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ORIGINAL ARTICLE

Clinical to Population Prevalence of Hypertrophic Cardiomyopathy Phenotype: Insights From the National Echo Database Australia

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Background There is a paucity of data describing the underlying prevalence of hypertrophic cardiomyopathy (HCM), a primary genetic disorder characterised by progressive left ventricular (LV) hypertrophy and sudden death, from both a clinical and a population perspective.

Methods We screened the echocardiographic reports of 155,668 men and 147,880 women within the multicentre National Echo Database Australia (NEDA) (2001–2019). End-diastolic wall thickness ≥15 mm anywhere in the left ventricle was identified as a characteristic of an HCM phenotype according to current guideline recommendations. Applying a septal-to-posterior wall thickness ratio >1.3 and LV outflow tract obstruction ≥30 mmHg (when documented), we further identified asymmetric septal hypertrophy and obstructive HCM (oHCM), respectively. The observed pattern of phenotypical HCM within the overall NEDA cohort (>650,000 cases) was then extrapolated to the ~539,000 (5.7% of adult population) and ~474,000 (4.8%) Australian men and women, respectively, who were investigated with echocardiography in 2021 on an age-specific basis.

Results Overall, 15,380 cases (mean age 71.1±14.6 years, 10,138 men [65.9%]) with the characteristic HCM phenotype within the NEDA cohort were identified. Of these 15,380 cases, 5,552 (36.1%) had asymmetric septal hypertrophy, and 2,276 of the 10,290 cases with LV outflow tract obstruction profiling data (22.1%) had obstructive HCM. A further 3,389 of 13,715 cases (24.7%) had evidence of LV systolic dysfunction (LV ejection fraction <55%). Within the entire NEDA cohort (including those without LV profiling), HCM was found in 10,138 of 342,161 men (2.96%; 95% confidence interval [CI] 2.91%–3.02%) and 5,242 of 308,539 women (1.70%; 95% CI 1.65%–1.75%). When extrapolated to the Australian population, we estimate that a minimum of 15,971 men and 8,057 women presented with echocardiographic features of phenotypical HCM in 2021. This translates into a minimum caseload/prevalence of ~17 adult men (~2.5 in those aged ≤50 years) and eight adult women (~1 in those aged ≤50 years) per 10,000 population meeting phenotypical HCM criteria.

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Conclusions Using contemporary Australian echocardiographic and population data, we estimate that a minimum of 15,971 (17.5 cases/10,000) men and 8,057 women (8.2 cases/10,000) had echocardiographic evidence of phenotypical HCM in 2021. These disease burden data are particularly relevant as new treatment options are emerging.

Keywords Hypertrophic cardiomyopathy • Asymmetric septal hypertrophy • Echocardiography • Prevalence

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary genetic disorder characterised by left ventricular (LV) hypertrophy and caused by a characteristic pattern of myofibre disarray [1]. HCM is an important cause of sudden death in young people, and of disabling symptoms, heart failure (HF), and premature death in people of all ages. For many reasons, including heterogeneity in clinical presentations, a definitive diagnosis of HCM is often delayed and/or absent in a significant number of cases. Such uncertainty influences our understanding of its epidemiological profile. This is reflected by a paucity of population-based studies that proactively screen for the condition (echocardiography being the main diagnostic tool). It has been suggested that HCM is more common than historically described and is a relatively common condition (affecting 1 in 200 people) [2]. However, accurately quantifying the number of affected individuals remains problematic [3]. The most quoted prevalence figure for HCM is derived from a report published by Maron et al. in 1995 [4], suggesting that 1 in 500 adults in the US population have HCM [2]. Whether such a figure translates into an equivalent prevalence/caseload in other high-income countries such as Australia remains unknown.

Recent clinical developments and treatment options have now increased the need to better identify those living with HCM to reduce their risk of developing HF and/or dying prematurely. Traditionally, treatments such as surgical or transcatheter septal reduction therapies were successfully used in a small subgroup of high-risk individuals with disabling symptoms and performed in expert centres [5]. However, the advent of the novel cardiac myosin inhibitor mavacamten [6] offers potential therapeutic value to a broader range of HCM cases. This includes those who present with asymmetric septal hypertrophy (ASH) even when their LV mass is normal [7].

Study Aims

Combining the unique resources and insights offered by the now world-renowned National Echo Database Australia (NEDA) [8] with a robust methodology used to determine the burden of disease imposed by HF [9] and atrial fibrillation [10], we sought to address the paucity of data describing the clinical caseload and broader population prevalence of HCM in Australia. Our primary aim was, therefore, two-fold. Firstly, we sought to determine the underlying prevalence of phenotypical changes in cardiac structure indicative of HCM (and its major subtypes) within the large, real-world, NEDA cohort of patients undergoing routine echocardiographic investigation on an age- and sex-specific basis over a 20-year period. Secondly, on the basis of contemporary echocardiography investigation rates combined with Australian population statistics [11], we aimed to apply these NEDA data (on an age- and sex-specific basis) to derive a conservative estimate of the number of adult Australians presenting with the HCM phenotype (regardless of aetiology) each year.

Materials and Methods

Study Design

This study is a retrospective analysis of data derived from the National Echo Database Australia (NEDA) [8], combined with official/publicly available cardiac investigation [12] and population statistics [11]. It conforms to the ethical standards of the Declaration of Helsinki [13] and the reporting of routinely collected observational and outcome data outlined by the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [14]. NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314). Ethical approvals have been obtained from all relevant human research ethics committees (lead ethics application #HREC/15/RPAH/530).

Study Cohort

As previously described in detail [8,15–20], the NEDA is a very large, ongoing observational registry that captures all individual echocardiographic data on both a retrospective and prospective basis from participating centres throughout Australia. As part of the second iteration of data collection, 23 centres contributed to the registry. NEDA captures echocardiograms from a diverse group of patients, reflecting typical clinical practice including both hospital inpatients and, more commonly, outpatients. These outpatients are typically referred by a general practitioner and/or cardiologist for the investigation or monitoring of heart disease. This approach ensures minimal referral bias.

Study Data

As noted above, three main sources of data (including NEDA) were used to address our study aims. Wherever possible, data were aligned on an age- and sex-specific basis. For these analyses, we firstly considered data collected from the whole NEDA cohort aged ≥18 years from 1 January 2001

to 21 May 2019 (last date of individual data linkage to the Australian Institute of Health and Welfare's National Death Index [21]). As described in more detail previously, without any form of reporting bias, NEDA collects and synthesises routine echocardiographic reporting data from all patients being investigated at all participating centres. For this study, we specifically focused on the 303,548 individuals (49.1% of the overall NEDA cohort) with detailed LV measurement data to identify those with phenotypical characteristics of HCM (Figure 1). We then applied standardised criteria (see below) to firstly identify any cases of the HCM phenotype and, if possible, the main subcategories of HCM, in 155,668 men and 147,880 women.

Case Definition of Hypertrophic Cardiomyopathy

We applied the following current American Society of Echocardiography criteria for detecting the presence of HCM (on two-dimensional echocardiography): end-diastolic wall thickness ≥15 mm anywhere (intraventricular septal thickness and/or LV posterior wall dimension) in the left ventricle, in the absence of another known cause of hypertrophy [1]. The following subcategories of HCM were then identified, where possible, according to availability of additional data:

- ***Asymmetric septal hypertrophy (ASH)*:** septal-to-posterior wall thickness ratio >1.3.
- ***Obstructive HCM (oHCM)*:** while NEDA does not specifically extract provocable LV outflow tract (LVOT) gradients during manoeuvres (such as the Valsalva manoeuvre), any increase in LVOT velocities (corresponding to a peak gradient ≥30 mmHg, noting continuous wave [CW] data were taken if the pulse-repetition frequency limit of pulsed wave Doppler was exceeded) on a resting transthoracic echocardiogram was assumed to indicate LVOT obstruction (LVOTO). oHCM was defined as LVOTO ≥30 mmHg.
- ***Non-obstructive HCM (No-HCM)*:** Left ventricular outflow tract obstruction <30 mmHg; by definition, this includes those defined as ASH (a major form of No-HCM) [22].

The severe HCM phenotype was further defined as end-diastolic wall thickness >30 mm anywhere in the left ventricle (intraventricular septal thickness and/or LV posterior wall dimension).

Having calculated the probable age- and sex-specific prevalence of the HCM phenotype within NEDA (Aim 1), we also considered the reported number of adult Australians accessing Medicare Benefits Schedule (MBS) items specific to echocardiography. These are reported as services per 100,000 population within three specific age-bands (18–44, 45–79, and ≥80 years) per calendar year, as part of Australia's Medicare system [23]. However, as these reports do not provide sex-specific data, we applied the ratio of men to women (1.14–1 overall) captured by NEDA to adjust the rate of investigation within each age-band.

Finally, we considered Australian Bureau of Statistics (ABS) population data on an age- and sex-specific basis and according to geographic locale as of June 2021 [11]. At that time point, Australia's estimated population was 25.42 million people of all ages, comprising 12.54 million men and 12.87 million women. Of these, 9.41 million and 9.92 million were adult men and women, respectively. Reflecting ABS reporting convention, data for all people aged between 20 and 84 years were grouped into 5-year age brackets, with 18–19 years and ≥85 years as the remaining groups.

The Hypertrophic Cardiomyopathy Phenotype in NEDA

The overall distribution of the HCM phenotype (and subtypes) identified within NEDA was classified according to biological sex and the discrete ABS-defined age groups described above. On the basis of the number of negative vs positive HCM cases observed, we calculated the number/proportion of positive cases per 1,000 investigations within each cohort using the following two denominators: (1) the 303,548 NEDA cases in which HCM could be more definitively identified, and (2) the overall cohort of 618,065 NEDA cases in which the absence of specific LV profiling/reporting was assumed to indicate the absence of LV abnormality/no HCM.

Hypertrophic Cardiomyopathy in Australia

To estimate the likely caseload of the same HCM phenotype detected by routine echocardiography in Australia each year (Aim 2), we firstly combined our more granular rates (sex- and age-specific) of echocardiographic investigations funded under the MBS with the ABS population statistics for 2021 [11] to provide a contemporary estimate/profile of adult Australians who were investigated with an echocardiogram in that year. In total, we conservatively estimate that in 2021 this number comprised ~539,000 men (5.7%, ranging from 1.3% to 24.2% among Australian men aged 18–19 to ≥85 years) and ~474,000 women (4.8%, ranging from 1.3% to 17.2% among Australian women aged 18–19 to ≥85 years) (Figure 2). We then applied the most conservative set of numerator/denominator figures used to identify the proportion of phenotypical HCM cases within NEDA to the corresponding (on an age- and sex-specific basis) number of Australians who underwent echocardiography in 2021.

Statistical Methods

Standard statistical methods are used to describe discrete (n/proportions) and continuous (median/interquartile range and mean standard deviation [±]) data, with the numerator/denominator groups clearly identified for: (1) the main NEDA cohort, (2) the NEDA cohort with detailed LV profiling, (3) Australians aged ≥18 years who were underwent echocardiography in 2021, and (4) all individuals aged ≥18 years living in Australia in 2021. Where appropriate, data are presented on an age- and sex-specific basis for Australia and its constituent states and territories. Rates of

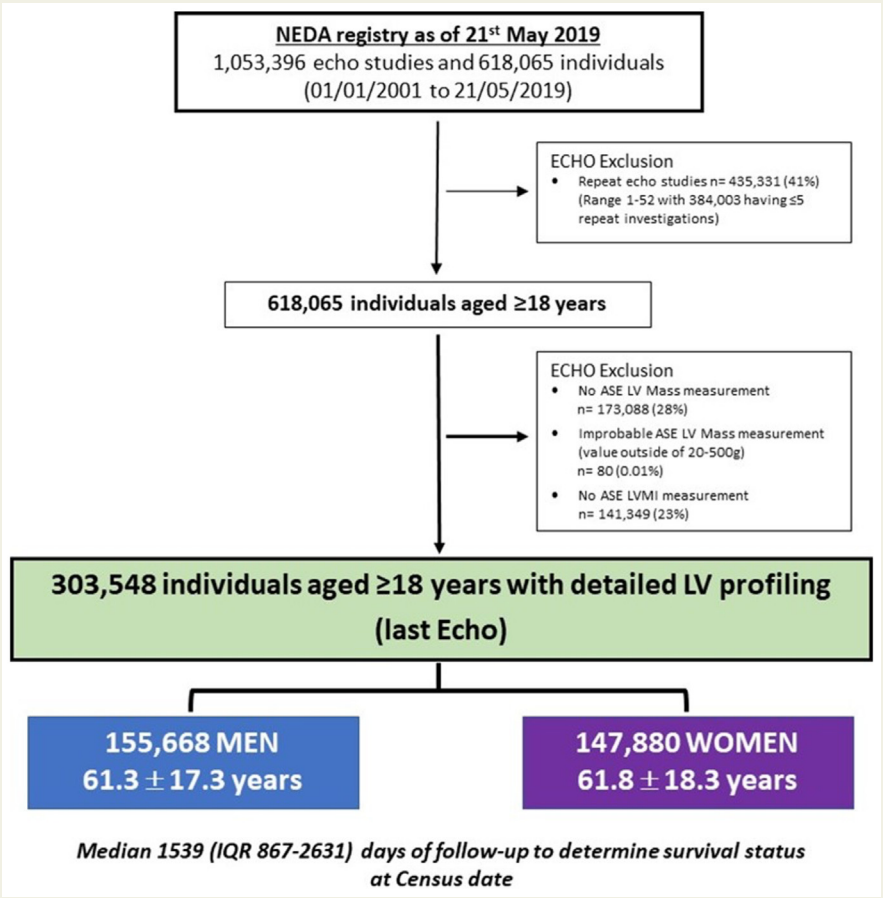


Figure 1 NEDA cohort with LV profiling data. The study schema shows the number of potentially eligible patients who formed the study cohort once key exclusion criteria were applied, according to their LV profiling. Abbreviations: NEDA, National Echo Database Australia; Echo, echocardiogram; LV, left ventricular; ASE, American Society of Echocardiography; LVMi, Left Ventricular Mass Index indexed to body mass (g/m^2); IQR, interquartile range.

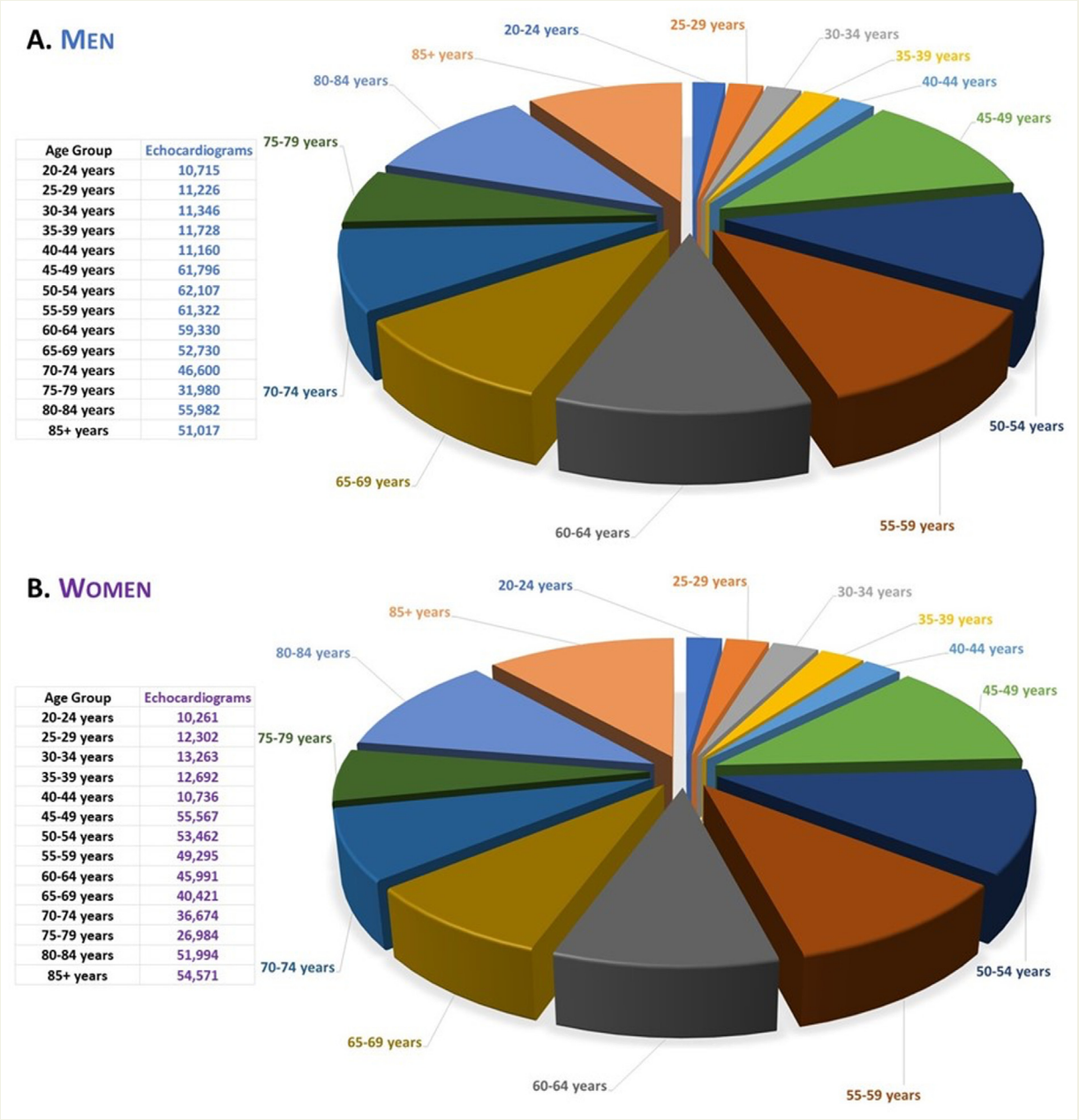
echocardiography and positive cases of HCM are presented in whole numbers, proportions, and rates per those at risk (per 1,000 or 10,000 people).

Results

Cohort Profile

As shown in Table 1, we identified a total of 15,380 individuals who met echocardiographic criteria for the HCM phenotype within the NEDA cohort. The mean age was 71.1±14.6 years, with a predominance of men (10,138 cases, 65.9%) evident (see Supplementary Tables S1 and S2 for sex-specific profiling). Overall, 5,552 of 15,380 cases (36.1%) had evidence of ASH (Table 1). Additionally, 2,276 of 10,290 cases with LVOTO profiling data (22.1%) were classified as oHCM (Supplementary Table S3). The characteristics of those classified as ASH and oHCM were similar to those of the overall cohort, except for the expected increase in LVOT/aortic valve (AV) peak gradient, larger left atrial volume, and higher proportion of moderate to severe mitral regurgitation in the oHCM group. Cases with the HCM phenotype and documented LV ejection fraction (LVEF) (13,715 cases) were further compared according to LVEF above (10,326, 75.3%) and below (3,389, 24.7%) a threshold of 55% (Supplementary Table S4). Impaired systolic function in combination with HCM was associated with more adverse diastolic function characteristics and more mitral regurgitation, but with larger LV diastolic dimensions and accompanying lower rates of LVOTO and lower LVOT/AV peak gradients.

We performed a sensitivity analysis to establish the potential influence of valvular aortic stenosis (AS) on the rising proportion of cases with the HCM phenotype identified in older individuals (Supplementary Table S5). Taking LVOT velocity into account (since LVOT velocities are not increased in the setting of valvular AS), only a small proportion of patients identified with potential HCM may have had AS as their principal diagnosis (898 of 10,361 patients, 8.7%). The echocardiographic characteristics of the "AS group" were similar to those of the HCM group, although impaired systolic function was more common in the AS group.



Age Group	Echocardiograms
20-24 years	10,715
25-29 years	11,226
30-34 years	11,346
35-39 years	11,728
40-44 years	11,160
45-49 years	61,796
50-54 years	62,107
55-59 years	61,322
60-64 years	59,330
65-69 years	52,730
70-74 years	46,600
75-79 years	31,980
80-84 years	55,982
85+ years	51,017

Age Group	Echocardiograms
20-24 years	10,261
25-29 years	12,302
30-34 years	13,263
35-39 years	12,692
40-44 years	10,736
45-49 years	55,567
50-54 years	53,462
55-59 years	49,295
60-64 years	45,991
65-69 years	40,421
70-74 years	36,674
75-79 years	26,984
80-84 years	51,994
85+ years	54,571

Figure 2 Estimated distribution of Echocardiographic Investigations in Australia (2021) according to sex and 5-year age groups from 20 years of age.

Overall, the accompanying echocardiographic report noted a specific general practitioner referral or suspicion of HF in ~6% to 9% of all identified cases with the HCM phenotype. Among those identified with ASH, these numbers markedly rose to ~25% to 38%.

Clinical Prevalence of HCM (NEDA)

Overall, echocardiographic evidence of the HCM phenotype was positively identified in 6.51% of men (10,138/155,668 cases) and 3.54% of women (5,242/147,880 cases), with detailed LV profiling captured by NEDA (representing those who had a definitive HCM status/identification possible). When adjusting for the full NEDA cohort, this equated to 2.96% (95% confidence interval [CI] 2.91%–3.02%) of men (10,138/342,161 cases) and 1.70% (95% CI 1.65%–1.75%) of women (5,242/308,539 cases). As summarised in Table 2, the underlying prevalence of phenotypical HCM rose from 0.36% of men and 0.13% of women aged 18 years to 6.09% of men and 4.49% of women aged ≥85 years, representing the increasing likelihood of at least one echocardiography study with increasing age. A total of

Table 1 Characteristics of HCM cases within the NEDA cohort.

Clinical and echocardiographic characteristics	HCM phenotype 15,380 cases	ASH 5,552 cases	oHCM 2,276 cases
Demographic			
Men %	65.92%	62.55%	62.92%
Age at last echo (years)	71.06±14.58	70.21±15.31	77.57±11.82
BMI (kg/m^2)	29.87±7.08	28.78±6.26	28.74±6.29
LV dimensions/function			
IV septal thickness	1.63±0.23	1.75±0.27	1.62±0.19
IV septal thickness ≥15 mm %	91.37%	100.00%	93.28%
LV posterior wall dimensions	1.35±0.29	1.07±0.19	1.41±0.25
LV posterior wall dimensions ≥15 mm %	40.88%	2.09%	52.94%
LV diastolic diameter	4.47±0.82	4.33±0.83	4.57±0.78
LV diastolic diameter <5.5 cm %	88.25%	91.17%	86.47%
Septal to posterior wall ratio	1.28±0.40	1.68±0.39	1.19±0.31
Septal to posterior wall ratio >1.3 %	36.10%	100.00%	25.66%
LVOT/AV peak gradient[a]	22.13±24.65	17.30±19.55	60.08±27.09
LVOT/AV peak gradient[a] ≥30 mmHg %	22.12%	14.92%	100.00%
LVEF	61.90±14.58	59.27±13.52	64.86±14.81
LVEF <55%	24.71%	26.98%	19.58%
LVEF ≥55%	75.29%	73.02%	80.42%
Mitral E wave velocity,	85.91±33.25	82.58±31.83	99.54±38.84
Mitral E wave velocity >90 cm/s %	36.73%	32.49%	52.57%
LV septal e′ velocity	6.11±2.21	5.90±2.18	5.98±2.17
LV septal e′ velocity <9 cm/s %	85.45%	89.52%	85.43%
Mitral E:e′ ratio	14.53±6.81	14.45±6.93	16.73±8.11
Mitral E:e′ ratio >9 %	84.30%	81.88%	91.58%
Left atrial volume index, mL/m^2	60.06±35.61	50.04±26.97	73.23±40.76
Left atrial volume index, >34 mL/m^2 %	76.91%	71.82%	87.75%
Moderate to severe mitral regurgitation, %	15.46%	18.63%	19.49%

[a]Continuous-wave Doppler evaluation of LVOT/AV velocities.

Abbreviations: HCM, hypertrophic cardiomyopathy; NEDA, National Echo Database Australia; ASH, asymmetric septal hypertrophy defined as septal to posterior wall thickness ratio >1.3; oHCM, obstructive hypertrophic cardiomyopathy defined as any increase in LVOT/AV velocities corresponding to a peak gradient ≥30 mmHg; BMI, body mass index; LV, left ventricular; IV, intraventricular; LVOT, left ventricular outflow tract; AV, aortic valve; LVEF, left ventricular ejection fraction.

6,144 of 10,138 men (60.6%) with the HCM phenotype were still alive in May 2019, with survival rates falling from 90%–100% among those aged <25 years to <50% among those aged >75 years (at baseline). In women, the equivalent proportion was 55.6% (2,917/5,242), with survival rates falling from 83%–96% among those aged <25 years to <50% among those aged >80 years.

Phenotypical HCM Prevalence Detected by Echocardiography in Australia

On the basis of the rate of phenotypical HCM found within the entire NEDA cohort (>600,000 individuals) applied to the population rate of echocardiographic investigations per annum, we estimate that a minimum of 15,971 men and 8,057 women presented with echocardiographic features of the HCM phenotype in 2021. This translates into a minimum prevalence of ~17 adult male and 8 adult female cases per 10,000 population, respectively. In those aged <55 years, the minimum indicative population prevalence of phenotypical HCM was estimated to be 5.0 cases per 10,000 adult men (or 3,071 cases) and 1.7 cases per 10,000 adult women (or 1,063 cases). Figure 3 shows the estimated age distribution of male (top) and female (bottom) cases (rate/1,000 at risk) of the HCM phenotype and how they are distributed across each major state and territory plus major population centre. Equivalent data for ASH cases are presented in Supplementary Figure S1.

Table 2 Age- and sex-specific distribution of cases with the HCM phenotype within the entire NEDA cohort.

Age group, yrs	Total NEDA Cohort (n=650,700)				HCM Cases (n=15,380)				
	Men		Women		All cases	Men		Women	
18–19	4,690	0.89%	4,491	0.90%	23	17	0.36%	6	0.13%
20–24	7,785	2.45%	8,531	2.58%	78	50	0.64%	28	0.33%
25–29	8,707	2.61%	10,178	3.19%	122	86	0.99%	36	0.35%
30–34	10,059	3.07%	10,886	3.55%	137	91	0.90%	46	0.42%
35–39	13,102	3.76%	12,604	3.86%	213	169	1.29%	44	0.35%
40–44	13,383	4.90%	12,034	4.77%	389	293	2.19%	96	0.80%
45–49	26,285	6.23%	22,626	6.09%	416	304	1.16%	112	0.50%
50–54	22,137	7.83%	17,795	7.40%	722	557	2.52%	165	0.93%
55–59	40,423	9.47%	31,335	8.48%	1,010	750	1.86%	260	0.83%
60–64	38,676	10.8%	29,648	9.54%	1,357	1,007	2.60%	350	1.18%
65–69	40,360	11.8%	31,763	10.5%	1,653	1,170	2.90%	483	1.52%
70–74	37,349	11.1%	31,514	10.3%	1,882	1,321	3.54%	561	1.78%
75–79	26,514	10.1%	24,625	10.4%	2,357	1,513	5.71%	844	3.43%
80–84	29,085	8.20%	31,111	9.16%	2,264	1,372	4.72%	892	2.87%
85+	23,606	6.80%	29,398	9.27%	2,757	1,438	6.09%	1,319	4.49%
All ages	342,161		308,539		15,380	10,138	2.96%	5,242	1.70%

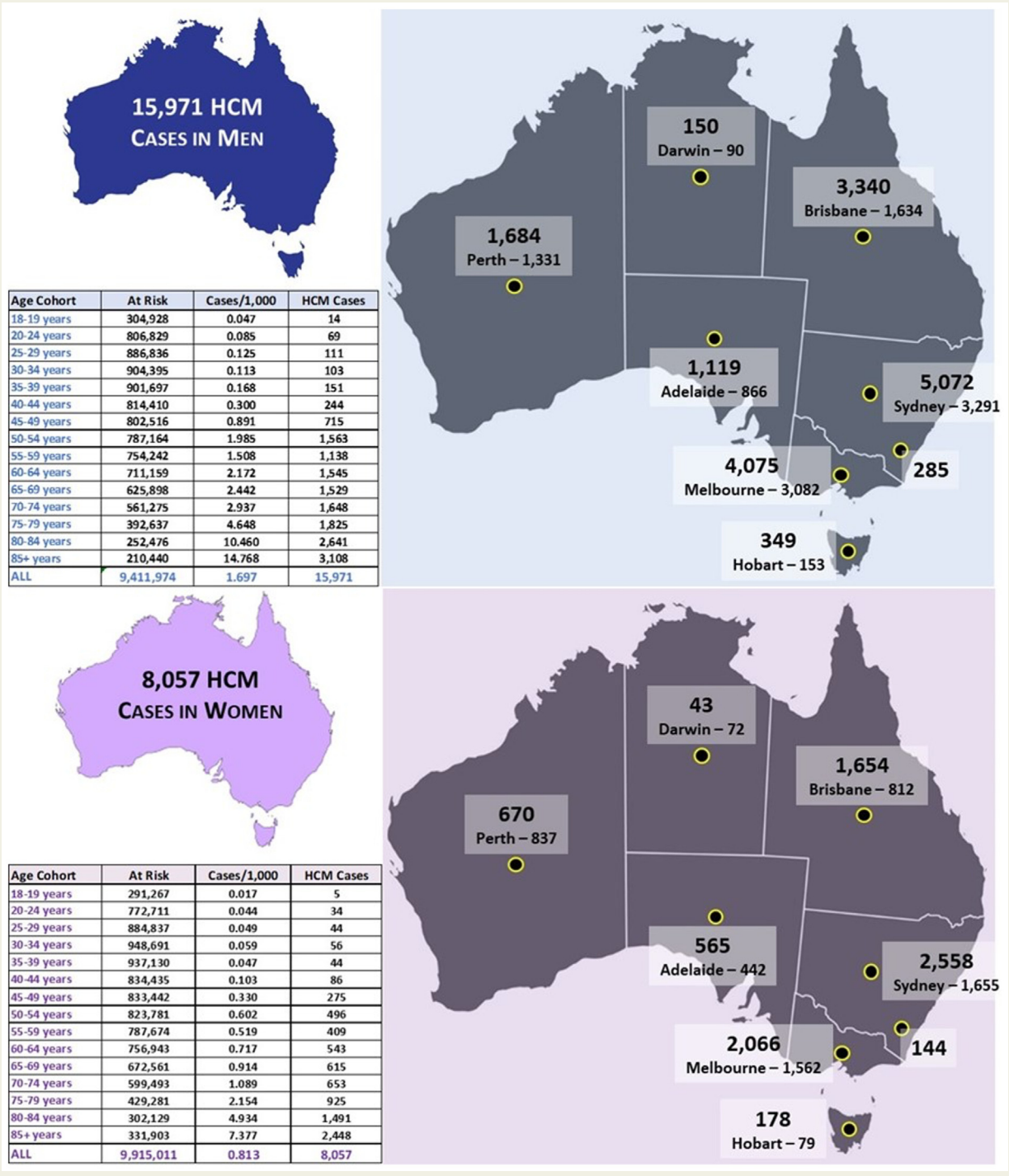
Abbreviations: HCM, hypertrophic cardiomyopathy defined as end-diastolic wall thickness ≥15 mm (intraventricular septal thickness and/or left ventricular posterior wall dimension) anywhere in the left ventricle, in the absence of another known cause of hypertrophy; NEDA, National Echo Database Australia.

Discussion

Applying the unique resources of NEDA, with routine reporting data collected for >600,000 individuals throughout Australia over 20 years, we identified a total of 10,138 men and 5,242 women (15,380 cases) with phenotypical HCM according to current echocardiographic criteria. Overall, these cases represented 2.96% and 1.70% of all men and women captured by NEDA during the study period. Despite the lack of clinical granularity (including the presence or absence of other causes of ventricular hypertrophy such as hypertension, AS, or cardiac amyloidosis; see limitations), to our knowledge, this still represents a substantial contribution to our knowledge about the burden of HCM from both a clinical and population perspective. Extrapolating these unique findings to the Australian population subject to echocardiographic investigation (on an age- and sex-specific basis), we estimate that ~16,500 adult men and ~8,150 adult women will present with phenotypical HCM each year (2021 figures). At the whole population level, this translates to an overall prevalence of approximately 17 cases per 10,000 adult men and eight cases per 10,000 adult women with the HCM phenotype. Importantly, when considering those aged <55 years (the likely cohort in which other causes of LV hypertrophy are less prevalent/influential, including hypertension and AS), the minimum indicative population prevalence of phenotypical HCM was estimated to be 5.0 cases per 10,000 adult men (or 3,071 cases) and 1.7 cases per 10,000 adult women (or 1,063 cases) in these specific age cohorts, noting that this age cohort is also less likely to have echocardiography performed without specific clinical indications.

With an approximate male-to-female ratio of 2:1 cases detected, the HCM phenotype within the NEDA cohort was characterised by increased intraventricular septal wall thickness, normal LV diastolic dimensions, normal LV systolic function but impaired diastolic function, and increased left atrial volume. These characteristics, while not universally present, are consistent with the previously published HCM phenotype characterised by increased LV wall thickness/normal systolic function, but abnormal myocardial relaxation in the setting of myofiber disarray, resulting in increased LV filling pressure [1]. Despite the marked differential in detected cases (noting the overall lower rate of investigations in women), the echocardiographic characteristics of phenotypical HCM were similar between men and women. This finding suggests that there are no significant sex-based differences in the cardiac phenotypic response to HCM. Obstructive HCM (oHCM), characterised by increased CW velocities across the LVOT/AV, was found in one in five individuals. When present, significant LVOTO and moderate to severe mitral regurgitation were more likely.

These data have significant implications for management strategies to identify clinically significant HCM and to minimise risk to individuals. The male predominance may be due to the current diagnostic criteria, since on average men are known to have larger hearts with higher LV mass and wall thickness. Thus, the lack of sex-specific diagnostic criteria may underestimate the number of women with less severe forms of HCM, and further work is needed to clarify whether sex-



Age Cohort	At Risk	Cases/1,000	HCM Cases
18-19 years	304,928	0.047	14
20-24 years	806,829	0.085	69
25-29 years	886,836	0.125	111
30-34 years	904,395	0.113	103
35-39 years	901,697	0.168	151
40-44 years	814,410	0.300	244
45-49 years	802,516	0.891	715
50-54 years	787,164	1.985	1,563
55-59 years	754,242	1.508	1,138
60-64 years	711,159	2.172	1,545
65-69 years	625,898	2.442	1,529
70-74 years	561,275	2.937	1,648
75-79 years	392,637	4.648	1,825
80-84 years	252,476	10.460	2,641
85+ years	210,440	14.768	3,108
ALL	9,411,974	1.697	15,971

Age Cohort	At Risk	Cases/1,000	HCM Cases
18-19 years	291,267	0.017	5
20-24 years	772,711	0.044	34
25-29 years	884,837	0.049	44
30-34 years	948,691	0.059	56
35-39 years	937,130	0.047	44
40-44 years	834,435	0.103	86
45-49 years	833,442	0.330	275
50-54 years	823,781	0.602	496
55-59 years	787,674	0.519	409
60-64 years	756,943	0.717	543
65-69 years	672,561	0.914	615
70-74 years	599,493	1.089	653
75-79 years	429,281	2.154	925
80-84 years	302,129	4.934	1,491
85+ years	331,903	7.377	2,448
ALL	9,915,011	0.813	8,057

Figure 3 Projected cases of the HCM phenotype uncovered by echocardiography in Australia (2021). This graph shows the estimated distribution of phenotypical HCM (total of 15,971 men and 8,057 women) based on the demographic/geographic distribution of the Australian population in 2021. The HCM phenotype is defined as end-diastolic wall thickness ≥15 mm anywhere (intraventricular septal thickness and/or left ventricular posterior wall dimension) in the left ventricle, in the absence of another known cause of hypertrophy. Abbreviation: HCM, hypertrophic cardiomyopathy.

specific diagnostic criteria are required, particularly in respect to mortality outcomes. The male predominance may also represent a difference in rates of echocardiography investigations between male and female patients suspected of having HCM. As recommended by clinical practice guidelines [24], other causes of ventricular hypertrophy such as hypertension, AS, and cardiac amyloidosis need to be excluded before a definitive HCM diagnosis.

The prevalence data provided in this report represent the minimum indicative prevalence of the HCM phenotype, since increased wall thickness outside of the intraventricular septal and posterior walls (including apical regions) is not captured by available measurement fields in routine echocardiography. Further work is required using natural language processing (NLP) and echocardiographic image recognition artificial intelligence (AI) to establish the true distribution of different forms of HCM in the community. NLP will also assist in identifying other non-HCM causes of ventricular hypertrophy.

Despite these caveats, our findings suggest that HCM is not a rare disease. Overall, we found 17.5 cases per 10,000 adult men and 8.2 cases per 10,000 adult women of the HCM phenotype in Australia. In specific comparison with the previous estimate of one in 500 cases in the United States [2,25], our (conservative) estimates are only slightly lower for men (0.9 cases/500 population) and 2.5 times lower (0.4 cases/500 population) for women. Approximately 70% of HCM cases exhibit obstruction at rest (when tested with preload reduction techniques such as the Valsalva manoeuvre) and/or during exercise [3]. HCM cases with significant obstruction are associated with increased risk of mitral regurgitation, limited exercise capacity and disabling symptoms, and increased risk of mortality [24]. Therefore, proactively identifying all adults with definitive HCM in Australia is clinically important, and it is likely that many cases of HCM currently remain undiagnosed/untreated. Systematic and reliable identification of HCM in all individuals undergoing echocardiography, and specifically all individuals who would benefit from sudden death risk stratification and disease-specific therapy such as mavacamten [6], will require new approaches with a focus on automation. Such innovations may include clinical risk algorithms, genetic screening, AI-based automated echocardiographic image phenotype recognition, and automatic application of clinical guidelines from echocardiographic measurement data [26].

An inherent strength of NEDA is that it enables examination of different forms of heart disease within an exceptionally large and heterogeneous (both in terms of ethnicity and underlying conditions) patient cohort with access to high-quality care. However, it also has certain limitations, which have been described in our previous reports. For example, NEDA does not (yet) capture important details on the cultural and socio-economic profiles of individual participants, and contributing centres are predominantly located in metropolitan regions of Australia. We cannot therefore exclude systematic biases in those being investigated and account for the confounding influence of socio-economic status on the presentation of cases for echocardiography and subsequent mortality outcomes. For now, in most cases, we do not have granular clinical information on conditions that led to their investigation (such as hypertension, coronary artery disease, or cardiac amyloidosis); we have therefore used conservative terminology ("HCM phenotype") to describe the cases of interest. We also did not have information on functional status and symptomatic profile to determine if patients had already developed the syndrome of HF. It is likely that some cases of HCM were missed in this study, since increased wall thickness is not necessarily captured in the measurement section of typical transthoracic echocardiography reports (e.g., apical wall thickness is not routinely measured). To identify these patients, more sophisticated techniques need to be applied using NLP and AI systems. NLP will also assist in identifying other causes of LV hypertrophy and additional diagnoses and symptoms to better identify HCM cases within NEDA. Additionally, we did not capture results of genetic testing. Thus, some patients with genetically confirmed HCM but with echocardiographic findings below the 15-mm cutoff were not identified in this study. However, we note that only a minority of patients with the typical HCM phenotype have an identifiable genetic abnormality [27].

The limitations of individual echocardiographic techniques used to measure LVOTO may have also influenced the detection of oHCM. For example, pulsed-wave Doppler is limited by the physical characteristics of the pulsed wave, with the maximum measurable velocity being half the pulse-repetition frequency. As a result, high velocities across the LVOT can only be accurately measured using CW Doppler, and on the basis of velocity/gradient information alone, CW data cannot be used to distinguish LVOTO from AS. Our sensitivity analysis (Supplementary Table S6) suggests that our methodology is robust, with minimal interference from native valve AS. Given the presence of the COVID-19 pandemic in 2021, the rate of echocardiographic investigations in the population may have differed from previous years, potentially influencing the number of detected cases. Finally, the smaller proportion of young adults exhibiting the HCM phenotype in our cohort most likely represents a referral bias given that individuals undergoing echocardiography are typically referred for known or suspected cardiac disease. A young individual with HCM is likely to have normal exercise tolerance and minimal symptoms, resulting in a lack of suspicion of cardiac disease and under-referral.

Conclusions

To our knowledge, we describe the prevalence and characteristics of the largest single cohort of the HCM phenotype identified from routinely acquired transthoracic echocardiographic measurement data. When extrapolating our findings from the large, well-established NEDA cohort (now reaching total numbers of echocardiograms that exceed those of MBS-funded investigations each year in Australia) to the population level, we found the minimum echocardiographic indicative caseload/prevalence of phenotypical HCM to be 17 cases per 10,000 Australian men and eight cases per 10,000 Australian women. As indicated by the echocardiographic profile of those identified and the proportion who survived study follow-up, HCM remains an important health

condition. Thus, there is a strong clinical imperative to identify all individuals with possible HCM based on echocardiographic criteria, and if identified, seek evidence for other possible underlying causes for hypertrophy. If HCM is subsequently confirmed, evidence-based treatments should be applied to improve the quality of life and prolong survival of those affected.

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Conflicts of Interest

There are no conflicts of interest to disclose.

Appendices

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2023.10.021.

References

[1] Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. Circulation. 2020;142(25):e558–631.

[2] Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015;65(12):1249–54.

[3] Raj MA, Ranka S, Goyal A. Hypertrophic Obstructive Cardiomyopathy. Treasure Island, FL: StatPearls; 2022.

[4] Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation. 1995;92(4):785–9.

[5] Cui H, Schaff HV, Wang S, Lahr BD, Rowin EJ, Rastegar H, et al. Survival following alcohol septal ablation or septal myectomy for patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2022;79(17):1647–55.

[6] Spertus JA, Fine JT, Elliott P, Ho CY, Olivotto I, Saberi S, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (Explorer-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397(10293):2467–75.

[7] Shiwani H, Hughes RK, Camaioni C, Augusto JB, Knott K, Rosmini S, et al. Asymmetric septal thickening is observed in hypertrophic cardiomyopathy mutation carriers without left ventricular hypertrophy: insights from AI analysis. Eur Heart J Cardiovasc Imaging. 2022;23:S2.

[8] Strange G, Celermajer DS, Marwick T, Prior D, Ilton M, Codde J, et al. The National Echocardiography Database Australia (NEDA): rationale and methodology. Am Heart J. 2018;204:186–9.

[9] Chan YK, Tuttle C, Ball J, Teng TK, Ahamed Y, Carrington MJ, et al. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. BMC Health Serv Res. 2016;16(1):501.

[10] Ball J, Thompson DR, Ski CF, Carrington MJ, Gerber T, Stewart S. Estimating the current and future prevalence of atrial fibrillation in the Australian adult population. Med J Aust. 2015;202(1):32–5.

[11] Australian Bureau of Statistics population: Australian Bureau of Statistics. Available at: https://wwwabsgovau/statistics/people/population. [accessed 1.1.23].

[12] Standard echocardiography, 18 years and over: Australian Commission on Safety and Quality in Health Care. Available at:. https://wwwsafetyandqualitygovau/our-work/healthcare-variation/third-atlas-2018/atlas-2018-4-cardiac-tests/44-standard-echocardiography-18-years-and-over. [accessed 1.1.23].

[13] World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ. 2001;79(4):373–4.

[14] Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.

[15] Stewart S, Chan YK, Playford D, Strange GA, NEDA investigators. Mild pulmonary hypertension and premature mortality among 154 956 men and women undergoing routine echocardiography. Eur Respir J. 2022;59(1):2021.

[16] Strange G, Stewart S, Celermajer DS, Prior D, Scalia GM, Marwick TH, et al. Threshold of pulmonary hypertension associated with increased mortality. J Am Coll Cardiol. 2019;73(21):2660–72.

[17] Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, et al. Poor long-term survival in patients with moderate aortic stenosis. J Am Coll Cardiol. 2019;74(15):1851–63.

[18] Stewart S, Chan YK, Playford D, Strange GA, NEDA Investigators. Incident aortic stenosis in 49 449 men and 42 229 women investigated with routine echocardiography. Heart. 2022;108(11):875–81.

[19] Stewart S, Playford D, Scalia GM, Currie P, Celermajer DS, Prior D, et al. Ejection fraction and mortality: a nationwide register-based cohort study of 499 153 women and men. Eur J Heart Fail. 2021;23(3):406–16.

[20] Playford D, Strange G, Celermajer DS, Evans G, Scalia GM, Stewart S, et al. Diastolic dysfunction and mortality in 436 360 men and women: the National Echo Database Australia (NEDA). Eur Heart J Cardiovasc Imaging. 2021;22(5):505–15.

[21] National death index (NDI). Australian Institute of Health nad Welfare. Available at: https://www.aihw.gov.au/about-our-data/our-data-collections/national-death-index. [accessed 1.1.23].

[22] Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol. 2014;64(1):83–99.

[23] Medicare Canberra. services Australia. Available at: https://www.servicesaustralia.gov.au/medicare. [accessed 1.1.23].

[24] Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Management of hypertrophic cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022;79(4):390–414.

[25] Massera D, Sherrid MV, Maron MS, Rowin EJ, Maron BJ. How common is hypertrophic cardiomyopathy... really?: disease prevalence revisited 27 years after CARDIA. Int J Cardiol. 2023;382:64–7.

[26] Playford D, Bordin E, Mohamad R, Stewart S, Strange G. Enhanced diagnosis of severe aortic stenosis using artificial intelligence: a proof-of-concept study of 530,871 echocardiograms. JACC Cardiovasc Imaging. 2020;13(4):1087–90.

[27] Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79(4):372–89.