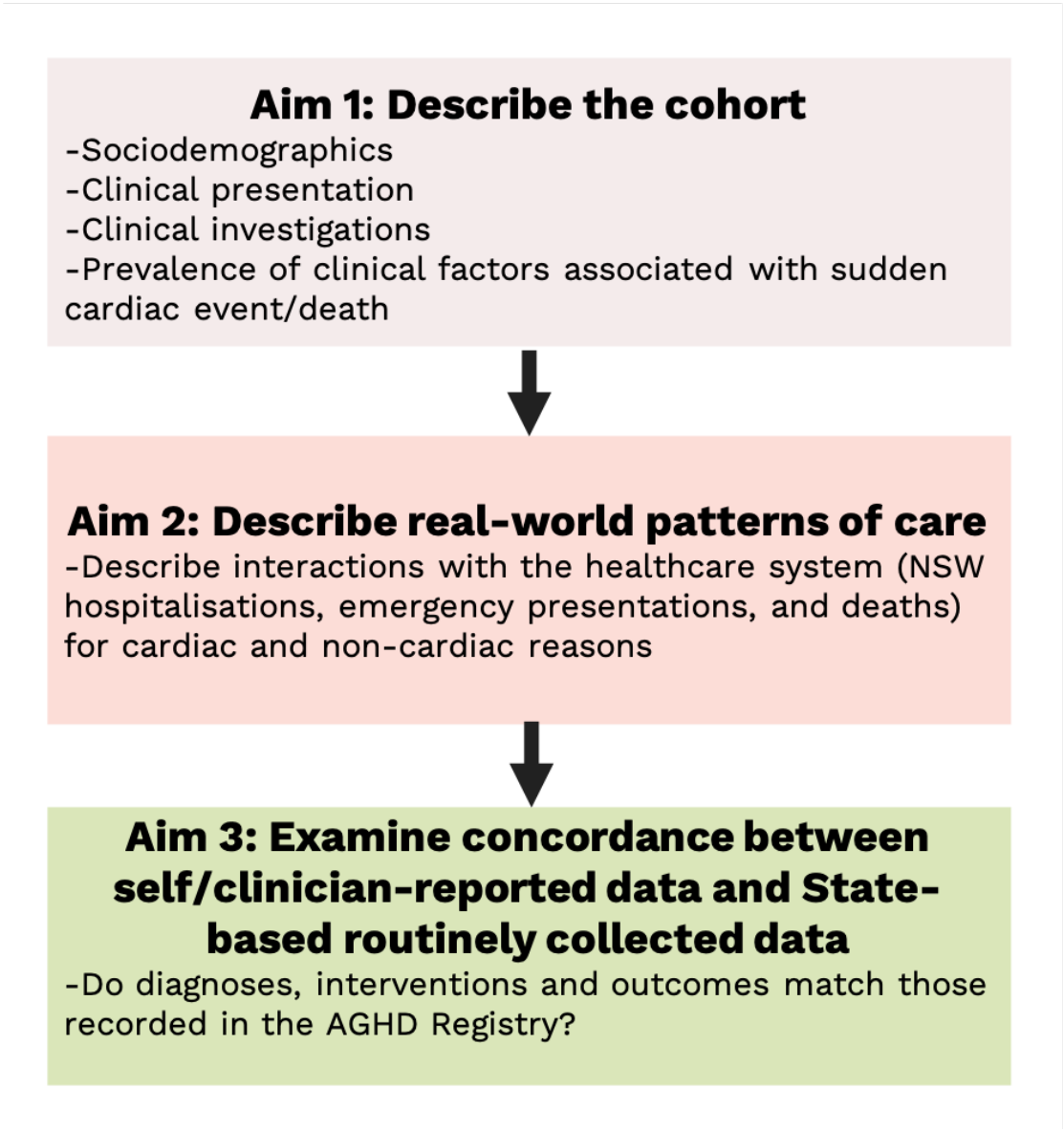

Figure 5.1: Aims of AGHD Registry Data linkage study

5.3.3 Recruitment and consent

Participants have been recruited to the AGHD Registry since 2007, with ethics approval from the Sydney Local Health District (RPAH zone) Human Research Ethics Committee (2020/ETHO00220). Two recruitment methods were used for the data linkage aspects of the study:

1. For participants enrolled in the AGHD Registry between 2007 and April 2017, an opt-out approach was coupled with a waiver of consent. This involved sending a letter to all AGHD Registry participants outlining the study and asking them to contact us if they wish to withdraw their consent for this study. If the participant did not contact us then the waiver of consent applied.
2. An amendment to include permission for access to linked datasets was made to the participant information and consent form. Every person enrolled in the AGHD Registry from May 2017 provided written, informed consent for their data to be linked to the administrative data collections mentioned herein.

As part of the AGHD Registry recruitment process, extensive demographic, clinical and genetic information was collected from the individual and their cardiologist.

While participants can withdraw their consent at any time for the AGHD Registry, data already included in the linkage before their withdrawal of consent cannot be removed as all extracted data held by the researchers is de-identified.

5.3.4 Data sources and variables

Table 5.2 lists and describes the datasets used in this study. The AGHD Registry was used for cohort definition and linking variables with the routinely collected health data. We linked to the following datasets:

NSW Admitted Patient Data Collection

The Admitted Patient Data Collection collates information on all admitted patient services provided by NSW public (including psychiatric hospitals and multi-purpose services) and private hospitals (including day procedure centres) Data include patient demographics (i.e., sex, birth date, country of birth, Statistical Local Area of residence at admission), episodes of care (i.e., date and time of admission and separation [the completion of treatment for an admitted patient because of death, discharge, or transfer to another facility or care type], referral source, diagnoses, procedures, service referred upon discharge) and facility information (i.e., hospital type, facility, local health district [LHD]). Up to 50 relevant diagnoses and procedures were included. These are coded according to standardised codes from the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-AM), and the Australian refined diagnosis-related group (AR-DRG).

This study included data on admissions between 1st July 2001-30th June 2019 (Figure 5.2). When linked with the AGHD Registry data, this period allowed us to examine patterns of care before and after a genetic heart disease diagnosis. The requested variables will allow us to examine the frequency and type of interactions and care received during hospitalisations.

NSW Emergency Department Data Collection

The Emergency Department Data Collection provides information about patient presentations to the emergency departments of public hospitals and contracted private hospitals in NSW. Each record represents a presentation to an emergency department for emergency care and treatment. Data include demographics (same as Admitted Patient

Data Collection), episodes of care (e.g., date of arrival and separation, diagnoses and status at separation) and facility information (e.g., facility identifier, LHD). Up to 50 relevant diagnoses are included and are coded according to standardised codes from the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-AM).

Data for the Emergency Department Data Collection was available from 1st January 2005 - 30 June 2019 (Figure 5.2). By combining the hospital data with the AGHD Registry data, we can analyse the emergency department episodes before and after their diagnosis during this period. These data will allow us to explore the frequency and reason for an emergency department presentation for any medical reason.

Mortality data

Two datasets contain mortality information for deaths occurring in NSW: the NSW Registry of Births, Deaths and Marriages death registrations and the Australian Coordinating Registry Cause of Death Unit Record File. All deaths are certified by a medical practitioner or coroner (if a coronial inquiry is required) and registered by the NSW Registry of Births, Deaths, and Marriages. Details of all registered deaths are forwarded to the Australian Coordinating Registry. Details include the date of death, underlying cause and up to 20 contributing causes of death. Causes of death are coded using the ICD-10 International coding system rather than the Australian Modification ICD-10-AM used in Australian hospitals. The Australian Coordinating Registry Cause of Death Unit Record File data is finalised considerably later than the NSW Registry of Births, Deaths, and Marriage's death registration data due to the time needed to confirm details on the death certificate.

Data from the NSW Registry of Births, Deaths and Marriages was available from 1st January 2007 to 30th June 2019, and the Australian Coordinating Registry Cause of Death Unit Record File from 1st January 2007 to 31st December 2017 (Figure 5.2). These variables will allow us to determine the reasons and causes of death.

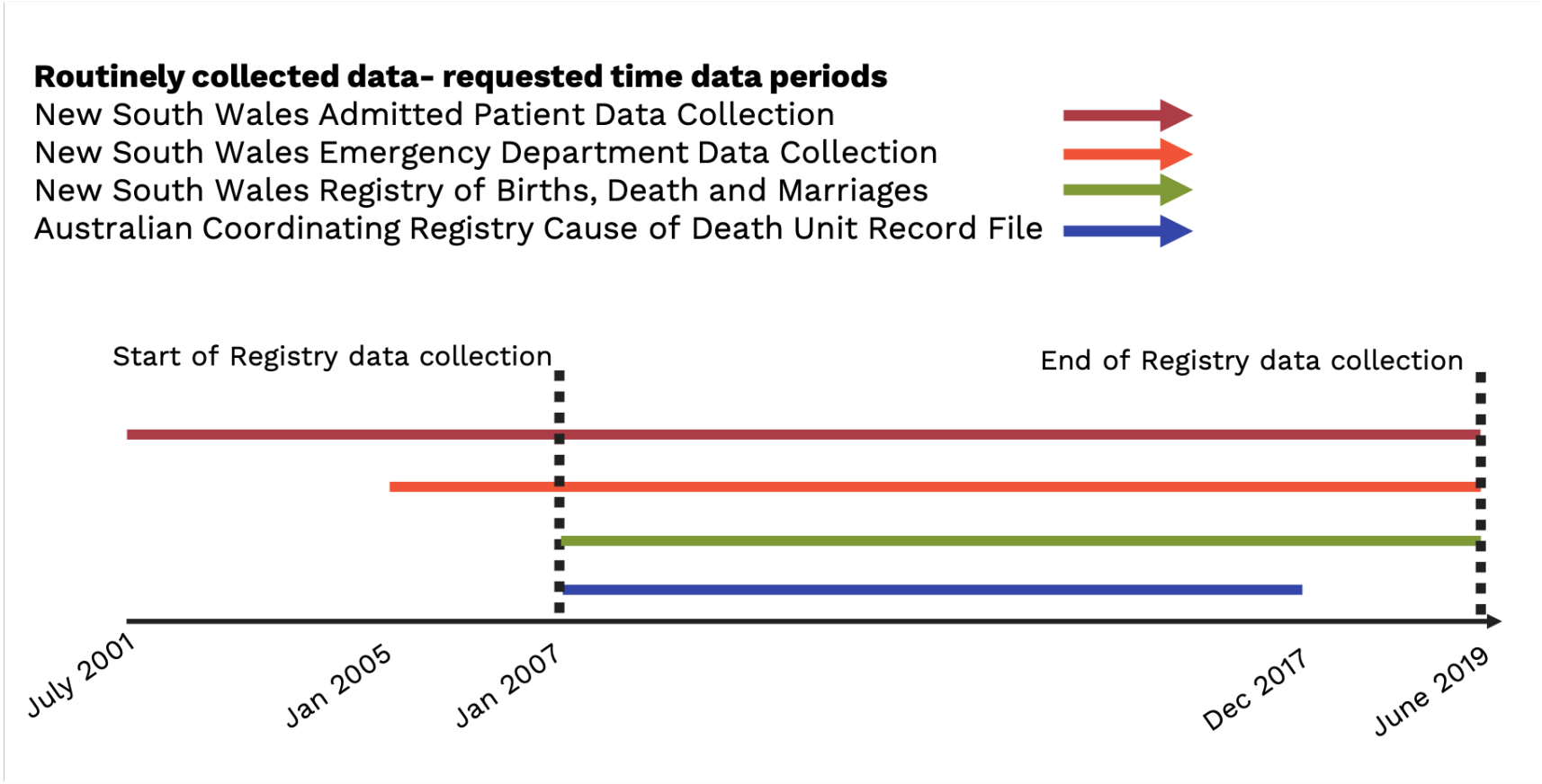

Figure 5.2: Period of data requested per routinely collected health dataset

5.3.5 Study procedures

Data linkage methods

Linkage of each AGHD Registry participant's demographic, clinical and genetic information with whole-population routinely collected health data was conducted by the CHeReL. The AGHD Registry data custodian (the individual responsible for the registry data and any related activities) provided CHeReL with two separate files. To protect privacy, identifier information including given names, last name, and current and past residential addresses (street, suburb, postcode, state), were separated from the content information (Registry clinical and genetic information). The two files from each dataset were stored and handled separately. CHeReL's Data Linkage Unit applied a combination of matching methods to the identifier data to identify and distinguish between individuals. The identifier data belonging to each individual was then assigned an arbitrary Person Number which replaced the name, address and other identifying details. Using an encrypted version of the arbitrary person number, CHeReL's Data Integration Unit created a research Project-specific person number (PPN). This PPN was used to join the AGHD Registry content data to the NSW state-wide Admitted Patient Data Collection, Emergency Department Data Collection and the mortality registries (Registry of Births, Death and Marriages and Australian Coordinating Registry Cause of Death Unit Record File). Once linkages were complete, the datasets were released to the research team in a fully de-identified form, ensuring the privacy and confidentiality of all individuals. The AGHD Registry custodian does not have access to the linked data to ensure that the linked data cannot be re-identified. These de-identification measures preclude the withdrawal of any individuals included in the data linkage study following the linkage taking place. Access to the de-identified linked data is only provided to individuals named in the approved Ethics protocol. The PPN combines records for the same person across different datasets.

5.3.6 Statistical Analysis

All data harmonisation and analyses will be conducted using R version 4.2.3. Harmonisation of the datasets will involve systematic identification and removal of any duplicate records, checking for a consistent number of person-level records across the datasets, consistency across variables (e.g admission dates before discharge dates), checking for outliers, and identification and flagging of missing or invalid data. We will analyse and report each dataset using descriptive statistics, including mean, median, standard deviation, interquartile ranges, and sample size (number). We will also conduct descriptive analysis stratified by factors including age, sex, relative socioeconomic disadvantage and advantage of patient residence and/or local health district of facility using the Australian Bureau of Statistics Socio-Economic Indexes for Areas[18] genetic status (Likely pathogenic/pathogenic gene identified vs no gene identified). Additionally, Cox regression models will be developed to identify independent factors associated with adverse outcomes, such as heart failure, atrial fibrillation, stroke and death.

5.3.7 Patient and Public Involvement

Patients and the public have not and will not be involved in the study design.

5.3.8 Ethics and Dissemination

Technical feasibility for the study was granted by the CHeReL, NSW Ministry of Health (ID#2016.38). Ethical approval has been granted by the NSW Population and Health Services Research Ethics Committee (2019/ETH0153) and Sydney Local Health District (RPAH zone) Human Research Ethics Committee (2020/ETHO00220). The current approval permits data storage at the Garvan Institute of Medical Research. We will disseminate project findings at scientific conferences and in peer-reviewed journals.

5.4 Discussion

This study represents the first in Australia to provide a comprehensive clinical dataset on healthcare utilisation patterns of individuals with a genetic heart disease and their at-risk relatives. It overcomes the limitations of previous studies, which rely on ICD codes to identify patients, by linking data from the AGHD Registry with routinely collected health data in New South Wales. The study will shed light on healthcare utilisation among individuals with a genetic heart disease in Australia, examining hospitalisations, emergency department presentations, and mortality rates over approximately 20 years; stratified by clinical diagnosis, age, sex, socioeconomic status, and genetic status. We will investigate the impact of these factors on patterns of care, including interactions with healthcare providers and on disease severity and outcomes. Overall, we aim to improve the diagnosis, prevention, and treatment options for individuals with a genetic heart disease by providing a better understanding of their healthcare utilisation and identifying areas for improvement in healthcare provision. Ultimately, the study's results will have a significant impact on the care of individuals with a genetic heart disease and their at-risk relatives.

Routinely collected data are commonly used in patterns of care studies. These studies are prolific when investigating cancer populations[19] as they provide the opportunity to describe a patient population and common treatment, as well as examine potential differences such as sex[20] and residential location.[21] In relation to cardiovascular diseases, patterns of care studies have predominantly focused on coronary heart disease or heart failure.[20–24] However, the population of individuals diagnosed with genetic heart diseases differ from those with these conditions, often being younger at diagnosis, with different risk factors and lifestyle constraints such as exclusion from high-level and competitive sports.[25] Therefore,

studies such as that described here are needed to examine the unique genetic heart disease population.

By linking the AGHD Registry to routinely collected health datasets, we have overcome a significant limitation of previous studies that relied exclusively on the ICD diagnosis coding system to identify patients with genetic heart diseases.[7] A previous systematic review by our team found that for countries such as Australia, only three of the twelve genetic heart diseases included in the search strategy had an explicit ICD diagnosis code.[7] Codes that best match the other nine genetic heart diseases being investigated were broad descriptive diagnoses (such as other cardiomyopathies used to describe ACM), which also encompasses other genetic heart diseases. Additionally, the ICD diagnosis coding system fails to explicitly identify rare diseases, with only 500 of the 6,000 rare diseases having an ICD diagnosis code.[26]

Procedure codes may provide a little more information with specific codes for implantable cardioverter defibrillator implantation and other interventions and surgeries associated with genetic heart diseases. However, as not all individuals undergo surgical procedures due to their condition, these codes also cannot identify all patients with a genetic heart disease. Due to these coding issues, studies to date have largely focused on those genetic heart diseases where discrimination from linked datasets is possible, i.e. HCM and Marfan syndrome.[7]

The clinical course for many patients with a genetic heart disease can be mild, meaning interactions with hospital and emergency departments could be infrequent or not required. However, when hospitalisation is necessary, these patients often require urgent and

potentially life-saving medical intervention. To date, there is limited research available regarding the healthcare system interactions of individuals with causative variants, and only one paper has used linked primary care hospital and mortality records in patients with HCM. Our study aims to address these gaps in knowledge and provide answers to these important questions. We will be able to observe the interaction of individuals with less severe clinical course who may never require treatment at a hospital or emergency department for genetic heart disease but present for other reasons.

Due to the absence of studies exploring care patterns associated with genetic heart diseases, it remains unclear whether care varies based on specific factors. Previous studies examining non-genetic cardiac conditions have found that patient factors, such as age, sex, and residential location impact care patterns.[20, 22, 27, 28] It is vital to examine the impact of socioeconomic factors, as the AGHD Registry contains a significant proportion of patients seen at specialist genetic heart diseases clinics in NSW which have been shown to over-represent socioeconomically advantaged individuals.[29] We will be able to investigate if patterns of care or outcomes vary based on the location of the facility and the relative socioeconomic disadvantage of that location. For instance, we will examine whether areas with relatively high disadvantage have fewer implantable cardioverter defibrillator surgeries than other facilities, as observed in other countries.[30]

Among studies using more than one data source, validating the agreement between data types such as self-reporting and routinely collected health data is important. Multiple studies have examined the concordance between these data types for many medical conditions including cardiac diseases.[20–23, 31–34] One study found the agreement between self-report data and health records was substantially lower for persons with heart failure than for other

chronic illnesses such as diabetes, hypertension, myocardial infarction and stroke.31 Patient factors associated with discordance include sex, age, education level and socioeconomic status.[33, 35] However, no studies have investigated the concordance in individuals with a genetic heart disease between self-reported and routinely collected health data.

5.4.1 Limitations

There are limitations in coding accuracy, especially for the Emergency Department Data Collection, which could affect the validity of the data collected. The study relies on AGHD Registry participants who are predominantly from a single tertiary centre, which has been shown to lack socioeconomic diversity.[29] We will be unable to ascertain the prevalence and incidence of genetic heart diseases accurately as the AGHD Registry does not include all patients in NSW with a genetic heart disease. However, even if our sample is not representative the relationships between variables are still valid.[36]

5.5 Conclusion

This study will provide valuable insights into the healthcare utilisation patterns of individuals with a genetic heart disease and their at-risk relatives. By linking data from the AGHD Registry with routinely collected health data in New South Wales, this study has established a comprehensive clinical dataset that can identify reasons for hospitalisation and emergency presentation that may reveal disparities and opportunities for preventive care. Overall, this study's findings will have a significant impact on the care of individuals with a genetic heart disease and their at-risk relatives, with the potential for better outcomes and quality of life.

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CHAPTER 6

THE AUSTRALIAN GENETIC HEART DISEASE REGISTRY: INSIGHTS INTO HEALTHCARE UTILISATION IN GENETIC HEART DISEASES

6 CHAPTER 6: THE AUSTRALIAN GENETIC HEART DISEASE REGISTRY: INSIGHTS INTO HEALTHCARE UTILISATION IN GENETIC HEART DISEASES

6.1 Preface to Chapter

This chapter presents data on health service use of individuals with genetic heart diseases by linking a well-characterised cohort of patients from the Australian Genetic Heart Disease (AGHD) Registry with routinely collected New South Wales (NSW) state-wide hospital admission, emergency department and mortality datasets. This chapter will be submitted for publication. Author contributions are outlined in the following author contribution statement.

Reference

Butters A[1-3], Blanch B[4], Kemp-Casey A[5], Do J,[1-2] Yeates L,[1-4,6] Leslie F,[1-2] Semsarian C,[3,4,6] Nedkoff L,[7,8] Briffa T,[7] Ingles J,[1,2,6] Sweeting J.[1,2]The Australian Genetic Heart Disease Registry: Insights into healthcare utilisation and outcomes for genetic heart diseases.

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Author contribution statement

This statement is to confirm the role of Alexandra Butters in the preparation and submission of the following manuscript. The convention is that the author with the principal contribution to the study is the first author.

The individual roles of co-authors are listed below:

Task	**Role of co-author**
Developing the concept of the study	AB, JS, JI
Literature search	AB
Drafting the manuscript	AB
Review and critical comments on draft manuscript	All authors

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As supervisor for the candidature upon which this thesis is based, I can confirm that the

authorship attribution statements above are correct.

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Sources of funding
JI acknowledges a National Heart Foundation of Australia Future Leader Fellowship (#106732). This work was partly supported by New South Wales Health Early Mid-Career Research Cardiovascular Grant. LY is a recipient of a co-funded National Heart Foundation of Australia / National Health and Medical Research Council (NHMRC) PhD scholarship (#102568/ #191351). CS is supported by an NHMRC Investigator Grant (#2016822) and an NSW Health Cardiovascular Disease Clinician Scientist Grant. LN is supported by a National Heart Foundation Future Leader Fellowship (#105038).

Disclosures
JI receives research grant support from Bristol Myers Squibb unrelated to this work. All remaining authors have nothing to disclose.

6.2 Introduction

Genetic heart diseases encompass a heterogeneous group of cardiovascular disorders, including inherited cardiomyopathies and primary arrhythmia syndromes. The most prevalent is hypertrophic cardiomyopathy (HCM) which affects at least 1 in 500 people.[1] These conditions can significantly burden affected individuals, their families, and healthcare systems.[2,3] Understanding the healthcare utilisation patterns in patients with genetic heart diseases is crucial for optimising clinical management, resource allocation, and identifying areas for improvement in healthcare delivery.

In recent years, the availability of large-scale administrative health databases has provided researchers with a unique opportunity to explore healthcare utilisation trends across diverse patient populations.[4,5] Routinely collected administrative datasets, including hospital admissions, emergency department episodes, and mortality records, offer comprehensive insights into patients' real-world clinical encounters and outcomes. When linked with disease registries, these administrative datasets can provide a wealth of information regarding care delivery patterns, disease trajectories, and outcomes among individuals, including those with genetic heart diseases.

Despite the immense potential of routinely collected health administrative data, few studies have investigated healthcare utilisation in genetic heart diseases. This is of importance as patients with genetic heart diseases are relatively younger than those with other cardiovascular diseases, with inherent risks posed to their family members and the potential for severe outcomes such as heart failure and sudden cardiac death.[6–8] Previous data linkage studies have used the International Classification of Diseases (ICD) diagnosis codes to identify and define their cohorts.[9,10] This approach has limitations as explicit ICD

diagnosis codes are available only for a limited number of genetic heart diseases, such as HCM and dilated cardiomyopathy (DCM). The remaining conditions are inconsistently categorised and broad descriptive diagnosis codes such as ‘other cardiomyopathies’ or ‘specified cardiac arrhythmias’ are often used.[10] By harnessing the power of administrative data linked to a genetic heart disease registry that has already identified clinically affected individuals, we can delve deeper into patients' healthcare experiences and gain valuable insights into resource utilisation.

Exploring healthcare utilisation patterns in patients with genetic heart diseases allows for examination of the role of socioeconomic status and sex. Socioeconomic factors have been shown to influence healthcare access, utilisation, and outcomes across various cardiovascular diseases.[11] Genetic heart diseases can have complex diagnostic and therapeutic requirements, in some cases requiring deep disease-specific expertise often only available in highly specialised referral centres.[6–8] Understanding how socioeconomic factors intersect with healthcare utilisation can provide valuable insights into potential barriers to care, differential treatment patterns, and health disparities among socioeconomic strata.[12] Additionally, sex differences have been observed in genetic heart disease presentation, management, and outcomes.[13,14] How sex influences healthcare utilisation and contributes to poor outcomes is largely unstudied. Investigating the influence of sex on healthcare utilisation may highlight specific healthcare needs and guide the development of sex-specific interventions and healthcare policies.

Here we describe patterns of care and healthcare utilisation among patients with genetic heart diseases by linking Australian Genetic Heart Disease (AGHD) Registry data with routinely collected hospital admission, emergency department, and mortality data.

Additionally, we aim to identify disparities and barriers to care by examining differences based on socioeconomic factors and sex. Our work will provide one of the first utilisations of administratively collected data in genetic heart diseases.

6.3 Methods

6.3.1 Study design and setting

Details of the AGHD Registry Data Linkage methods have been described in Chapter 5 of this thesis. In brief, this retrospective cohort study uses AGHD Registry participant data linked with routinely collected unit record administrative health data between 2007-2019. The study was approved by the Sydney Local Health District (RPAH) Human Research Ethics Committee and the NSW Population and Health Services Research Committee (PHSREC).

6.3.2 Data sources

AGHD Registry data and routinely collected administrative data were linked at a person level. The AGHD Registry has actively recruited individuals with a genetic heart disease and their at-risk relatives living in Australia since 2007.[15,16] The registry collects extensive demographic, clinical, and genetic information from the individual and their cardiologist. The data sources linked and used in this study included: (1) AGHD Registry data including NSW-based participants; (2) NSW Hospital admissions between 1st July 2001 to 30th June 2019 (Admitted Patient Data Collection); (3) NSW emergency department presentations between 1st January 2005 to 30th June 2019 (Emergency Department Data Collection); (4) Mortality registry data between 1st January 2007 to 31st December 2017 (NSW Registry of Births, Deaths and Marriages, Australian Coordinating Registry Cause of Death Unit Record File). The linkage of Admitted Patient Data Collection, Emergency Department Data Collection, NSW Registry of Birth, Deaths and Marriages, and Australian Coordinating Registry Cause of Death Unit Record File to AGHD registry data was conducted by the NSW Centre for Health Record Linkage.

Facility setting (i.e., metropolitan or regional/rural) was determined from the facility's local health district (LHD). Socioeconomic status was assessed based on postcodes using the Index of Relative Socio-Economic Advantage and Disadvantage, one of the four indexes provided by the Australian Bureau of Statistics Socio-Economic Indexes for Areas.[17] These indexes offer measures of socioeconomic conditions based on geographic areas. A higher decile signifies a relative advantage and a minimal level of disadvantage, whereas a lower decile indicates a relative disadvantage and a lack of advantage. For instance, areas ranking within the top 10% receive a decile of 10, whereas areas in the bottom 10% are assigned a decile of 1.

6.3.3 Participant inclusion and exclusion

Study eligibility included AGHD Registry participants who resided in NSW and had a confirmed diagnosis of any inherited cardiomyopathy (HCM, DCM, arrhythmogenic cardiomyopathy [ACM] or left ventricular non-compaction [LVNC]), or primary arrhythmia syndromes (long QT syndrome [LQTS], Brugada syndrome [BrS] or catecholaminergic polymorphic ventricular tachycardia [CPVT]). Participants were excluded if they had another diagnosis (Danon disease, Fabry disease, Noonan disease, bicuspid aortic valve, mitral valve prolapse etc.), only had a possible diagnosis or were at-risk relatives. Individuals were excluded if they did not link to any of the routinely collected administrative health datasets.

6.3.4 Statistical analysis

Data harmonisation involved systematically identifying and removing duplicate records, evaluating consistency in number of person-level records across the datasets, consistency across variables (e.g., admission dates before discharge dates), identifying outliers, and

identifying and flagging missing or invalid data. Descriptive statistics were used to report and analyse each dataset stratified by genetic heart disease diagnosis, socioeconomic status and sex. Baseline characteristics are presented as number (percentage) for categorical variables, mean (standard deviation) for approximately symmetrical continuous variables, and median (range) for asymmetrical continuous variables. Categorical variables were compared using the $\chi 2$ test, while continuous variables were compared using the unpaired t-test or the Kruskal-Wallis test (for asymmetrical variables). All analyses were conducted using R version 4.1.2.

6.4 Results

6.4.1 Participant characteristics

A linkage was established from 1720 participants in the AGHD registry with hospital admissions, emergency department, and mortality data from NSW, Australia. A total of 1384 AGHD Registry participants had linkages to the NSW Admitted Patient Data Collection (11610 records), NSW Emergency Department Data Collection (7032 records), NSW Registry of Births, Deaths and Marriages (60 records), or the Australian Coordinating Registry Cause of Death Unit Record File (45 records). Individuals with no linkages to the routinely collected datasets were removed from further analysis (n=336 [19.5%]). After excluding 99 participants with possible disease, 72 individuals with other diagnoses, 130 clinically unaffected at-risk relatives, and 67 with unknown disease status, 1016 individuals remained. Among them, 808 had an inherited cardiomyopathy (661 HCM, 67 DCM, 30 ACM, and 50 LVNC), while 165 had a primary arrhythmia syndrome (88 LQTS, 50 BrS, and 27 CPVT). This resulted in a dataset of 8,023 hospital admission records, 4,740 emergency department records, and 46 death records (Figure 6.1). The mean age of participants at the end of the study follow-up was 54.4 ± 17.5 years, 587 (57.8%) were male, and 642 (82.2%) were of self-reported European ethnicity (Table 6.1).

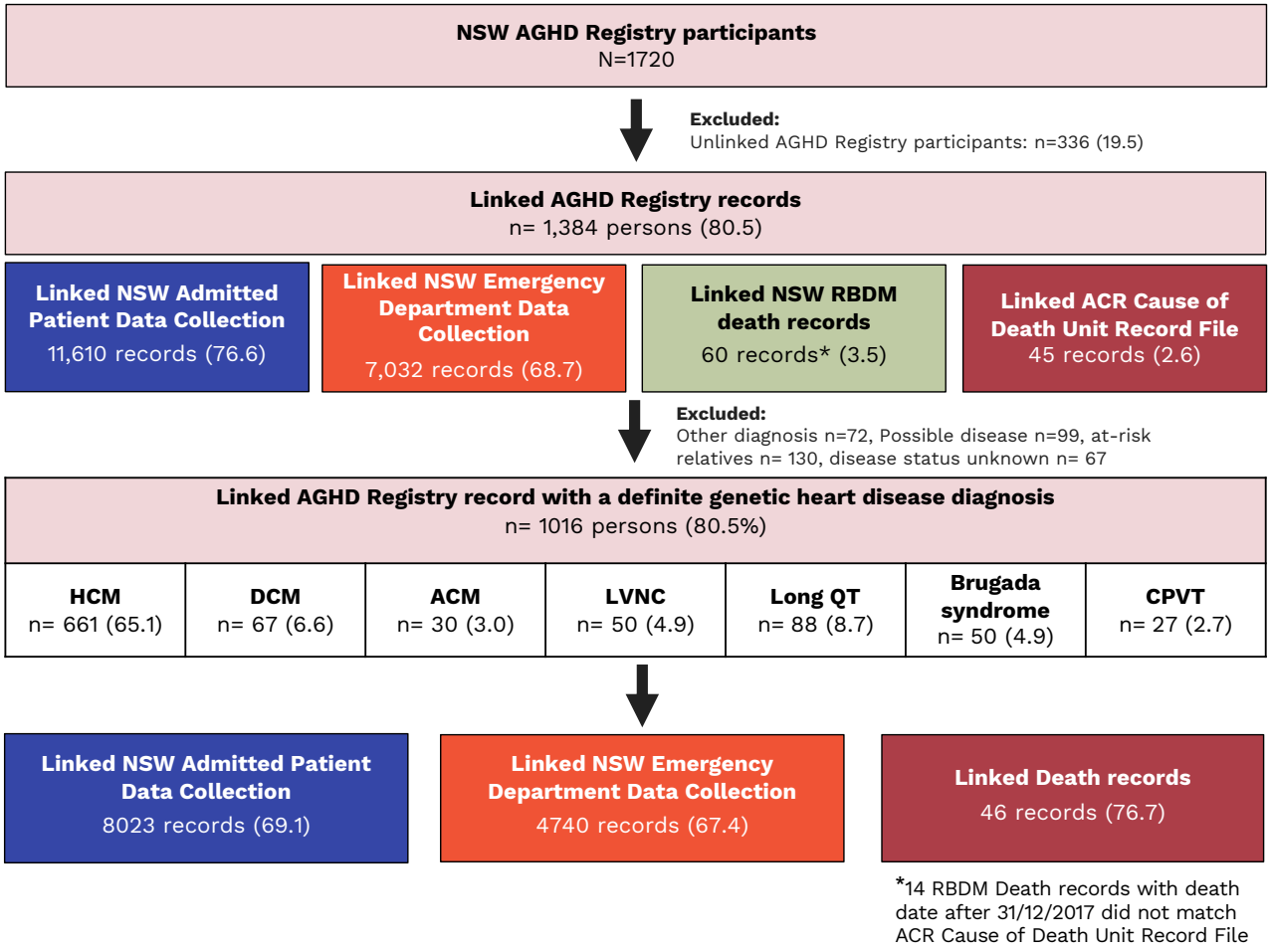

Figure 6.1: Flow diagram of AGHD Registry participants and records from each NSW routinely collected dataset datasets

Categorical data shown as n (%)

Abbreviations: NSW, New South Wales; AGHD, Australian Genetic Heart Disease; RBDM, Registry of Births, Deaths and Marriages; ACR, Australian Coordinating Registry; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia

6.4.2 AGHD Registry clinical characteristics by clinical diagnosis

Table 6.1 presents a descriptive analysis of AGHD Registry variables by genetic heart disease diagnosis. Whilst overall, more individuals were male, a higher percentage of LVNC and LQTS patients were female (60.0% and 72.7%, respectively). Most individuals were of European ancestry (n=642 [82.2%]). The average age at diagnosis varied, ranging from 28.6 ± 18.0 years for those with CPVT to 45.4 ± 13.4 years for DCM. There were 497 (52.9%) individuals who were symptomatic at diagnosis, with the highest proportion having ACM (n=21 [75%]). A total of 717 (78.1%) individuals had undergone genetic testing, with the highest testing rates among those with CPVT and LQTS (100% and 85.7%, respectively). Of those who underwent genetic testing, a causative variant was identified in 394 (61%) individuals, ranging from 31.6% in BrS to 69.6% in LQTS.

Clinical characteristics varied by genetic heart disease diagnosis. Sudden cardiac death events (resuscitated cardiac arrest, appropriate implantable cardioverter-defibrillator shock, ventricular tachycardia or sudden cardiac death) were most common for patients with CPVT (n=14 [60.9%]). Syncope occurred in 250 (28.4%) individuals and most commonly among those with CPVT (n=12 [48%]). Non-sustained ventricular tachycardia occurred in 212 (24.9%) of cases and was most prevalent in CPVT (n=71.4%). Atrial fibrillation was more common for those with cardiomyopathies compared to those with arrhythmia syndromes, particularly in ACM individuals (n=5 [41.7%]), followed by DCM (n=11 [34.4%]) and HCM (n=136 [26.4%]). A total of 66 (7.6%) individuals had heart failure, with the highest prevalence among those with DCM (n=18 [41.9%]). Of these, 17 (2.3%) had received a heart transplant. There were 410 individuals (81.8%) who had an implantable cardioverter-defibrillator, with the highest proportions in ACM patients (n=27 [100%]) and CPVT patients (n=21 [95.5%]).

Table 6.1: Descriptive analysis of Australian Genetic Heart Disease Registry cohort by clinical diagnosis

		Total cohort	HCM	DCM	ACM	LVNC	LQTS	BrS	CPVT
Number of individuals		**1016**	**661 (65.1)**	**67 (6.6)**	**30 (3.0)**	**50 (4.9)**	**88 (8.7)**	**50 (4.9)**	**27 (2.7)**
Demographics									
Age at end of follow-up, years		54.4 ± 17.5	57.0 ± 17.0	57.2 ± 13.4	53.7 ± 15.2	46.6 ± 16.4	43.6 ± 18.4	49.6 ± 15.8	40.6 ± 19.9
Male sex (%)		587 (57.8)	434 (62.8)	37 (55.2)	17 (56.5)	20 (40.0)	24 (27.3)	41 (65.1)	14 (51.9)
Ethnicity	European	642 (82.2)	474 (79.5)	32 (91.4)	16 (94.1)	25 (96.2)	42 (95.5)	32 (78.1)	21 (95.5)
	East Asian	37 (4.7)	29 (4.9)	1 (2.9)	0 (0)	0 (0)	0 (0)	7 (17.1)	0 (0)
	South Asian	29 (3.7)	28 (4.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.4)	0 (0)
	Middle Eastern and Northern African	44 (3.7)	41 (6.9)	1 (2.9)	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)
	Other	29 (3.7)	24 (4.0)	1 (2.9)	1 (5.9)	1 (3.8)	1 (2.3)	1 (2.4)	0 (0)
IRSAD from postcode, decile		6.9 ± 2.9	6.8 ± 3.0	7.0 ± 2.9	7.6 ± 2.8	7.4 ± 2.6	7.5 ± 2.7	7.0 ± 3.0	6.9 ± 3.1
Clinical characteristics									
Age at diagnosis, years		41.6 ± 17.6	42.7 ± 17.8	45.4 ± 13.7	45.1 ± 13.4	41.0 ± 15.6	33.0 ± 18.6	42.4 ± 14.9	28.6 ± 18.0
Symptomatic at diagnosis		497 (52.9)	335 (51.2)	34 (68.0)	21 (75.0)	27 (60.0)	41 (48.8)	22 (42.3)	17 (68.0)
Sudden death event ever*		119 (13.1)	58 (9.1)	5 (10.9)	14 (50.0)	1 (2.5)	16 (19.8)	11 (21.2)	14 (60.9)
Syncope ever		250 (28.4)	153 (24.8)	9 (20.0)	9 (36.0)	10 (27.0)	39 (45.9)	18 (37.5)	12 (48.0)
Non-sustained VT		212 (24.9)	159 (26.1)	5 (13.5)	12 (57.1)	6 (15.4)	9 (11.7)	6 (13.0)	15 (71.4)
Atrial fibrillation		171 (24.4)	136 (26.4)	11 (34.4)	5 (41.7)	5 (19.2)	6 (9.0)	3 (10.4)	5 (10.4)
Heart failure		66 (7.6)	39 (6.3)	18 (41.9)	2 (10.0)	6 (13.3)	0 (0)	0 (0)	1 (7.1)
Heart transplant		17 (2.3)	15 (2.6)	2 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ICD		410 (81.8)	260 (77.4)	25 (86.2)	27 (100.0)	3 (21.4)	41 (91.1)	25 (89.3)	21 (95.5)
Smoker status	Never	236 (53.4)	160 (51.5)	9 (39.1)	4 (33.3)	10 (58.8)	37 (71.2)	13 (61.9)	3 (50.0)
	Past	164 (37.1)	120 (47.8)	11 (47.8)	7 (58.3)	6 (35.3)	10 (19.2)	7 (33.3)	3 (33.3)

	Current	42 (9.5)	31 (10.0)	3 (13.0)	1 (8.3)	1 (5.9)	5 (9.6)	1 (4.8)	1 (8.3)
Genetics									
Genetic testing		717 (78.1)	532 (82.5)	28 (82.5)	17 (70.8)	13 (34.2)	66 (85.7)	35 (59.3)	26 (100.0)
Gene status	Positive	394 (61.0)	316 (61.8)	11 (68.8)	9 (66.7)	5 (55.6)	39 (69.6)	6 (31.6)	9 (39.1)
	Negative	252 (39.0)	195 (38.2)	5 (31.3)	4 (33.3)	4 (44.4)	17 (30.4)	13 (68.4)	14 (60.9)
Family history									
Family history of disease		483 (49.6)	325 (48.2)	47 (81.0)	12 (42.9)	19 (43.2)	53 (65.4)	14 (22.6)	13 (48.2)
Family history of SCD		238 (24.4)	139 (20.6)	24 (38.7)	6 (21.4)	10 (22.2)	37 (45.7)	15 (24.2)	7 (29.2)
Cardiac Investigations									
Max LV wall thickness, mm		17.3 ± 6.2	19.2 ± 5.2	9.7 ± 1.8	9.5 ± 1.6	9.3 ± 1.6	9.3 ± 1.9	11.3 ± 7.6	9.8 ± 2.6
Posterior wall thickness, mm		10.4 ± 2.5	10.8 ± 2.5	8.8 ± 1.4	9.4 ± 1.4	8.7 ± 1.5	8.8 ± 1.9	9.5 ± 1.4	8.3 ± 1.5
LV ejection fraction (%)		59.8 ± 12.6	62.3 ± 11.4	44.0 ± 10.8	58.6 ± 12.6	50.1 ± 13.5	60.6 ± 6.7	61.7 ± 8.3	60.4 ± 5.2
Left atrial size, mm		42.9 ± 8.6	43.6 ± 8.7	44.9 ± 6.7	43.2 ± 7.1	38.2 ± 4.1	34.9 ± 5.0	33.2 ± 5.5	40.7 ± 3.1
QTc interval, msec		431.2 ± 39.9	431.4 ± 32.8	413.6 ± 65.0	447.2 ± 33.3	414.4 ± 55.1	464.6 ± 47.1	399.1 ± 23.0	417.7 ± 48.4

Categorical data shown as n (%) and continuous data shown as mean ± SD or median (range)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; IRSAD, Index of Relative Social Advantage and Disadvantage; VT, ventricular fibrillation; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death; LV, left ventricular.
*Resuscitated cardiac arrest, appropriate ICD shock, conscious VT, sustained VT and/or sudden cardiac death

6.4.3 Admitted Patient Data Collection by clinical diagnosis

Table 6.2 presents the descriptive analysis of variables from the Admitted Patient Data Collection by clinical diagnosis. There was a total of 8,023 hospital admissions for both cardiac admissions and any other diagnosis. The majority of admissions were individuals with HCM who accounted for 5,830 admissions (72.7%), followed by BrS with 535 admissions (6.7%), LQTS with 502 admissions (6.3%), LVNC with 365 admissions (4.6%), DCM with 337 admissions (4.2%), ACM with 285 admissions (3.6%), and CPVT with 169 admissions (2.1%).

Males accounted for 4,317 admissions (53.8%), with the greatest number observed in the HCM group (n= 3415 [58.6%]). The median number of episodes of care across all genetic heart disease diagnoses was 7 (range 1-99). HCM had the highest median number of episodes (n=8 [1-99]) while CPVT had the lowest (n=6 [1-34]). Regarding length of stay per episode, the median episode length across all diagnoses was 1 day (range 1-248 days). The longest median length of stay was for those with BrS, with a range of 1-115 days, while DCM had the lowest (1-44 days). The mean age at first admission was 42.8 ± 17.0, ranging from 23.1 ± 18.3 in CPVT to 45.6 ± 16.0 in HCM.

Most hospital admissions (n=3270, 58.0%) did not involve the emergency department. However, 399 admissions (7.1%) occurred solely within the emergency department, while 1967 admissions (34.9%) comprised episodes that encompassed both the emergency department and subsequent admission to a ward. A total of 336 admissions (4.2%) included admission to the intensive care unit (ICU), with the highest proportion being those with CPVT (n= 12 [7.1%]). The median hours spent in the ICU for the entire cohort was 41.5

hours (range 1-1350 hours), with the greatest median observed among those with BrS (56 hours [6-840]) and the fewest hours for those with LVNC (24 hours [3-53]).

Most admissions occurred within a public hospital (n= 4,515 [56.3%]), with the highest proportion in CPVT (n=111 [65.7]). Regional/rural hospitals accounted for 2,171 (27.1%) admissions, with HCM patients more likely to present to these hospitals (n=1761 [30.2%]). The proportion of admissions who did not have or did not use private health insurance also varied by genetic heart disease. CPVT patients had the highest proportion with full private health insurance (n=89 [60.5%]), while LQTS patients had the highest proportion of admissions with no private health insurance (n=245 [51.6%]).

Regarding the mode of separation, most admissions ended with the patients being discharged (7352 [91.6%]), with the highest proportion with DCM (320 [95.0%]). Transfers to other facilities accounted for 581 (7.2%) admissions, while a small percentage (n=62 [0.8%]) were a type change separation (i.e., where the patient continues the hospital stay, but there is a change in the type of episode of care). A further 28 (0.4%) patients died during their hospital admission

Table 6.2: Descriptive analysis of NSW Admitted Patient Data Collection variables by clinical diagnosis

		Total cohort	HCM	DCM	ACM	LVNC	LQTS	BrS	CPVT
Number of individuals		**807**	**568**	**41**	**25**	**40**	**57**	**56**	**20**
Total admissions		8023	5830 (72.7)	337 (4.2)	285 (3.6)	365 (4.6)	502 (6.3)	535 (6.7)	169 (2.1)
Admissions by Male sex		4317 (53.8)	3415 (58.6)	113 (42.0)	151 (53.0)	155 (42.5)	128 (25.5)	284 (53.1)	71 (42.0)
Median episodes of care		7 (1-99)	8 (1-99)	6 (1-62)	7 (1-69)	7 (1-62)	6.5 (1-49)	8 (1-81)	6 (1-34)
Median episode length of stay (days)		1 (1-248)	1 (1-248)	1 (1-62)	1 (1-44)	1 (1-61)	1 (1-52)	1 (1-115)	1 (1-22)
Mean age at any admission (years)		53.4 ± 16.6	55.8 ± 15.6	49.4 ± 12.4	53.8 ± 14.5	46.5 ± 17.9	42.4 ± 18.3	50.1 ± 16.5	34.2 ± 21.4
Mean age at first admission (years)		42.8 ± 17.0	45.6 ± 16.0	44.4 ± 13.1	44.1 ± 13.9	34.9 ± 17.2	29.0 ± 18.6	39.5 ± 15.0	23.1 ± 18.3
Public hospital		4515 (56.3)	3369 (57.8)	148 (42.9)	139 (48.8)	136 (37.2)	314 (62.6)	298 (55.7)	111 (65.7)
Regional/rural facility		2171 (27.1)	1761 (30.2)	81 (24.0)	39 (13.7)	27 (7.4)	138 (27.5)	77 (14.4)	48 (28.4)
Marital status	Married (incl. de facto)	4982 (65.3)	3767 (68.5)	232 (71.2)	129 (48.7)	250 (69.1)	173 (35.4)	347 (66.0)	84 (51.5)
	Never Married	1404 (18.4)	780 (14.2)	41 (12.6)	40 (15.1)	89 (24.6)	224 (45.8)	152 (28.9))	78 (47.9)
	Widowed	426 (5.6)	308 (5.6)	1 (0.3)	67 (25.3)	0 (0)	47 (9.6)	3 (0.6)	0 (0)
	Divorced	600 (7.9)	445 (8.1)	51 (15.6)	25 (9.4)	22 (6.1)	42 (8.6)	15 (2.9)	0 (0)
	Separated	216 (2.8)	197 (3.6)	1 (0.3)	4 (1.5)	1 (0.3)	3 (0.6)	9 (1.7)	1 (0.6)
Health insurance	No cover	2963 (39.5)	2242 (40.9)	81 (24.7)	77 (27.9)	95 (32.7)	245 (51.6)	201 (39.4)	22 (15.0)
	Full cover	3176 (42.3)	2306 (42.1)	177 (54.0)	98 (35.5)	118 (40.6)	174 (36.6)	214 (41.9)	89 (60.5)
	Basic cover	1253 (18.0)	924 (16.8)	69 (21.0)	101 (36.6)	75 (25.8)	56 (11.8)	92 (18.0)	36 (24.5)
ED status	Entire episode within ED	399 (7.1)	291 (7.0)	13 (7.2)	12 (5.9)	12 (4.9)	24 (6.7)	35 (9.5)	12 (9.8)
	Episode includes ED and ward	1967 (34.9)	1472 (35.4)	66 (36.7)	79 (38.7)	48 (19.7)	159 (44.3)	107 (29.0)	36 (29.5)
	Episode with no ED involvement	3270 (58.0)	2395 (57.6)	101 (56.1)	113 (55.4)	184 (75.4)	176 (49.0)	227 (61.5)	74 (60.7)

Number admitted to ICU		336 (4.2)	226 (3.9)	18 (5.3)	18 (6.3)	10 (2.7)	19 (3.8)	33 (6.2)	12 (7.1)
Median time in ICU, hours		41.5 (1-1350)	41 (1-1359)	39 (12-237)	46.5 (1-169)	24 (3-53)	30 (4-527)	56 (6-840)	36 (9-147)
Mode of separation	Discharged	7352 (91.6)	5345 (91.7)	320 (95.0)	255 (89.5)	339 (92.9)	465 (92.6)	478 (89.4)	150 (88.8)
	Transferred	581 (7.2)	416 (7.1)	17 (5.1)	23 (8.1)	25 (4.3)	37 (7.4)	44 (8.2)	44 (8.2)
	Type change separation	62 (0.8)	43 (0.7)	0 (0)	5 (1.8)	1 (0.3)	0 (0)	13 (2.4)	0 (0)
	Died	28 (0.4)	26 (0.5)	0 (0)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)

Categorical data shown as n (%) and continuous data shown as mean ± SD or median (range)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ED, emergency department; ICU, intensive care unit

6.4.4 Time from genetic heart disease diagnosis to first hospital admission

The time from genetic heart disease diagnosis to first hospital admission is shown in Figure 6.2A-B. Figure 6.2A shows admissions for all major primary diagnosis categories, while Figure 6.2B shows admissions only related to the circulatory system. Comparison between the two shows that most admissions for genetic heart disease patients occur around the time of their diagnosis or post-diagnosis being made (Figure 6.2B), while prior to diagnosis most admissions are for other reasons (Figure 6.2A).

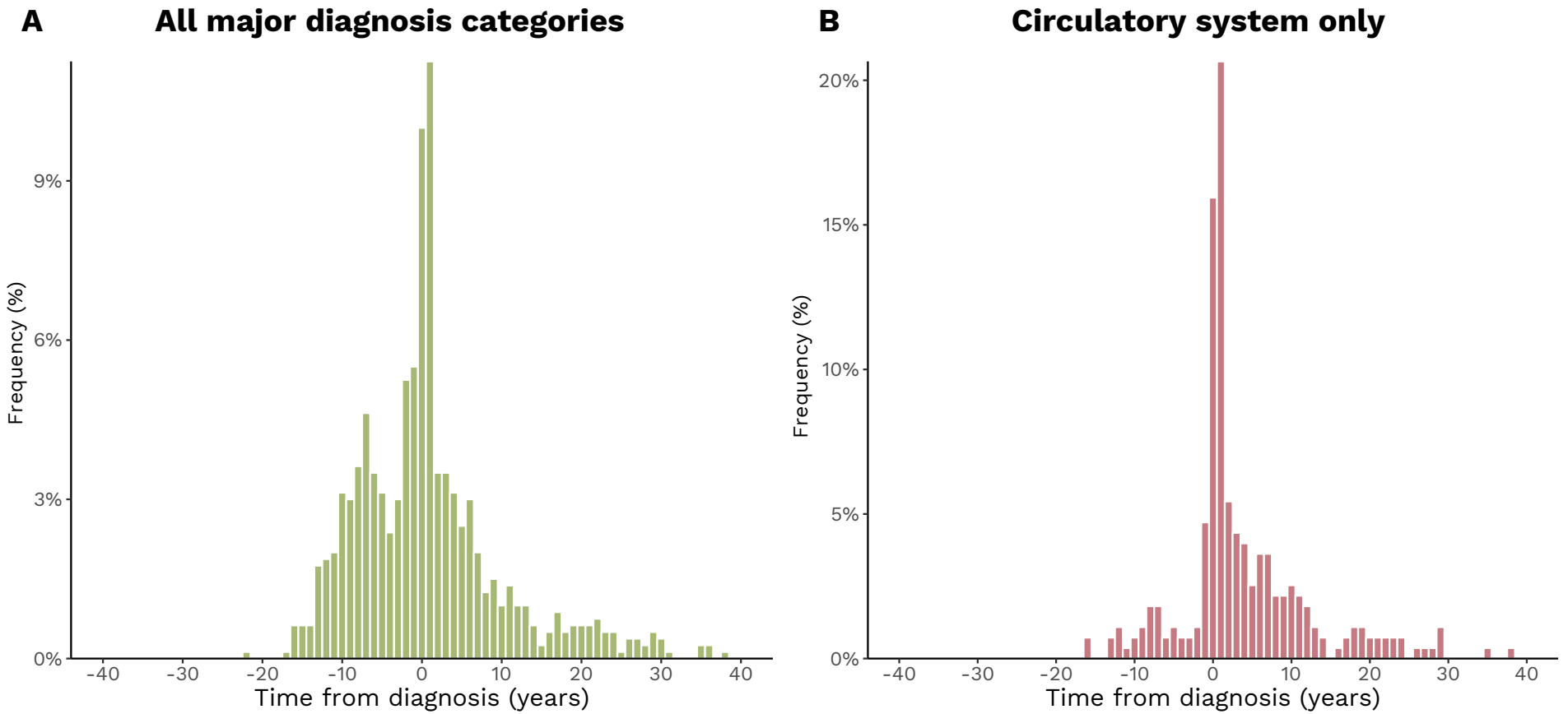

Figure 6.2: Time in years from diagnosis of genetic heart disease to first hospital admission for (A) admissions for all major diagnosis categories and (B) admissions related to the circulatory system only. The majority of admission occurs around the time of genetic heart disease diagnosis. Most admissions for other reasons occur before diagnosis.

The distribution of the Major Diagnosis Category (MDC) at admission is shown in Figure 6.3A. Many individuals had hospital presentations related to the circulatory system (n=2596 [37.7%]). This was particularly the case for those with ACM and CPVT, in which over 50% of admission were associated with the circulatory system. A substantial number also attend due to diagnoses related to the digestive system (n=773 [11.2%]), factors influencing health status and contact with health services (i.e circumstances other than a disease, injury or external cause) (n=544 [7.9%]), and musculoskeletal system and connective tissues (n=501 [7.3%]). A high proportion of women with LVNC had admissions related to pregnancy, childbirth and puerperium (i.e., the 6 weeks after childbirth) (n=35 [13.6%]).

The Service Related Group (SRG) distribution is shown in Figure 6.3B. The SRG categorises admitted patient episodes into groups representing clinical divisions of hospital activity based on aggregations of Australian Refined Diagnosis Related Groups (AR-DRGs). A significant proportion of patients were seen by cardiology (n=1156 [29.5%]) or interventional cardiology (n=422 [10.8%]), particularly those with ACM and CPVT. Other services utilised included non-subspecialty medicine (n=280 [7.2%]), gastroenterology (n=239 [6.1%]), respiratory medicine (n=188 [4.8%]), non-subspecialty surgery (n=176 [4.5%]), neurology (n=153 [3.9%]), orthopaedics (n=131 [3.4%]), gynaecology (n=89 [2.3%]), obstetrics (n=98 [1.5%]) and neurosurgery (n=41 [1.1%]).

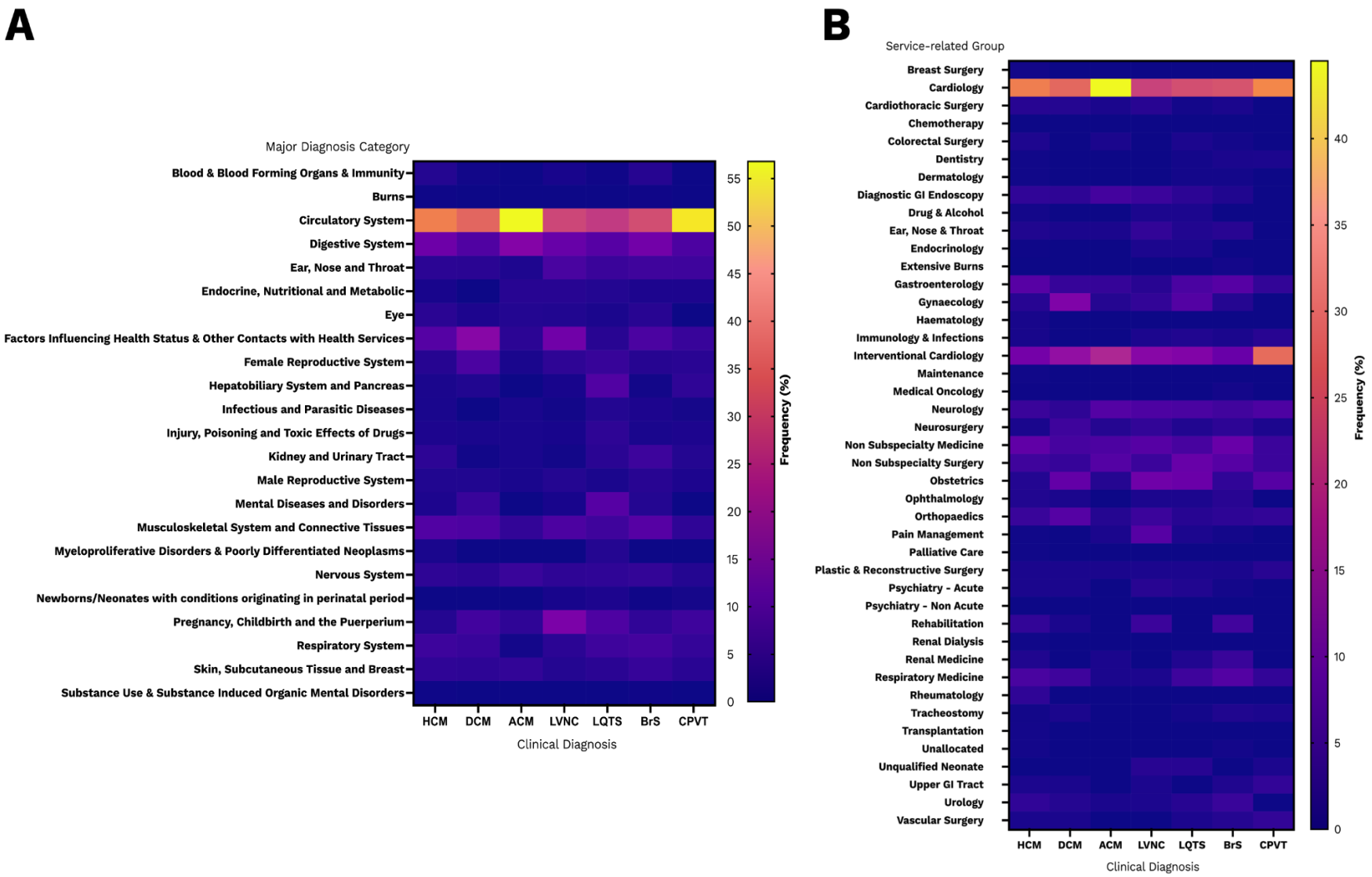

Figure 6.3: Heat maps showing the distribution of (A) Major Diagnosis Category (MDC) and (B) Service-Related Group (SRG) at hospital admission by genetic heart disease diagnosis. Admissions were Predominantly due to diagnoses related to the circulatory system, and therefore cardiology and interventional cardiology were the most required services.

Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

6.4.5 Emergency Department Data Collection by clinical diagnosis

Table 6.3 presents the descriptive analysis of variables from the Emergency Department Data Collection by clinical diagnosis. There was a total of 4740 emergency department episodes. The majority were individuals with HCM (n=3355 episodes, 70.7%), followed by BrS (n=312 episodes, 6.6%), DCM (n=166 episodes, 3.5%), ACM (n=152 episodes, 3.2%), CPVT (n=111 episodes, 2.3%), LQTS (n=478 episodes, 1.0%) and LVNC (n=166 episodes, 1.0%). Males accounted for more emergency department episodes (n=2613 [55.1%]). However, more females with LQTS and DCM presented to the emergency department (75.5% and 56.0%, respectively). Additionally, a considerable portion of the episodes involved individuals born overseas (n=1184 [25.5%]), with the greatest number observed having ACM (n=61 [42.1%]), followed by BrS (n=109 [35.2%]). Regional/rural facilities were responsible for 1984 episodes (41.9%).

The median number of episodes of care was 5, ranging from 1 to 70. Patients with BrS had the highest median episodes of care at 8, ranging from 1 to 70, while LVNC had the least with a median of 3 episodes, ranging from 1 to 13. When examining the age distribution, the mean age at the first episode was 44.9 ± 18.0, with HCM patients having the oldest mean age (47.7 ± 17.4 years) and CPVT patients having the youngest (27.3 ± 19.2 years).

At separation from the emergency department, approximately half of the episodes resulted in discharge due to completion of treatment (n=2336, 49.1%). This ranged from 65 episodes (42.8%) among those with ACM to 73 episodes (65.8%) in CPVT. Additionally, 1309 (27.6%) episodes ended with admission to a non-critical care ward, and 452 (9.6%) episodes ended with admission to a critical care ward. Two (0.04%) participants were dead

on arrival at the emergency department, while a further 3 (0.06%) died in the emergency department.

Table 6.3: Descriptive analysis of NSW Emergency Department Data Collection variables by clinical diagnosis

	Total cohort	HCM	DCM	ACM	LVNC	LQTS	BrS	CPVT
Number of individuals	**721**	**505**	**35**	**22**	**33**	**55**	**51**	**20**
Total ED episodes	4740 (100)	3355 (70.7)	166 (3.5)	152 (3.2)	166 (1.0)	478 (1.0)	312 (6.6)	111 (2.3)
Episode by male sex	2613 (55.1)	2026 (60.4)	73 (44.0)	95 (62.5)	78 (47.0)	122 (25.5)	164 (52.6)	55 (49.6)
Episode by born overseas	1184 (25.5)	905 (27.6)	34 (21.1)	61 (42.1)	36 (22.2)	35 (7.4)	109 (35.2)	4 (3.6)
Regional/rural facility	1984 (41.9)	1532 (45.7)	42 (25.3)	48 (31.6)	33 (19.9)	193 (40.4)	85 (27.2)	51 (46.0)
Median episodes of care	5 (1-70)	5 (1-70)	4 (1-30)	4 (1-28)	3 (1-13)	8 (1-70)	5 (1-40)	4 (1-17)
Mean age at any episode, years	48.8 ± 18.8	51.7 ±17.7	44.5 ± 12.6	53.1 ± 14.6	39.3 ± 20.0	38.3 ± 20.4	45.8 ± 18.1	28.5 ± 18.8
Mean age at first episode, years	44.9 ± 18.0	47.7 ± 17.4	45.9 ± 13.5	47.0 ± 14.0	37.4 ±18.2	31.9 ± 18.8	41.7 ±15.9	27.3 ± 19.2
Status at separation								
Departed: Treatment completed	2326 (49.1)	1564 (46.6)	90 (54.2)	65 (42.8)	103 (62.1)	281 (58.8)	150 (48.1)	73 (65.8)
Departed: Transferred to another hospital	60 (3.2)	47 (1.4)	0 (0)	0 (0)	6 (3.6)	1 (0.2)	6 (1.9)	0 (0)
Departed: For other clinical service location	51 (1.1)	37 (1.1)	2 (1.2)	3 (2.0)	3 (1.8)	4 (0.8)	0 (0)	2 (1.8)
Departed: Did not wait	151 (3.2)	97 (2.9)	8 (4.8)	3 (2.0)	4 (2.4)	22 (4.6)	13 (4.2)	4 (3.6)
Departed: Left at own risk	86 (1.8)	60 (1.8)	5 (3.0)	0 (0)	0 (0)	15 (3.1)	6 (1.9)	0 (0)
Admitted: Ward/inpatient unit, not a critical care	1309 (27.6)	963 (28.4)	48 (28.9)	61 (40.1)	36 (21.8)	111 (23.2)	79 (25.3)	21 (18.9)
Admitted: critical care ward	452 (9.6)	367 (10.9)	5 (3.0)	14 (9.2)	5 (3.0)	27 (5.7)	26 (8.3)	8 (7.2)
Admitted and discharged as inpatient within ED	195 (4.1)	148 (4.4)	4 (2.4)	3 (3.6)	6 (3.6)	12 (2.5)	20 (6.4)	2 (1.8)
Admitted: Transferred to another hospital	87 (1.8)	63 (1.9)	2 (1.2)	3 (2.0)	0 (0)	1 (0.2)	1 (0.3)	0 (0)
Admitted: Via operating suite	13 (0.3)	9 (0.3)	2 (1.2)	0 (0)	0 (0)	1 (8.0)	1 (0.3)	0 (0)
Admitted: Left at own risk	5 (0.1)	5 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Admitted: Died in ED	3 (0.06)	3 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dead on arrival	2 (0.04)	2 (0.06)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Categorical data shown as n (%) and continuous data shown as mean ± SD or median (range)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ED, emergency department

6.4.6 Top 10 diagnoses and procedures for circulatory system hospital presentations by genetic heart disease diagnosis

Circulatory system hospital presentations by genetic heart disease diagnosis

Figure 6.4A displays the top 10 primary diagnoses by genetic heart disease for admissions with a circulatory system major diagnosis category. It reveals a considerable diagnosis overlap, including atrial fibrillation, ventricular tachycardia, chest pain, cardiac device management, and complications.

The diagnostic codes for HCM and DCM closely align with the confirmed clinical diagnoses, indicating a strong correlation between the two. Patients with cardiomyopathies are associated with specific cardiomyopathy codes such as obstructive HCM, other HCM, DCM, other cardiomyopathies, and unspecified cardiomyopathy. In contrast, primary arrhythmias are linked to arrhythmia codes, including ‘other specified conduction disorders’ and ‘other specified cardiac arrhythmias’. The burden of these conditions becomes evident through many symptomatic admissions related to chest pain, syncope and collapse, and palpitations.

Figure 6.4B displays the top 10 primary procedures by genetic heart disease for admissions with a circulatory system major diagnosis category. ‘Cardioversion’ was frequently utilised in these individuals and this fits with the high number of atrial fibrillation diagnoses. Additionally, a significant number of procedures related to pacemakers and defibrillators were observed, particularly the insertion and replacement of cardiac defibrillator generators. Moreover, ‘coronary angiography with left heart catheterisation’ was performed frequently in individuals diagnosed with HCM and DCM, but was additionally observed in individuals with ACM, LVNC, LQTS and BrS.

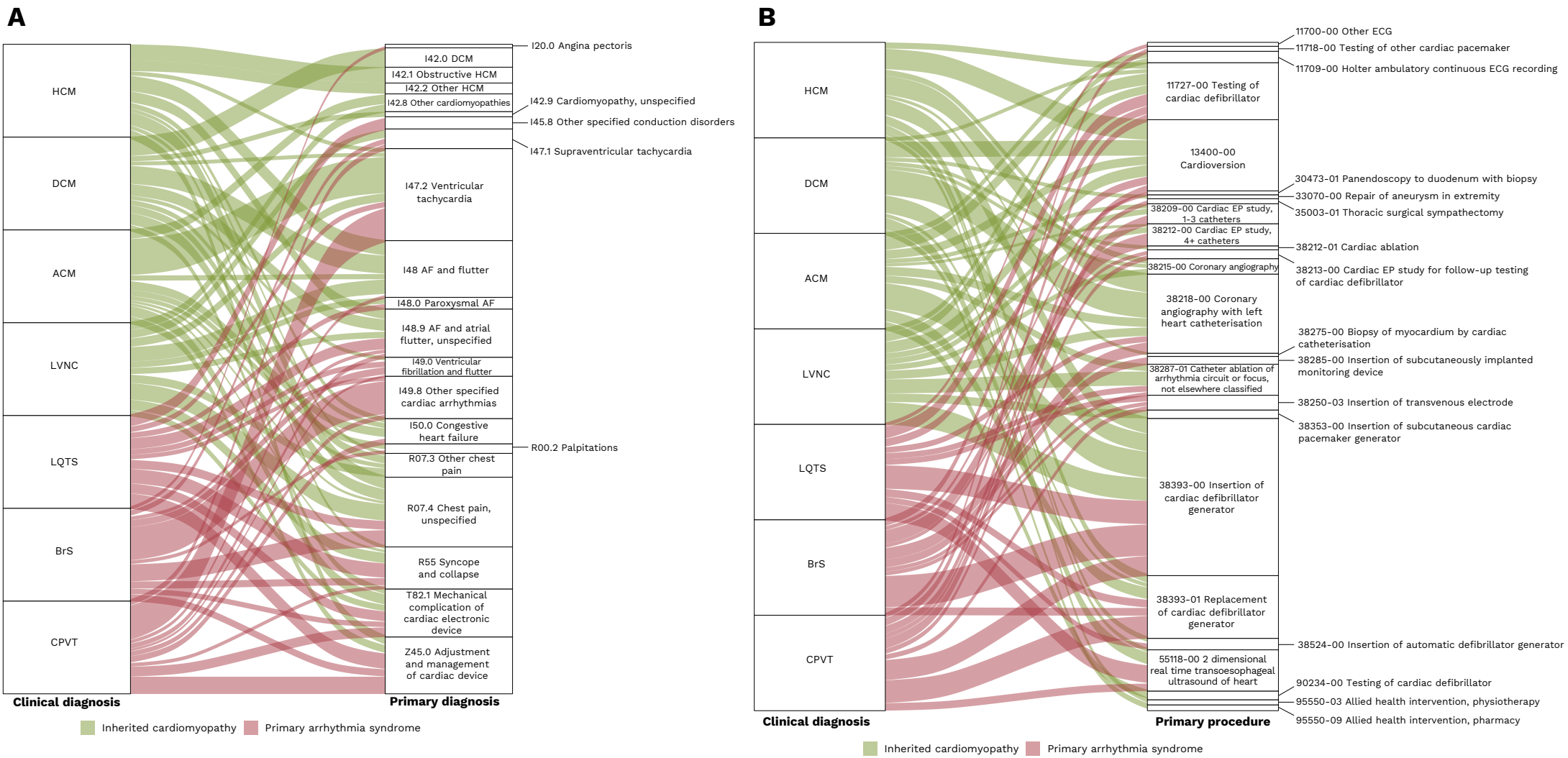

Figure 6.4: Circulatory system hospital presentations by genetic heart disease diagnosis. (A) Top 10 primary diagnoses at admission; (B) Top 10 primary procedures at admission.

Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; AF, atrial fibrillation.

6.4.7 Top 10 primary diagnoses and procedures for all hospital admissions and emergency department episodes

Figure 6.5 displays the top 10 primary hospital diagnoses, hospital procedures, and emergency department diagnoses for all admissions by inherited cardiomyopathy. Below we report top diagnoses for hospital admissions and procedures by clinical diagnosis. Where specific findings appear to be oversubscribed due to very small numbers of participants, we also report the sample size.

HCM

The top three primary diagnoses for hospital admissions in HCM patients were: obstructive HCM (217 [14.9%]), atrial fibrillation and flutter (217 [13.7%]), and unspecified chest pain (193 [12.2%]). The main procedures performed for HCM patients include allied health interventions like physiotherapy (334 [20.9%]), coronary angiography with left heart catheterisation (184 [11.5%]), and cardioversion (179 [11.2%]). The top three emergency department diagnoses were chest pain (294 [40.0%]), atrial fibrillation (169 [23.0%)], and palpitations (54 [7.4%]). Other notable findings included diagnosis codes for the management of cardiac devices, follow-up examinations after surgery, and care involving rehabilitation procedures.

DCM

The top three primary diagnoses for hospital admissions in DCM patients were: care involving rehabilitation procedures (41 [33.9%]), dilated cardiomyopathy (17 [14.0%]) and atrial fibrillation and flutter (14 [11.6%]). The primary procedures performed are coronary angiography with left heart catheterisation (38 [31.7%]), insertion of cardiac defibrillator (15 [2.5%]), and cardioversion (15 [2.5%]). The top emergency department diagnoses were chest pain (21 [29.9%]), palpitations (14 [19.2%]), and atrial fibrillation (10 [13.7%]). Other

notable findings included diagnosis codes for congestive heart failure, abdominal pain, and various complications and episodes related to depressive disorder.

ACM

The top three primary diagnoses for hospital admissions in ACM patients were: ventricular tachycardia (45 [32.6%]), pharmacotherapy session for neoplasm (18 [13.0%]), and mechanical complications of cardiac electronic devices (13 [9.4%]). The main procedures performed are the insertion of cardiac defibrillator generators (18 [17.5%]), intravenous administration of antineoplastic agents (18 [17.5%] (these admissions occurred in ≤3 patients), and fibreoptic colonoscopy to the caecum (12 [11.7%]). The top emergency department diagnoses consist of chest pain (9 [21.4%], ventricular tachycardia (9 [21.4%]), and disorders of implantable defibrillators (6 [14.3%]). Other notable findings included diagnosis codes for congestive heart failure, palpitations, and various cardiac-related conditions such as supraventricular tachycardia, atrial fibrillation, and flutter.

LVNC

The top three primary diagnoses for hospital admissions in LVNC patients were: severe depressive episodes (57 [41.3%]; n= ≤3 patients), care involving rehabilitation procedures (20 [14.5%]; n= ≤3 patients), and cervicalgia (16 [11.6%]; n= ≤3 patients). The main hospital procedures performed were other psychotherapies or psychosocial therapies (57 [38.8%] n= ≤3 patients), hydrotherapy (19 [12.9%] n= ≤3 patients), and allied health intervention for physiotherapy (16 [10.9] n= ≤3 patients). The top emergency department diagnoses were chest pain (14 [26.9%]), atrial fibrillation (7 [13.5%]), and atypical chest pain (6 [11.5%]). Other notable findings included diagnosis codes for abdominal pain, palpitations, and various conditions such as low back pain, syncope, and falls.

A

Hypertrophic cardiomyopathy

Top 10 APDC primary diagnosis codes				Top 10 primary APDC procedure codes				Top 10 EDDC diagnosis codes			
	Diagnosis	N	Admissions (%)		Procedure	N	Admissions (%)		Diagnosis	N	Admissions (%)
1	I42.1 Obstructive HCM	164	236 (14.9)	1	95550-03 Allied health intervention, physiotherapy	95	334 (20.9)	1	29857009 Chest Pain	166	294 (40.0)
2	I48 Atrial fibrillation and flutter	69	217 (13.7)	2	38218-00 Coronary angiography with left heart catheterisation	142	184 (11.5)	2	49436004 Atrial fibrillation	52	169 (23.0)
3	R07.4 Chest pain, unspecified	113	193 (12.2)	3	13400-00 Cardioversion	68	179 (11.2)	3	80313002 Palpitations	41	54 (7.4)
4	I48.9 Atrial fibrillation and atrial flutter, unspecified	67	185 (11.7)	4	32090-00 Fibreoptic colonoscopy to caecum	120	170 (10.6)	4	21522001 Abdominal pain	36	42 (5.7)
5	I42.2 Other HCM	135	165 (10.4)	5	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	104	169 (10.6)	5	267036007 Dyspnoea	26	32 (4.4)
6	Z45.0 Adjustment and management of cardiac device	105	161 (10.2)	6	38393-00 Insertion of cardiac defibrillator	135	147 (9.2)	6	128045006 Cellulitis	22	31 (4.2)
7	Z09.0 Follow-up examination after surgery for other conditions	36	130 (8.2)	7	30473-01 Panendoscopy to duodenum with biopsy	90	131 (8.2)	7	271594007 Syncope	27	31 (44.2)
8	Z50.9 Care involving use of rehabilitation procedure, unspecified	37	125 (7.9)	8	38393-01 Replacement of cardiac defibrillator	80	97 (6.1)	8	102589003 Atypical chest pain	22	28 (3.8)
9	H26.9 Cataract, unspecified	54	92 (5.8)	9	38275-00 Biopsy of myocardium by cardiac	14	95 (6.0)	9	394659003 Acute coronary syndrome	24	27 (3.7)
10	I50.0 Congestive heart failure	43	81 (5.1)	10	95550-02 Allied health intervention, occupational	30	94 (5.9)	10	V62.6 Refusal of treatment for reasons of religion or conscience	20	28 (4.1)

B

Dilated cardiomyopathy

Top 10 APDC primary diagnosis codes				Top 10 primary APDC procedure codes				Top 10 EDDC diagnosis codes			
	Diagnosis	N	Admissions (%)		Procedure	N	Admissions (%)		Diagnosis	N	Admissions (%)
1	Z50.9 Care involving use of rehabilitation procedure, unspecified	≤3	41 (33.9)	1	38218-00 Coronary angiography with left heart catheterisation	7	38 (31.7)	1	29857009 Chest pain	11	21 (28.8)
2	I42.0 Dilated cardiomyopathy	12	17 (14.0)	2	38393-00 Insertion of cardiac defibrillator	13	15 (2.5)	2	80313002 Palpitations	4	14 (19.2)
3	I48 Atrial fibrillation and flutter	5	14 (11.6)	3	13400-00 Cardioversion	11	11 (9.2)	3	49436004 Atrial fibrillation	5	10 (13.7)
4	I48.9 Atrial fibrillation and atrial flutter, unspecified	≤3	11 (9.1)	4	30473-01 Panendoscopy to duodenum with biopsy	≤3	10 (8.3)	4	42343007 Congestive heart failure	≤3	7 (9.6)
5	R07.4 Chest pain, unspecified	7	9 (7.4)	5	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	5	10 (8.3)	5	21522001 Abdominal pain	≤3	5 (6.6)
6	F33.2 Recurrent depressive disorder, current episode severe without psychotic	≤3	7 (5.8)	6	95550-02 Allied health intervention, occupational	7	10 (8.3)	6	85898001 Cardiomyopathy	≤3	4 (5.5)
7	R07.3 Other chest pain	5	6 (5.0)	7	55118-00 2 dimensional real time transoesophageal ultrasound of heart	≤3	9 (7.5)	7	102589003 Atypical chest pain	≤3	3 (4.1)
8	T82.1 Mechanical complication of cardiac electronic device	≤3	6 (5.0)	8	32090-00 Fibreoptic colonoscopy to caecum	6	7 (5.8)	8	194828000 Angina pectoris	≤3	3 (4.1)
9	F32.20 Mild depressive episode	≤3	5 (4.1)	9	32090-01 Fibreoptic colonoscopy to caecum, with biopsy	6	6 (5.0)	9	230690007 Cerebrovascular accident	≤3	3 (4.1)
10	I42.9 Cardiomyopathy, unspecified	5	5 (4.1)	10	38218-00 Coronary angiography with left heart catheterisation	3	4 (3.3)	10	394659003 Acute coronary syndrome	≤3	3 (4.1)

C

Arrhythmogenic cardiomyopathy

Top 10 APDC primary diagnosis codes				Top 10 primary APDC procedure codes				Top 10 EDDC diagnosis codes			
	Diagnosis	N	Admissions (%)		Procedure	N	Admissions (%)		Diagnosis	N	Admissions (%)
1	I47.2 Ventricular tachycardia	16	45 (32.6)	1	38393-00 Insertion of cardiac defibrillator generator	17	18 (17.5)	1	29857009 Chest pain	7	9 (21.4)
2	Z51.1 Pharmacotherapy session for neoplasm	≤3	18 (13.0)	2	96199-00 Intravenous administration of pharmacological agent, antineoplastic agent	≤3	18 (17.5)	2	25569003 Ventricular tachycardia	8	9 (21.4)
3	T82.1 Mechanical complication of cardiac electronic device	6	13 (9.4)	3	32090-00 Fibreoptic colonoscopy to caecum	6	12 (11.7)	3	234228008 Disorder of implantable defibrillator	5	6 (14.3)
4	Z45.0 Adjustment and management of cardiac device	11	13 (9.4)	4	38393-01 Replacement of cardiac defibrillator generator	10	12 (11.7)	4	271594007 Syncope	≤3	4 (9.5)
5	I42.8 Other cardiomyopathies	7	11 (8.0)	5	11727-00 Testing of cardiac defibrillator	6	9 (8.7)	5	386705008 Lightheadedness	≤3	3 (7.1)
6	I50.0 Congestive heart failure	≤3	10 (7.3)	6	95550-03 Allied health intervention, physiotherapy	≤3	8 (7.8)	6	6456007 Supraventricular tachycardia	≤3	3 (7.1)
7	Z31.2 In vitro fertilisation	≤3	9 (6.5)	7	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	5	7 (6.8)	7	102587001 Acute chest pain	≤3	2 (4.8)
8	R00.2 Palpitations	≤3	7 (5.1)	8	38218-00 Coronary angiography with left heart catheterisation	7	7 (6.8)	8	14140009 Hyperkalaemia	≤3	2 (4.8)
9	I48 Atrial fibrillation and flutter	≤3	6 (4.4)	9	13400-00 Cardioversion	5	6 (5.8)	9	21522001 Abdominal pain	≤3	2 (4.8)
10	M17.1 Other primary gonarthrosis	≤3	6 (4.4)	10	30473-01 Panendoscopy to duodenum with biopsy	4	6 (5.8)	10	34014006 Viral disease	≤3	2 (4.8)

D

Left ventricular non-compaction

Top 10 hospital primary diagnosis codes				Top 10 primary hospital procedure codes				Top 10 ED diagnosis codes			
	Diagnosis	N	Admissions (%)		Procedure	N	Admissions (%)		Diagnosis	N	Admissions (%)
1	F32.20 Severe depressive episode without psychotic symptoms, not specified	≤3	57 (41.3)	1	96180-00 Other psychotherapies or psychosocial therapies	≤3	57 (38.8)	1	29857009 Chest pain	10	14 (26.9)
2	Z50.9 Care involving use of rehabilitation procedure, unspecified	≤3	20 (14.5)	2	96153-00 Hydrotherapy	≤3	19 (12.9)	2	49436004 Atrial fibrillation	4	7 (13.5)
3	M54.2 Cervicalgia	≤3	16 (11.6)	3	95550-03 Allied health intervention, physiotherapy	≤3	16 (10.9)	3	102589003 Atypical chest pain	6	6 (11.5)
4	R07.4 Chest pain, unspecified	7	9 (6.5)	4	30473-01 Panendoscopy to duodenum with biopsy	9	12 (8.2)	4	21522001 Abdominal pain	6	6 (11.5)
5	I48 Atrial fibrillation and flutter	≤3	7 (5.1)	5	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	7	10 (6.8)	5	80313002 Palpitations	4	6 (11.5)
6	M54.5 Low back pain	≤3	7 (5.1)	6	38393-00 Insertion of cardiac defibrillator generator	8	9 (6.1)	6	271594007 Syncope	≤3	4 (7.7)
7	I48.9 Atrial fibrillation and flutter, unspecified	≤3	6 (4.4)	7	32090-00 Fibreoptic colonoscopy to caecum	5	8 (5.4)	7	44465007 Sprain of ankle	≤3	3 (5.8)
8	O8 Single spontaneous delivery	≤3	6 (4.4)	8	90481-00 Suture of first or second degree tear of perineum	≤3	6 (4.1)	8	12441001 Epistaxis (nose bleed)	≤3	2 (3.9)
9	K01.1 Impacted teeth	5	5 (3.6)	9	12203-00 Polysomnography	5	5 (3.4)	9	161898004 Falls	≤3	2 (3.9)
10	R55 Syncope and collapse	5	5 (3.6)	10	13400-00 Cardioversion	4	5 (3.4)	10	230690007 Cerebrovascular accident	≤3	2 (3.9)

Figure 6.5: Top 10 diagnoses and procedures for hospital and emergency department admissions for inherited cardiomyopathies. A: Hypertrophic cardiomyopathy; B: Dilated cardiomyopathy; C: Arrhythmogenic cardiomyopathy; D: Left-ventricular non-compaction

Figure 6.6 displays the top 10 primary hospital diagnoses, hospital procedures, and emergency department diagnoses for all admissions by primary arrhythmia syndrome.

LQTS

The top three primary diagnoses for hospital admissions in LQTS patients were: anorexia nervosa (31 [22.5%]; n= ≤3 patients), adjustment and management of cardiac device (19 [13.8%]), and alcoholic hepatic failure (16 [11.6%]; n=≤3 patients). The main hospital procedures performed are psychological skills training (31 [25.4%]; ≤3 patients), insertion of cardiac defibrillator generator (15 [12.3%]), and allied health intervention for physiotherapy (13 [10.7%]). The top emergency department diagnoses included chest pain (25 [21.2%]), syncope (24 [20.3%]), and abdominal pain (14 [11.9%]). Other notable findings included conduction disorders, atrial fibrillation, and various conditions such as hypertensive disorder, cataracts, and hepatic encephalopathy.

BrS

The top three primary diagnoses for hospital admissions in BrS patients were: other specified cardiac arrhythmias (39 [27.9%]), other primary gonarthrosis (23 [16.4%]; n= ≤3 patients), and chest pain (19 [13.6%]). The main hospital procedures performed were allied health intervention related to physiotherapy (31 [23.7%]), fibreoptic colonoscopy to the caecum (19 [14.5%]), and insertion of cardiac defibrillator generator (17 [13.0%]). The top emergency diagnoses consisted of chest pain (21 [27.6%]) palpitations (15 [19.7%]), and syncope (11 [14.5%]). Other notable findings included various conditions such as ventricular fibrillation and flutter, asthma, spinal stenosis, unstable angina, and falls.

CPVT

The top three primary diagnoses for hospital admissions in CPVT patients were: ventricular tachycardia (28 [34.6%]), adjustment and management of cardiac device (16 [19.8%]), and disorder of implantable defibrillator (9 [11.1%]). The main procedures performed were replacement of cardiac defibrillator generator (11 [22.4%]), insertion of cardiac defibrillator generator (8 [16.3%]), and fibreoptic colonoscopy to the caecum (5 [10.2%]). The top emergency department diagnoses included disorder of implantable defibrillator (4 [14.3%]), syncope (4 [14.3%]), and abdominal pain (3 [10.7%]). Notable findings included congestive heart failure, atrial fibrillation, obstructive sleep apnoea syndrome, and supraventricular tachycardia.

A

Long QT syndrome

	Top 10 APDC primary diagnosis codes			Top 10 primary APDC procedure codes			Top 10 EDDC diagnosis codes		
	Diagnosis	N	Admissions (%)	Procedure	N	Admissions (%)	Diagnosis	N	Admissions (%)
1	F50.0 Anorexia nervosa	≤3	31 (22.5)	96001-00 Psychological skills training	≤3	31 (25.4)	29857009 Chest pain	17	25 (21.2)
2	Z45.0 Adjustment and management of cardiac device	11	19 (13.8)	38393-00 Insertion of cardiac defibrillator generator	14	15 (12.3)	271594007 Syncope	16	24 (20.3)
3	K70.4 Alcoholic hepatic failure	≤3	16 (11.6)	95550-03 Allied health intervention, physiotherapy	7	13 (10.7)	21522001 Abdominal pain	9	14 (11.9)
4	R55 Syncope and collapse	11	15 (10.9)	55118-00 2 dimensional real time transoesophageal ultrasound of heart	4	11 (9.0)	38341003 Hypertensive disorder, systemic arterial	≤3	11 (9.3)
5	I45.8 Other specified conduction disorders	8	11 (8.0)	95550-01 Allied health intervention, social work	5	11 (9.0)	80313002 Palpitations	4	9 (7.6)
6	I48.9 Atrial fibrillation and atrial flutter, unspecified	≤3	11 (8.0)	30473-01 Panendoscopy to duodenum with biopsy	8	10 (8.2)	234239006 Inappropriate shocks from implanted defibrillator	7	8 (7.6)
7	T82.1 Mechanical complication of cardiac electronic device	5	11 (8.0)	30406-00 Abdominal paracentesis	≤3	8 (6.6)	102589003 Atypical chest pain	7	7 (5.9)
8	H26.9 Cataract, unspecified	5	8 (5.8)	95550-00 Allied health intervention, dietetics	≤3	8 (6.6)	13920009 Hepatic encephalopathy	≤3	7 (5.9)
9	O80 Single spontaneous delivery	6	8 (5.8)	96199-00 Intravenous administration of pharmacological agent, antineoplastic agent	≤3	8 (6.6)	49436004 Atrial fibrillation	≤3	7 (5.9)
10	R07.4 Chest pain, unspecified	7	8 (5.8)	11727-00 Testing of cardiac defibrillator	4	7 (5.7)	44465007 Sprain of ankle	4	6 (5.1)

B

Brugada syndrome

	Top 10 APDC primary diagnosis codes			Top 10 primary APDC procedure codes			Top 10 EDDC diagnosis codes		
	Diagnosis	N	Admissions (%)	Procedure	N	Admissions (%)	Diagnosis	N	Admissions (%)
1	I49.8 Other specified cardiac arrhythmias	30	39 (27.9)	95550-03 Allied health intervention, physiotherapy	5	31 (23.7)	29857009 Chest pain	17	21 (27.6)
2	M17.1 Other primary gonarthrosis	≤3	23 (16.4)	32090-00 Fibreoptic colonoscopy to caecum	11	19 (14.5)	80313002 Palpitations	8	15 (19.7)
3	R07.4 Chest pain, unspecified	7	19 (13.6)	38393-00 Insertion of cardiac defibrillator generator	16	17 (13.0)	271594007 Syncope	9	11 (14.5)
4	Z45.0 Adjustment and management of cardiac device	5	11 (7.9)	30473-01 Panendoscopy to duodenum with biopsy	6	13 (9.9)	49436004 Atrial fibrillation	≤3	6 (7.9)
5	I49.0 Ventricular fibrillation and flutter	5	8 (5.7)	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	7	12 (9.2)	411.1 Unstable angina	≤3	5 (6.6)
6	J45.9 Asthma, unspecified	≤3	8 (5.7)	12203-00 Polysomnography	4	10 (7.6)	161898004 Falls	≤3	4 (5.3)
7	M48.06 Spinal stenosis, lumbar region	4	8 (5.7)	36851-00 Endoscopic administration of agent into bladder wall	≤3	8 (6.1)	780.4 Dizziness and giddiness	≤3	4 (5.3)
8	N99.8 Other intraoperative and postprocedural disorder of genitourinary	≤3	8 (5.7)	36812-00 Cystoscopy	7	7 (5.3)	91302008 Sepsis	≤3	4 (5.3)
9	R55 Syncope and collapse	6	8 (5.7)	38212-00 Cardiac electrophysiological study, >= 4 catheters	5	7 (5.3)	127348004 Motor vehicle accident victim	≤3	3 (4.0)
10	Z48.8 Other specified surgical follow-up care	4	8 (5.7)	38218-00 Coronary angiography with left heart catheterisation	6	7 (5.3)	21522001 Abdominal pain	≤3	3 (4.0)

C

Catecholaminergic polymorphic ventricular tachycardia

	Top 10 APDC primary diagnosis codes			Top 10 primary APDC procedure codes			Top 10 EDDC diagnosis codes		
	Diagnosis	N	Admissions (%)	Procedure	N	Admissions (%)	Diagnosis	N	Admissions (%)
1	I47.2 Ventricular tachycardia	15	28 (34.6)	38393-01 Replacement of cardiac defibrillator generator	9	11 (22.4)	234228008 Disorder of implantable defibrillator	2	4 (14.3)
2	Z45.0 Adjustment and management of cardiac device	9	16 (19.8)	38393-00 Insertion of cardiac defibrillator generator	8	8 (16.3)	271594007 Syncope	3	4 (14.3)
3	T82.1 Mechanical complication of cardiac electronic device	8	9 (11.1)	32090-00 Fibreoptic colonoscopy to caecum	3	5 (10.2)	21522001 Abdominal pain	2	3 (10.7)
4	I47.1 Supraventricular tachycardia	3	6 (7.4)	11727-00 Testing of cardiac defibrillator	4	4 (8.2)	29857009 Chest pain	3	3 (10.7)
5	I50.0 Congestive heart failure	1	5 (6.2)	12203-00 Polysomnography	2	4 (8.2)	80313002 Palpitations	3	3 (10.7)
6	I48.9 Atrial fibrillation and atrial flutter, unspecified	2	4 (4.9)	32093-00 Fibreoptic colonoscopy to caecum, with polypectomy	2	4 (8.2)	Z76.0 Encounter for issue of repeat prescription	2	3 (10.7)
7	I49.8 Other specified cardiac arrhythmias	3	4 (4.9)	38209-00 Cardiac electrophysiological study, <= 3 catheters	3	4 (8.2)	3110003 Acute otitis media	1	2 (7.1)
8	G47.32 Obstructive sleep apnoea syndrome	2	3 (3.7)	13400-00 Cardioversion	2	3 (6.1)	314212008 Abdominal pain- cause unknown	2	2 (7.1)
9	I48 Atrial fibrillation and atrial flutter	1	3 (3.7)	30473-01 Panendoscopy to duodenum with biopsy	3	3 (6.1)	780.9 Semicoma, stupor	1	2 (7.1)
10	R55 Syncope and collapse	1	3 (3.7)	55118-00 2 dimensional real time transoesophageal ultrasound of heart	2	3 (6.1)	49436004 Atrial fibrillation	1	2 (7.1)

Figure 6.6: Top 10 diagnoses and procedures for hospital and emergency department admissions for primary arrhythmia syndromes. A: Long QT Syndrome; B: Brugada syndrome; C Catecholaminergic polymorphic ventricular tachycardia.

6.4.8 Death registry data by genetic heart disease diagnosis

NSW Registry of Birth, Deaths and Marriages Death records were available for 60 individuals. However, due to the Australian Coordinating Registry Cause of Death Unit Record File only containing deaths up to 31st December 2017, 14 records did not match (Table 6.4). This left 46 records with cause of death data available. There were 42 (91.3%) deaths that occurred in individuals who had HCM, 1 (2.2%) with DCM, 2 (4.4%) ACM, and 1 (2.2%) had LVNC. Of the 46 deaths, 2 occurred in those aged <50 years, 13 between the ages of 50-69 years and 31 after >70 years of age.

Table 6.4: Descriptive analysis of Mortality data

		Total cohort	HCM	DCM	ACM	LVNC	LQTS	BrS	CPVT
Number of individuals		46	42 (91.3)	1 (2.2)	2 (4.4)	1 (2.2)	0 (0)	0 (0)	0 (0)
Male sex		27 (58.7)	23 (54.8)	1 (100.0)	2 (100.0)	1 (100.0)	0 (0)	0 (0)	0 (0)
Age at death	<50 years	2 (4.4)	2 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	50-69 years	13 (28.3)	13 (31.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	70+ years	31 (67.4)	27 (64.3)	1 (100.0)	2 (100.0)	1 (100.0)	0 (0)	0 (0)	0 (0)

Categorical data shown as n (%)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

The top 10 primary causes of death are presented in Figure 6.7. Individuals with a diagnosis of HCM had ICD codes that corresponded to causes of death related to HCM. This included: other hypertrophic cardiomyopathy (n=9 [29.1%]), cardiomyopathy, unspecified (n=5 [21.7%]), stroke (n=2 [8.7%]), disorders of the mitral and aortic valves (n=1 [4.4%]) and hypertensive heart with congestive heart failure (n=1 [4.4%]). Regarding cause of death, 1 patient with DCM died from chronic ischaemic heart disease, and the LVNC patient died from cardiomyopathy. The cause of death for the 2 ACM patients was unavailable (Figure 6.7).

A

Top 10 causes of death for HCM			
	Diagnosis	**N**	**n (%)**
1	I42.2 Other hypertrophic cardiomyopathy	9	9 (39.1)
2	I42.9 Cardiomyopathy unspecified	5	5 (21.7)
3	I64 Stroke, not specified as haemorrhage or infarction	2	2 (8.7)
4	C85.1 B-cell lymphoma, unspecified	1	1 (4.4)
5	C90.0 Multiple myeloma	1	1 (4.4)
6	I08.0 Disorders of both mitral and aortic valves	1	1 (4.4)
7	I11.0 Hypertensive heart disease with (congestive) heart failure	1	1 (4.4)
8	I21.9 Acute myocardial infarction, unspecified	1	1 (4.4)
9	I25.1 Atherosclerotic heart disease	1	1 (4.4)
10	I25.9 Chronic ischaemic heart disease, unspecified	1	1 (4.4)

B

Top causes of death for DCM			
	Diagnosis	**N**	**n (%)**
1	I25.9 Chronic ischaemic heart disease, unspecified	1	1 (100)

C

Top causes of death for ACM			
	Diagnosis	**N**	**n (%)**
1	NA	NA	2 (100)

D

Top causes of death for LVNC			
	Diagnosis	**N**	**n (%)**
1	I42.9 Cardiomyopathy unspecified	1	1 (100)

Figure 6.7: Top causes of death. A: Hypertrophic cardiomyopathy; B: Dilated cardiomyopathy; C: Arrhythmogenic cardiomyopathy; D: Left-ventricular non-compaction. Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction

6.4.9 Healthcare utilisation by socioeconomic status

As measured by the IRSAD decile and shown previously in Table 6.1, socioeconomic status varied among each genetic heart disease diagnosis. The overall mean IRSAD decile was 6.9 ± 2.9. Patients with ACM had the highest mean decile of 7.6 ± 2.8, indicating a higher socioeconomic advantage, while patients with DCM had the lowest, 6.8 ± 3.0 (Table 6.1). The overall distribution of postcode IRSAD decile is shown in Figure 6.8, with a significant number of individuals residing in areas with a decile of 10 representing the top most advantaged and least disadvantaged in New South Wales.

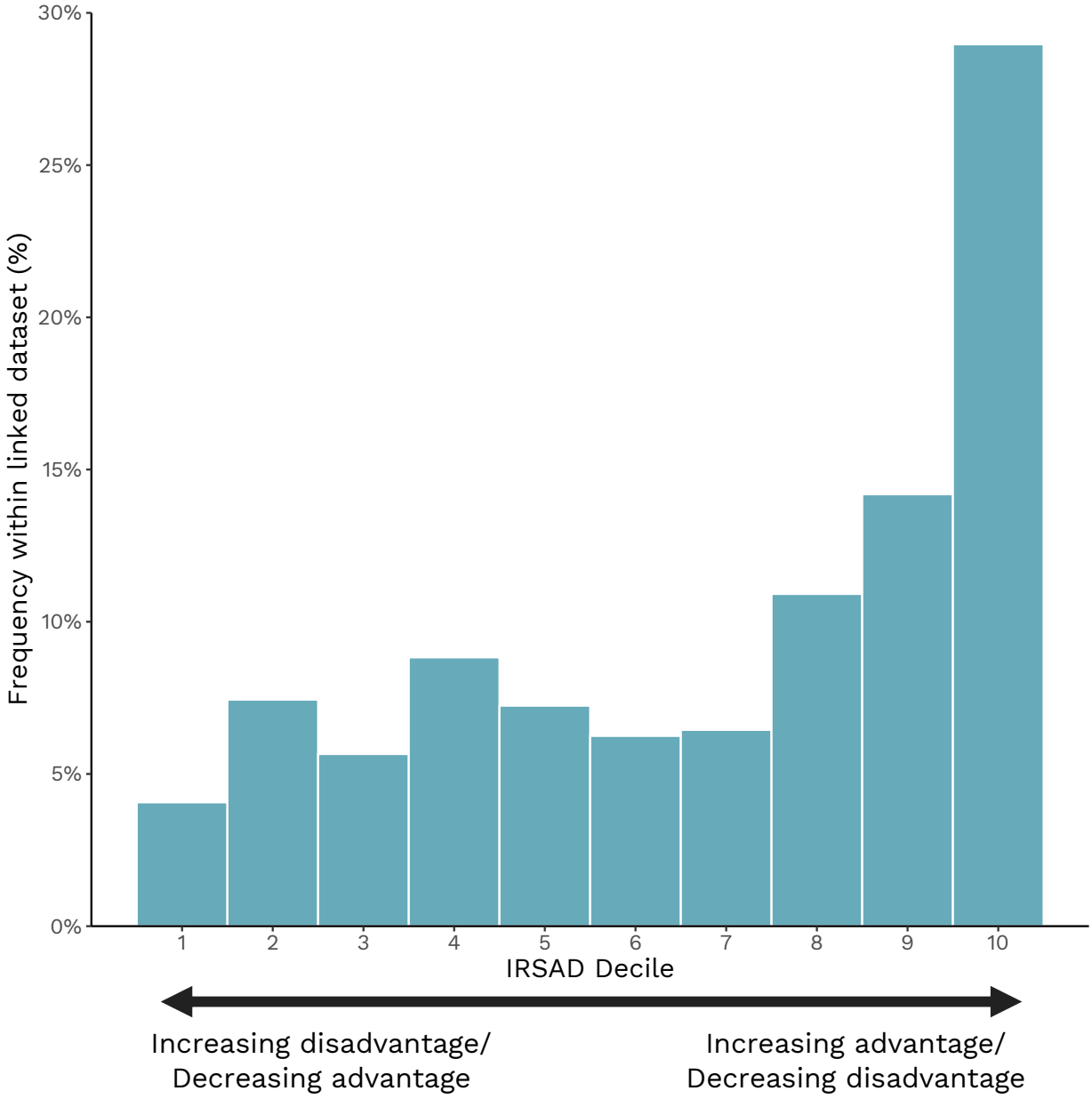

Figure 6.8: Distribution of socioeconomic status by Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) within AGHD Registry participants linked to routinely collected health data

IRSAD decile was stratified into the following groups: 1-5 (low socioeconomic status) and 6-10 (high socioeconomic status), representing the top and bottom 50% of socioeconomic advantage/disadvantage. We investigated if differences existed in healthcare utilisation using these groupings (Table 6.5). There were 335 (33.0%) patients in the high socioeconomic group (IRSAD decile 1-5), indicating a relatively lower level of socioeconomic advantage and higher disadvantage, and 673 (66.2%) in the low socioeconomic group (IRSAD decile 6-10), indicating higher socioeconomic advantage and lower disadvantage. There was no significant difference in the distribution of males and females between these two socioeconomic groups ($p=0.337$). Furthermore, the age at the end of follow-up, age at diagnosis, sudden cardiac death events, syncope, non-sustained ventricular tachycardia, atrial fibrillation, heart failure, genetic testing, and implantation of ICD did not show significant differences between the two decile groups ($p>0.05$).

For hospital admissions, notable differences were observed between the socioeconomic groups. The median number of episodes of care and the median length of stay were significantly different ($p<0.0001$). Individuals in the low socioeconomic group had more admissions (median of 8 episodes of care; range: 1 to 74), compared those in the high socioeconomic group (median of 7 episodes of care; range: 1 to 99). The median length of stay was the same for both low and high socioeconomic groups at 1 day but with a significant difference in range (range: 1 to 127 days vs range: 1 to 248 days, respectively; $p<0.0001$). However, there were no significant differences in the mean age at first admission or mean age at any admission between the two decile groups.

Public hospitals were the most common setting for both socioeconomic groups to attend, but there was a significant difference in their distribution ($p<0.0001$). In the low

socioeconomic group, 2033 (68.7%) admissions were in public hospitals, while in the high socioeconomic group, 2471 (49.0%) were in public hospitals. The proportion of individuals receiving care in regional/rural facilities also differed significantly between the two socioeconomic groups, with significantly more patients from low socioeconomic areas having admissions that occurred in regional/rural hospitals (1623 [54.9%] versus 546 [10.8%]; $p<0.0001$). This is expected as regional/rural areas often comprise lower socioeconomic status than metropolitan areas.

Health insurance coverage at admission was different between the socioeconomic groups ($p<0.0001$). Individuals in the low socioeconomic group were more likely to either not have or not use health insurance coverage at their admission (n= 1581 [58.0%]), while those in the high socioeconomic group more often had full health insurance cover (n=1377 [49.1%]). Additionally, the mode of separation from the emergency department differed significantly between the two socioeconomic groups ($p<0.0001$). While the majority of individuals in both decile groups were most often discharged, the low socioeconomic group had a higher proportion of transfers (n=267 [9.0%]).

Regarding emergency department episodes, a significant difference was found in the proportion of individuals born overseas by socioeconomic status ($p=0.038$), with those in the high socioeconomic group more likely to be born overseas (730 [29.7%] vs 411 [19.2%]). The median number of episodes of care in the emergency department differed significantly ($p<0.0001$), with individuals in the low socioeconomic group having a median of 7 episodes (range: 1 to 70). In comparison, those in the high socioeconomic group had a median of 4 episodes (range: 1 to 46). Moreover, the mean age at any episode showed no significant difference in mean age at first admission ($p=0.896$).

Table 6.5: Healthcare utilisation grouped by low or high socioeconomic status using Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) decile determined from residential postcodes

	Total cohort	Low socioeconomic status (IRSAD decile 0-5)	High socioeconomic status (IRSAD decile 6-10)	p value
	1008	335 (33.0)	673 (66.2)	
Male sex	584 (57.9)	187 (55.8)	397 (59.0)	0.337
Age at end of follow-up, years	54.4 ±17.5	55.0 ± 17.5	54.1 ± 17.6	0.434
Age at diagnosis, years	41.6 ± 17.6	41.0 ± 18.3	41.9 ± 17.4	0.459
SCD event	118 (13.1)	34 (11.5)	84 (13.8)	0.343
Syncope	249 (28.5)	89 (31.1)	160 (27.2)	0.224
NSVT	212 (25.1)	78 (29.1)	134 (23.3)	0.067
Atrial fibrillation	169 (24.3)	54 (24.4)	115 (24.2)	0.949
Heart failure	65 (7.5)	21 (7.5)	44 (7.5)	0.992
Genetic testing	713 (78.1)	484 (78.2)	229 (77.9)	0.919
ICD	394 (82.8)	258 (84.0)	136 (80.5)	0.324
Admitted Patient Data Collection				
Median episodes of care	7 (1-99)	8 (1-74)	7 (1-99)	<0.0001
Median episode length of stay (days)	1 (1-248)	1 (1-127)	1 (1-248)	<0.0001
Mean age at any admission (years)	53.4 ± 16.6	53.0 ± 16.2	53.6 ± 16.2	0.135
Mean age at first admission (years)	42.8 ± 17.0	42.4 ± 17.1	43.0 ± 17.0	0.652
Public Hospital	4504 (56.3)	2033 (68.7)	2471 (49.0)	<0.0001
Regional/rural facility	2169 (27.1)	1623 (54.9)	546 (10.8)	<0.0001
Health insurance No cover	2958 (39.5)	1581 (58.0)	1377 (28.9)	<0.0001
Full cover	3160 (42.2)	826 (30.3)	2334 (49.1)	

	Basic cover	1352 (18.1)	309 (11.3)	1043 (21.9)	
Mode of separation	Discharged	7331 (91.6)	2666 (90.1)	4665 (92.5)	<0.0001
	Transferred	580 (7.3)	267 (9.0)	313 (6.2)	
	Type change separation	62 (0.8)	18 (0.6)	44 (0.9)	
	Died	28 (0.4)	9 (0.3)	19 (0.4)	
Emergency Department Data Collection					
Born overseas		1141 (24.8)	411 (19.2)	730 (29.7)	0.038
Median episodes of care		5 (1-70)	7 (1-70))	4 (1-46)	<0.0001
Mean age at any episode, years		48.8 ± 18.8	47.9 ± 18.1	49.5 ± 19.3	0.003
Mean age at first episode, years		44.9 ± 18.0	44.8 ± 18.1	45.0 ± 18.0	0.896

Categorical data shown as n (%) and continuous data shown as mean ± SD or median (range)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

6.4.10 Healthcare utilisation by sex

We investigated if differences existed in healthcare utilisation by sex (Table 6.6). For AGHD Registry data, there was no significant difference by sex for age at the end of follow-up or age at diagnosis. Females were more likely to have experienced a syncopal episode than males (n=125 [33.8%] vs 125 [24.5%]; p=0.003). Males were more likely to have atrial fibrillation compared to females (n=114 [28.5%] vs n=57 [18.9%]; p=0.004). Other clinical characteristics did not differ by sex, including sudden cardiac death events, non-sustained VT, implantable cardioverter defibrillator implantation and genetic testing (p>0.05).

For hospital admissions, there was a significant difference in the number of admissions (p<0.0001) and the length of stay (p=0.013) between the sexes. Females had a median of 8 admissions (range: 1-74), while males had a median of 7 admissions (range: 1-99). The median number of days was 1 for women and men, ranging from 1-127 and 1-248, respectively. There was no significant sex difference in mean age at first admission (p=0.142), however, a significant difference did exist for mean age at any admission, with women younger than men (52.0 ± 17.1 versus 54.6 ± 16.2; p<0.0001) (Figure 6.9).

Females were more likely to receive care at a public hospital compared to men (n=2161 [58.2] vs n= 2354 [54.6%]); however, there was no difference in facility location with females as likely as men to receive their care in a regional/rural facility (p=0.292). In terms of health insurance coverage, females were more likely to have no private health insurance at their admission (42.5%) compared to males (36.8%); p<0.0001. The mode of separation from hospital showed that most participants (91.6%) were discharged, with no significant sex difference (p=0.862).

Regarding emergency department episodes, men were more likely to be born overseas than women (26.9% vs 22.3%; p=0.0003). The median number of episodes of care in the emergency department differed significantly (p<0.0001), with females having a median of 6 episodes (range: 1 to 70), while males had a median of 5 episodes (range: 1 to 48). No significant differences existed in age at any episode or age at the first episode among the cohort (p=0.535 and p=0.976, respectively).

Table 6.6: Healthcare utilisation by Sex

	Total cohort	Female	Male	p value
	1016	429 (42.2)	587 (57.8)	
Age at end of follow-up, years	54.4 ± 17.5	54.3 ± 18.1	54.4 ± 17.1	0.973
Age at diagnosis, years	41.6 ± 17.6	41.7 ± 18.1	41.5 ± 17.3	0.878
SCD event	119 (13.1)	56 (14.7)	63 (11.9)	0.218
Syncope	250 (28.4)	125 (33.8)	125 (24.5)	0.003
NSVT	212 (24.9)	82 (23.0)	130 (26.3)	0.283
Atrial fibrillation	171 (24.4)	57 (18.9)	114 (28.5)	0.004
Heart failure	66 (7.6)	27 (7.4)	39 (7.7)	0.895
Genetic testing	717 (78.1)	294 (77.6)	423 (78.5)	0.744
Implantable cardioverter defibrillator	397 (82.7)	158 (81.4)	2389 (83.6)	0.546
Admitted Patient Data Collection				
Median episodes of care	7 (1-99)	8 (1-74)	7 (1-99)	<0.0001
Median episode length of stay (days)	1 (1-248)	1 (1-127)	1 (1-248)	0.013
Mean age at any admission (years)	53.4 ± 16.6	52.0 ± 17.1	54.6 ± 16.2	<0.0001
Mean age at first admission (years)	42.8 ± 17.0	41.7 ± 17.4	43.5 ± 16.6	0.142
Public Hospital	4515 (56.3)	2161 (58.2)	2354 (54.6)	0.0012
Regional/rural facility	2171 (27.1)	984 (26.5)	1187 (27.6)	0.292
Health insurance No cover	2963 (39.5)	1488 (42.5)	1475 (36.8)	<0.0001
Full cover	3176 (42.3)	1460 (41.7)	1716 (42.9)	
Basic cover	1353 (18.0)	548 (15.7)	805 (20.1)	

Mode of separation	Discharged	7352 (91.6)	3406 (91.8)	3946 (91.5)	0.862
	Transferred	581 (7.2)	268 (7.2)	313 (7.3)	
	Type change separation	62 (0.8)	27 (0.7)	35 (0.8)	
	Died	28 (0.5)	11 (0.3)	17 (0.4)	
ED Data Collection					
Born overseas		1142 (24.8)	462 (22.3)	680 (26.9)	0.0003
Median episodes of care		5 (1-70)	6 (1-70)	5 (1-48)	<0.0001
Mean age at any episode, years		48.8 ± 18.5	48.6 ± 19.0	48.9 ± 18.6	0.535
Mean age at first episode, years		44.9 ± 18.0	44.9 ± 18.3	44.9 ± 17.8	0.976

Categorical data shown as n (%) and continuous data shown as mean ± SD or median (range)
Abbreviations: HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy, ACM, arrhythmogenic cardiomyopathy, LVNC, left ventricular non-compaction; LQTS; long QT Syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; SCD, sudden cardiac death; NSVT, nonsustained ventricular tachycardia; ED, emergency department.

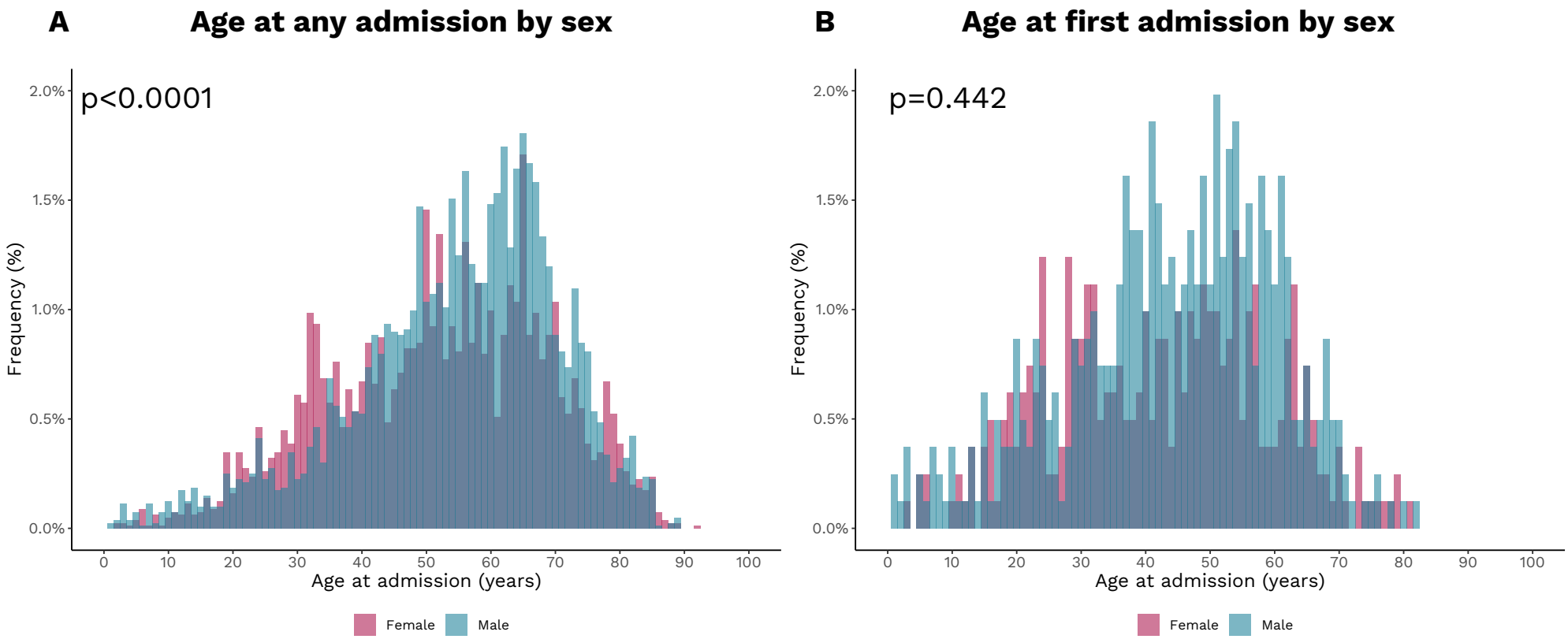

Figure 6.9: Distribution of age at hospital admission by sex. A: Age at any admission; B: Age at first admission

6.5 Discussion

We explore healthcare utilisation patterns of individuals with genetic heart diseases by establishing a crucial link between a well-characterised cohort of consented participants from the AGHD Registry and comprehensive datasets encompassing hospital admissions, emergency department visits, and mortality records collected throughout NSW. Our findings shed light on several key insights: firstly, a significant proportion of hospital admissions and emergency department episodes are directly related to cardiac diagnoses, highlighting the burden of these diseases on healthcare services. Secondly, we show differences in healthcare utilisation and the primary reasons patients attend hospitals and emergency departments stratified by clinical diagnosis. Lastly, we reveal notable variations in healthcare utilisation patterns based on socioeconomic status and sex, emphasising the need for unbiased datasets to comprehensively understand the burden of care and ensure equitable access to healthcare services.

The frequency of hospital admissions and emergency department visits due to cardiac symptoms highlights the significant burden imposed on healthcare systems and resources required to manage individuals with genetic heart diseases. Furthermore, we reveal that many hospital admissions occur close to the time of genetic heart disease diagnosis. The symptom burden associated with these diseases is well-documented and includes palpitations, chest pain, dyspnoea, presyncope, and syncope.[6–8] Those with inherited cardiomyopathies are also at increased risk of developing heart failure and experiencing sudden cardiac arrest/death. The burden of disease has previously been shown to vary by genotype,[18] highlighting the need for comprehensive care strategies that encompass symptom management, early detection, and timely interventions to prevent disease progression and enhance patient outcomes. Indeed, we emphasise the importance of

increasing awareness among healthcare providers regarding cardiac symptoms of genetic heart diseases. This would enable earlier recognition, appropriate referrals, and improved access to specialised care.

Challenges exist in using linked datasets to understand genetic heart diseases, with previous work from our team highlighting the lack of ICD codes for many genetic heart diseases.[10] Indeed, even where explicit codes do exist, they are used inconsistently, making accurate identification of all cases in the community unreliable using this method alone. As such only limited studies have utilised routinely collected health data to investigate the healthcare utilisation and needs of patients with genetic heart diseases, the majority focusing on HCM and Marfan syndrome.[9,19–25] Linkage to an existing disease registry such as the AGHD Registry means patient identification is reliable and based on robust clinical investigations, allowing one of the few descriptive analyses of healthcare utilisation to be reported. The addition of distinct ICD codes, in addition to methods to ensure reliable use, would be beneficial to further our understanding of healthcare utilisation in these populations.

A number of intriguing observations can be made from our findings, among them the high number of pregnancy admissions for LVNC. Previous research has indicated that LV trabeculations can develop during pregnancy. [26,27] LVNC is characterised by excessive trabeculations within the left ventricle, which can in some cases be physiological or associated with a disease process including various cardiovascular complications, including heart failure, arrhythmias, and thromboembolic events.[28] The increased prevalence of pregnancy-related LVNC admissions could signal a potential link between the physiological changes occurring during pregnancy and the development or exacerbation of LV

trabeculations. Further investigations into this association and the underlying mechanisms and clinical implications could provide valuable insights into the pathophysiology of LVNC and inform optimal management strategies for pregnant women with this finding.

Differences in healthcare utilisation based on socioeconomic status and sex reveal interesting patterns. We show that individuals of low socioeconomic status with genetic heart diseases have a higher number of hospital admissions and emergency department episodes. While the median length of hospital stay was only one day for both socioeconomic groups, the high socioeconomic group had a longer range. This fits with previous research in countries where access to primary care and hospitals is available under a universal healthcare system, showing that people with lower socioeconomic status visit more general practitioners and are hospitalised more than those with higher socioeconomic status.[29–34] Low socioeconomic patients were more likely to be transferred as their mode of discharge compared to high socioeconomic patients, which likely relates to the significantly higher number of hospital admissions occurring in regional and rural hospitals that require transport to larger metropolitan hospitals.

We highlight the issue of bias within patient-consented registries with 30% of the linked dataset including individuals in the highest IRSAD decile, representing those with the most advantage and least disadvantage. Although valuable sources of information, these registries tend to predominantly include patients who are more educated, motivated, and proactive about their health.[35] This bias can inadvertently skew the representation of the population and limit the generalisability of research findings and healthcare interventions. Recognising that patients from diverse backgrounds and socioeconomic statuses may have distinct healthcare needs and experiences is essential. Therefore, efforts should be made

to ensure that patient registries are more inclusive, encompassing a wider range of individuals and capturing the diversity of patient populations. This will enable a more comprehensive understanding of health outcomes and help deliver equitable and effective healthcare.

The low socioeconomic group were more likely not to have health insurance during their hospital admission compared to the high socioeconomic group. Similarly, women were more likely to not use private health insurance during hospital admissions than men. This could be attributed, at least partially, to the limited availability of private hospitals, which leaves people with no choice but to opt for public healthcare facilities and forego the utilisation of their insurance coverage, especially in regional areas. A study conducted in Australia has shown that despite the financial incentives provided by the government to encourage private health insurance adoption, individuals with private health insurance still heavily rely on public hospitals for both public and private patient services.[36]

Insufficient awareness among women and physicians of sex-specific symptoms and presentation of cardiovascular diseases has been identified in multiple studies.[37–40] Banco et al. showed that young women (<55 years) presenting to the emergency department are less likely to be triaged as emergent (i.e. cannot safely wait until space in the clinical area becomes available) and subsequently wait longer for evaluation than men. They also identified that women were less likely to be admitted to the hospital or to observation.[40] We show that women with genetic heart diseases have more hospital admissions and emergency department episodes than men and that the range in length of stay is greater in men. It could be postulated that the greater number of hospital and emergency department admissions in women may result from not receiving the care they required at the first

emergency department presentation. Further research is required to disentangle these findings and determine why there are disparities in healthcare utilisation by sex.

6.5.1 Future directions

Several potential directions could be pursued to enhance our understanding of genetic heart diseases and improve healthcare outcomes. For example, incorporating distinct ICD codes and undertaking training and evaluation of their use for each genetic heart disease. This would allow robust identification of genetic heart disease cases without the need to link to a disease registry, such as the AGHD Registry. This population-based approach using an unbiased, diverse dataset would provide an even greater understanding of the burden of disease. Such data would enable identification of potential areas for intervention and facilitate the development of targeted preventive measures and treatment strategies. As Australia moves to electronic medical health records, development of tools that can reliably identify cases with specific diagnoses from clinical investigations and letters would be even more informative, potentially recognising cases even before they receive a diagnosis from their doctor.[41] Linkage to the Perinatal Data Collection could also provide a comprehensive understanding of the impact of genetic heart diseases across different stages of life. Including these data would enable researchers to explore female-specific risk factors related to pregnancy and their association with outcomes in genetic heart diseases. By identifying and analysing these specific risk factors, tailored interventions and treatment strategies can be developed to address the unique needs of different patient populations.

6.5.2 Limitations

Potential limitations of our study include the possibility of inaccurate or incomplete coding of routinely collected healthcare data, which is known to be especially poor for the SNOMED codes used for diagnosis in the Emergency Department Data Collection. This has the

potential to introduce inaccuracies in the results. Secondly, the study primarily relies on participants from a single tertiary centre, as obtained from the AGHD Registry. The homogeneity of the participant pool could introduce a bias, as the experiences and characteristics of individuals from different socioeconomic backgrounds may differ significantly. These limitations highlight the need for further research involving diverse populations and comprehensive data collection methods to enhance the generalisability and validity of future studies on genetic heart diseases.

6.6 Conclusion

Our study provides valuable insights into the healthcare utilisation patterns of individuals with genetic heart disease, establishing a crucial link between the AGHD Registry cohort and comprehensive routinely collected health datasets from NSW. We highlight the substantial burden of these diseases with a significant proportion of hospital admissions and emergency department episodes directly related to cardiac diagnoses. We also show differences by socioeconomic status and sex. Overall, this is a step towards a better understanding of healthcare utilisation patterns of individuals with genetic heart diseases and provides insights that can inform strategies for improving care, early detection and equitable access to healthcare services.

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CHAPTER 7

DISCUSSION AND CONCLUSION

7 CHAPTER 7: DISCUSSION AND CONCLUSION

7.1 Overall summary of findings

Providing equitable care to all patients with a genetic heart disease requires a comprehensive understanding of the underlying health disparities contributing to differential outcomes among the entire population. The work outlined in the thesis has focused on improving our understanding of health disparities that impact patients with genetic heart diseases, including women, diverse ethnic groups and individuals from lower socioeconomic backgrounds.

The current evidence supporting the clinical management of patients with genetic heart diseases is predominantly based on studies conducted using relatively small patient populations attending tertiary care centres. These patient populations often lack diversity and can be overrepresented by the most highly educated and well-resourced individuals (Chapter 1). Furthermore, with gaps in our knowledge and a need for more research in specific areas, management guidelines heavily rely on expert consensus opinions rather than evidence-based recommendations.

Due to this lack of representation of the entire population in published evidence relating to genetic heart diseases, there is limited understanding of the disease burden among women, underrepresented ethnic groups, and individuals from low socioeconomic backgrounds or non-metropolitan geographic regions. Social determinants globally influence health outcomes, but the impact of these factors in the context of genetic heart diseases has rarely been investigated. We have previously shown an overrepresentation of socioeconomically advantaged patients in our specialised clinics in the setting of hypertrophic cardiomyopathy (HCM).[1] Patients from lower socioeconomic backgrounds had

more complex disease, including multiple comorbidities, showed worse psychological well-being and health-related quality of life and had limited understanding of their disease. The cohort also lacked diversity by sex (60% male) and ethnicity (60% self-reported European). We hypothesised that patients of lower socioeconomic status were less likely to attend a specialised metropolitan-based clinic unless there were significant or complex medical needs. This study determined that socioeconomic status and geographic location disparities present barriers to access to specialised care even in a universal health care system.

Similarly, the way we understand how genetic heart diseases affect males and females in the population is poorly understood. Among patients with cardiovascular disease, the contribution of physiological and social factors leading to differences has become a focus of intense research. Indeed, sex disparities have been recently reported for patients with HCM. Women have an increased risk of developing heart failure, independent of other risk factors,[2] with worse all-cause survival rates than men.[3] Sex differences have also been noted in dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM).[4] Notably, the critical studies that have shaped existing guideline recommendations typically included only 30-40% women (Chapter 1).

Figure 1 summarises the key findings from this thesis which build on our understanding of how health disparities, i.e., sex, ethnicity, ancestry and socioeconomic status, have limited our evidence base in specific populations. With increased inclusive approaches to research, we can address critical gaps in our knowledge that would benefit not just the patient group in question but the entire patient population. These key findings will move us towards more equitable outcomes in diagnosing and managing genetic heart diseases.

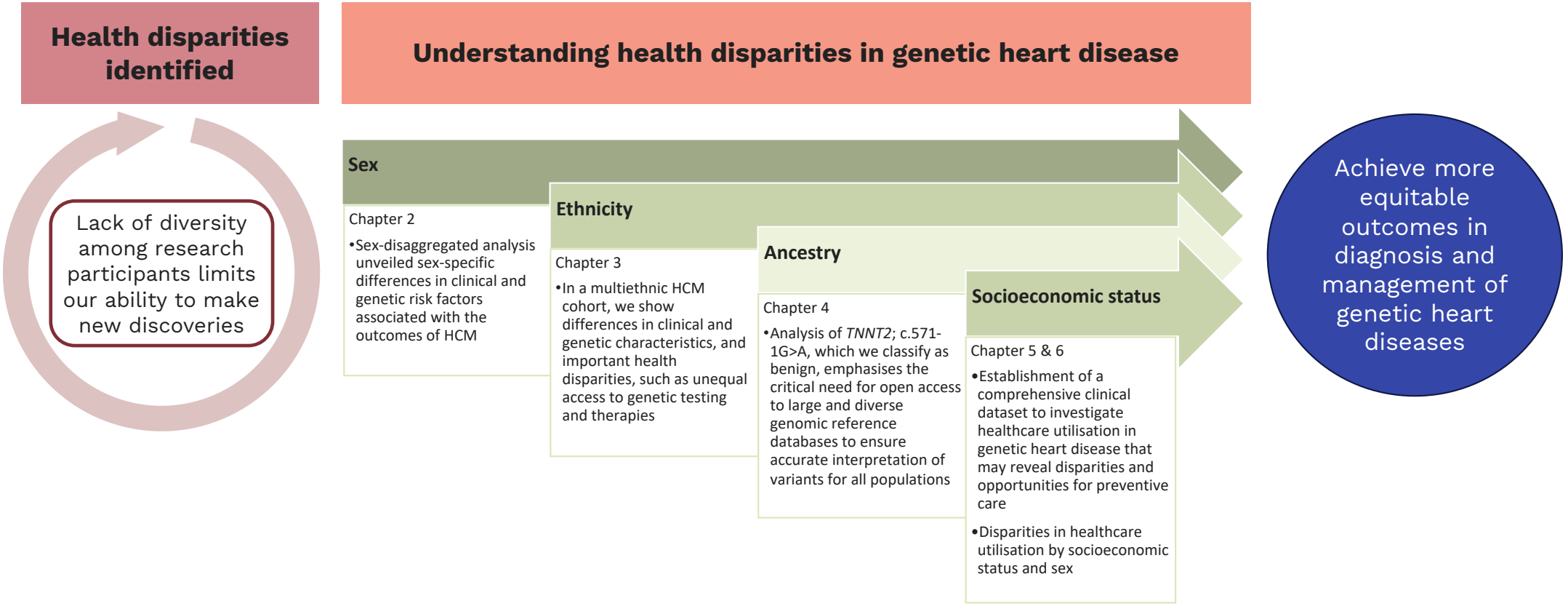

Figure 7.1: Summary of the outcomes of this research

7.2 Current status of knowledge

Genetic heart diseases comprise various genetic disorders that affect the heart's structure, function, and conduction.[5–7] Significant progress has been made in understanding the underlying mechanisms, clinical manifestations, and genetic basis of these conditions.[8, 9] However, despite these advancements, critical gaps remain in our understanding of the phenotypic spectrum and genetic architecture of these diseases.[10]

Genetic heart diseases are phenotypically heterogeneous, with variable expression and incomplete penetrance. In some cases, clinical diagnosis can be challenging, and heterogeneity amongst individuals has limited our ability to predict those who will develop the most severe outcomes accurately. Genetically, we can identify an underlying genetic variant as a cause of disease in approximately 40% of probands;[10,11] however, a substantial proportion have no clear monogenic cause of disease even after comprehensive genetic testing.[10] Furthermore, even when a genetic variant is identified, its precise clinical implications are typically poorly understood, highlighting that there is more to understand about contributors to disease beyond the monogenic variant.[13, 14] Unravelling the full spectrum of genetic factors involved in genetic heart diseases and their impact on disease expression and progression is a constantly evolving area of research that holds the potential to understand and manage patients with genetic heart diseases using personalised medicine approaches.

The limitations in our understanding of genetic heart diseases are expected to be further magnified in populations historically underrepresented in research. The existing knowledge gaps may exacerbate disparities in diagnosis, treatment, and outcomes among these populations. Sex is crucial in physiology and disease, encompassing natural biological

variations and intricate societal and environmental discrepancies. Consequently, it presents numerous instances across various disease states that illustrate the impact of these knowledge gaps.[15] Within cardiovascular disease (CVD), women frequently encounter distinct challenges.[16] Studies have shown that compared to men; women lack awareness of their CVD risk,[17–19] are less likely to undergo screening, experience diagnosis delays,[20–22] exhibit atypical symptoms,[23–25] receive inaccurate initial diagnoses,[26] and subsequently receive suboptimal primary and secondary prevention treatments.[27–31] These factors contribute to poorer outcomes for women.[28, 30, 32, 33]

To achieve equitable outcomes in diagnosing and managing genetic heart diseases, we must design studies that improve our understanding of why the differences and disparities exist. Using sex-disaggregated analysis, we revealed sex-specific differences in clinical and genetic risk factors that influence outcomes in HCM (Chapter 2). We found that men with sarcomere variants risk heart failure and death more than women. In contrast, women with sarcomere-negative HCM exhibited an increased risk of heart failure, likely reflecting the elevated risk observed in the general population. We discovered that women carrying *MYBPC3* variants demonstrated a reduced risk of heart failure, a benefit not observed in men. Additionally, we identified sex-specific variations in the European Society of Cardiology (ESC) risk score performance, indicating the need for tailored risk assessment strategies based on sex. By designing comprehensive studies investigating the reasons behind these differences, we can strive for equitable outcomes in diagnosing and managing genetic heart diseases.

7.3 Lack of diversity in research cohorts

The persistent lack of diversity within cohorts has significantly hindered the ability to make insightful discoveries that benefit the whole population. Findings from research that predominantly include those from a narrow demographic cannot be generalised to the broader population. This limitation undermines the study's validity and perpetuates health disparities and inequities, leading to poorer outcomes for these populations.

7.3.1 Underrepresentation of women

Women have been underrepresented in or excluded from CVD clinical trials, despite CVD being the leading cause of death among women worldwide.[34] A recent study examined all completed CVD trials between 2010 and 2017 and revealed that only 38.2% of the trial participants were women.[35] Women's representation also varied by disease prevalence, being higher in pulmonary hypertension, comparable in hypertension, and lower in stroke, arrhythmia, coronary heart disease, acute coronary syndrome, and heart failure.[35] Given that clinical trials are used to develop clinical guidelines for medical therapies, evidence based on data from male-dominated trials is a significant issue.

Clinical trials are vital in demonstrating not only the effectiveness but also the safety of medical therapies.[34–36] Many physiological, hormonal, and genetic factors contribute to dimorphisms between the sexes that may translate into differences in pharmacokinetics and pharmacodynamics for specific drugs. For example, a comprehensive review investigating the relationship between sex differences in pharmacokinetics and adverse drug reactions revealed that, when administered a standard drug dosage, women experience higher concentrations of the drug in their blood and longer elimination times compared to men. Consequently, this increased exposure is likely responsible for the nearly

twofold rise in adverse drug reactions among female patients, raising concerns about potential overmedication.[37] This overmedication issue has been documented in heart failure with reduced ejection fraction (HFrEF).[38] A recent study demonstrated that women reached peak benefit when beta-blocker doses reached 50–60% of the traditional guideline-recommended target or 40-60% of the dose for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[39] In contrast, the risk in men continued to decline as both classes of heart failure medication were up-titrated to the target dose. These findings suggest that no additional benefit may be gained as the dose of guideline-directed HFrEF medications is up-titrated in women. These findings stress the importance of including women in clinical trials and conducting sex-disaggregated analyses to ensure accurate and tailored medical treatment for both sexes.

Likewise, the lack of representation and sex-specific data in clinical management guidelines for HCM is concerning (Chapter 1). Having fewer women enrolled in studies that inform guideline recommendations limits our understanding of how HCM manifests and affects women, potentially leading to suboptimal diagnostic and treatment strategies for female patients. By relying predominantly on male-centric data, we risk overlooking important nuances and tailored approaches that could benefit women with HCM. Therefore, there is an urgent need to address this disparity by conducting inclusive research encompassing diverse cohorts, including women, and integrating gender-specific considerations into developing HCM guidelines. Only through such efforts can we ensure equitable and effective care for all individuals affected by this condition.

7.3.2 Lack of ethnic diversity in research

Among research publications reporting patients with HCM, nearly one-third originate from the United States, with Japan being the only other country surpassing a 10% contribution.[40] Despite the United States being a multicultural population, the level of diversity among research participants is generally low, as they are frequently drawn from single-centre clinic experiences, with comparisons only made between Europeans and African Americans.[41] Additionally, this lack of ethnic diversity in research participants poses a significant challenge in understanding the full spectrum of HCM across different racial and ethnic groups. By predominantly focusing on Europeans, valuable insights into the disease's prevalence, clinical manifestations, and treatment responses among other populations are being overlooked.

We investigated differences within a multi-ethnic Australian cohort and identified a few clinical differences and significant health disparities concerning access to genetic testing and implantable cardioverter-defibrillators (Chapter 3). Among our findings, South Asians had a significantly lower prevalence of atrial fibrillation than other ethnic groups, indicating that genetic and environmental factors influence this arrhythmia's development in different populations. East Asians, conversely, had a higher likelihood of apical hypertrophy and were more likely to have causative variants in other sarcomere genes (*TNNT2, TNNI3, MYL2, MYL3 or TPM1*). Middle Eastern and North African patients were more likely to present with left ventricular outflow tract obstruction. These results highlight the phenotypic and genetic heterogeneity of HCM across different ethnic groups.

7.3.3 Lack of ancestral diversity in genomic research

Inequality exists in access to and outcomes of genetic testing within the population. This disparity can be attributed to a historical lack of diversity, especially in terms of ancestral diversity, in genomic research. This lack of diversity is evident in disease cohorts and reference databases, and it has contributed to a divide in the effectiveness of genetic testing in diverse populations.[42, 43] Among patients with genetic heart diseases characterised by significant clinical heterogeneity, obtaining a genetic diagnosis opens up options for cascade genetic testing for at-risk relatives and clarifies the clinical diagnosis for the individual being tested.[10] Furthermore, a genetic diagnosis can provide valuable prognostic and therapeutic benefits. By incorporating ancestral diversity into genomic studies, we can create comprehensive repositories of causal alleles, enhancing our ability to distinguish disease-causing variants from natural variations.

Lack of ancestral diversity is seen in the traditional setting of genetic testing for monogenic diseases and newer, population-focused genetic applications. Genome-wide association studies (GWAS) have emerged as the preferred approach for identifying the genetic factors associated with common diseases. These studies have yielded numerous significant associations between genetic variants and biological traits, illuminating the underlying biological mechanisms behind various conditions. However, GWAS participants mainly consist of individuals of European descent, representing only 16% of the global population but accounting for approximately 79% of all GWAS participants (Figure 7.2).[44] This unequal representation of the world's population has significant implications for the use of polygenic risk scores (PRS), which are used to estimate an individual's lifetime genetic risk of developing certain diseases.[44, 45] Notably, studies conducted thus far utilising well-powered GWAS to assess the predictive value of PRS across different traits and populations have

consistently observed that PRS are more accurate in predicting individual risk among Europeans than non-Europeans.[44, 46–49]

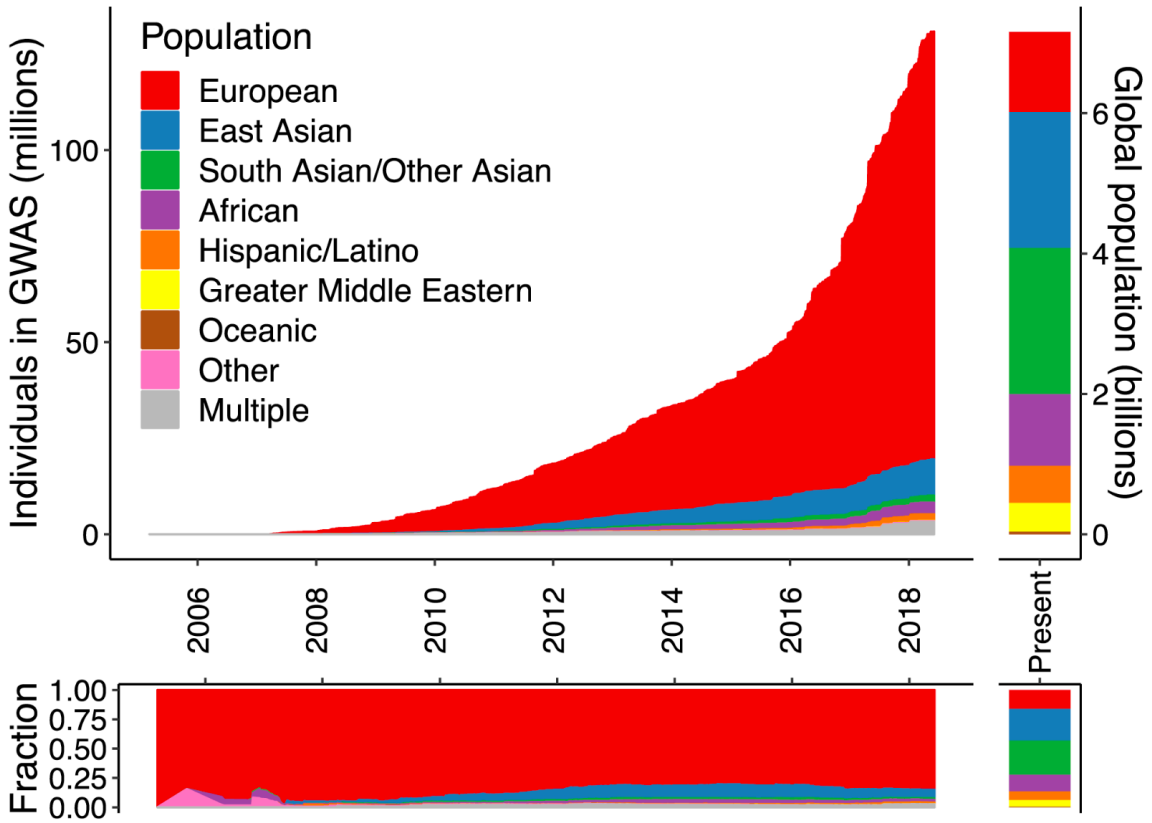

Figure 7.2: Ancestry of genome-wide association study (GWAS) participants over time compared to the global population.[44]

There is a notable absence of ancestral diversity in existing genomic reference databases. It is crucial to emphasise the urgent need for openly accessible and comprehensive genomic reference databases encompassing many populations. The absence of population-specific reference genomic databases dramatically increases the risk of misclassifying variants within diverse ancestral populations.[10, 43, 50] Our findings support this with Middle Eastern and Northern African, and South Asian individuals exhibiting higher rates of variants of uncertain significance compared to Europeans (Chapter 3).

These databases play a crucial role in ensuring the accurate interpretation of genetic variants and the value of genetic testing. We highlight this by investigating a rare variant in cardiac troponin T (*TNNT2*; NM_001001430.2: c.571-1G>A), which we identified in two unrelated individuals with cardiac phenotypes and Pacific ancestry (Chapter 4). In addition, we identified 26 cases, of which 18 were reported as having Pacific ancestry. We contacted laboratories and research groups with sequencing data from Pacific individuals to address the lack of ancestry-matched reference data. Population-specific data revealed that the variant was present at frequencies ranging from 0.9% to 8.8%. Consequently, despite some supporting evidence suggesting pathogenicity (PS4, PM4, PP3), the allele frequency matching the specific ancestry indicates that this variant is likely benign (BA1). The need for diverse and inclusive genomic reference databases becomes increasingly evident as our research underscores the importance of accurate variant interpretation and the value of genetic testing across populations.

7.4 Need for unbiased and comprehensive clinical datasets

We have demonstrated a critical need for unbiased and comprehensive clinical datasets to understand health disparities in genetic heart disease. These datasets need to not only be

inclusive of all populations by sex, ethnicity and socioeconomic status, but they need to comprehensively collect variables that enable us to understand the root cause of differences and disparities. For example, this may include the collection of sex-specific variables such as those related to the reproductive system and pregnancy in women or linkage to routinely collected health data to enable investigation of the healthcare utilisation and burden of these diseases.

There is immense potential to improve our understanding of these diseases by linking clinical variables with routinely collected hospitalisation, emergency department and mortality data (Chapters 5 & 6). Our findings show a significant proportion of hospital admissions and emergency department episodes are directly related to cardiac diagnoses, highlighting the burden of these diseases on healthcare services. Secondly, we show differences in healthcare utilisation and the primary reasons patients attend hospitals and emergency departments stratified by clinical diagnosis. Lastly, we reveal notable variations in healthcare utilisation patterns based on socioeconomic status and sex. The most significant finding was the high proportion of individuals in the highest Index of Relative Social Advantage and Disadvantage (IRSAD) category with the highest and lowest disadvantages (Chapter 6). Our findings emphasise the need for linkage to datasets with diverse recruitment to create unbiased, comprehensive datasets to increase our understanding of health disparities in genetic heart diseases.

7.5 Difficulties achieving inclusivity and diversity in research

Achieving diversity is challenging, as numerous factors inhibit an individual's participation in research. These obstacles stem directly from the conventional methods used in conducting research.[51, 52] For example, relying on specialised clinics for recruitment reduces

accessibility, only providing study materials in English creates language barriers,[53] previous wrongdoings have instilled a continual mistrust of researchers in some communities.[54, 55] Deep engagement with the community is crucial to overcome these challenges.[52, 56] This entails identifying and comprehending the barriers and motivations for participation. Community needs, desires, and benefits should be at the forefront of all research endeavours. It is imperative to reassess current research processes thoroughly. For example, simplifying the complex informed consent procedures, which often require high levels of health literacy and proficiency in English, should be considered. Furthermore, providing more explicit information about the intended uses of the collected data is essential, balancing transparency and respecting the community's wishes regarding data sovereignty.

The current research system also poses obstacles to achieving inclusive recruitment. The short time frames associated with research cycles and the pressure to produce quick results often shift the focus away from ensuring inclusivity and diversity. Researchers face time-consuming and demanding grant application processes, leaving them less capacity for community engagement and developing inclusive research strategies. The emphasis on securing funding can overshadow the importance of fostering inclusivity and diversity as researchers prioritise financial support for their projects. To promote inclusivity, changes are needed in the research system to provide more extended time frames and reduce the burden of securing funding, allowing researchers to dedicate additional attention to inclusivity and diversity efforts.

7.6 Conclusion

My research has highlighted the critical need for a more inclusive and diverse approach to research on genetic heart disease. The findings demonstrate the health disparities among underrepresented populations, including women, diverse ethnic groups, and individuals from lower socioeconomic backgrounds. The current state of knowledge in this field is limited due to the lack of diversity in research participants, which hinders our understanding of disease burden, clinical management, and genetic implications across different populations. By recognising the limitations of the current research paradigm and taking proactive steps to address them, we can foster an inclusive and diverse research landscape that achieves equitable outcomes in the diagnosis, management, and understanding of genetic heart disease, ultimately benefiting all individuals, regardless of their sex, ethnicity, socioeconomic background, or geographic location.

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