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Demographic-Based Personalized Left Ventricular Hypertrophy Thresholds for Hypertrophic Cardiomyopathy Diagnosis

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ABSTRACT

BACKGROUND Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death. Current diagnosis emphasizes the detection of left ventricular hypertrophy (LVH) using a fixed threshold of ≥15-mm maximum wall thickness (MWT). This study proposes a method that considers individual demographics to adjust LVH thresholds as an alternative to a 1-size-fits-all approach.

METHODS Left ventricular MWT was measured in 3 cohorts: a Reference Cohort of healthy adults (n = 5,067, no comorbidities), a Population Cohort (n = 43,239, with comorbidities), and an HCM Cohort from 6 international centers (n = 2,424). Measurement used cardiovascular magnetic resonance (CMR) and a validated artificial intelligence algorithm. The Reference Cohort was used to developed demographically adjusted LVH thresholds, and individualized *z*-scores based on age, sex, and body surface area (BSA), which were used to explore the other cohorts.

RESULTS The traditional ≥15-mm threshold classified 4.3% (n = 1,854) of the Population Cohort as hypertrophic, with a significant sex skew (89% male). Demographic-adjusted LVH thresholds (range: 10-17 mm) reduced ascertainment to 2.2% (n = 945), reducing the sex skew (56% male). Similar reductions in bias with height, weight, and age also occurred. The HCM cohort was found to have a 2:1 male-to-female ratio. A significant proportion of patients received diagnoses of HCM despite having MWT below the traditional LVH threshold (<15 mm): 27% of female individuals and 18% of male individuals. Using demographic-adjusted LVH thresholds reduced these proportions to 7% of female individuals and 15% of male individuals ($P < 0.0001$). Female patients had lower absolute MWT (18 mm vs 19 mm; $P < 0.001$) but higher MWT *z*-scores (5.1 vs 4.5; $P = 0.05$).

CONCLUSIONS Age, sex, and body size influence the normal heart MWT. Using a fixed LVH threshold ≥15 mm biases LVH ascertainment in both population and HCM cohorts. A demographic-adjusted approach for LVH improves ascertainment and diagnostic accuracy. (JACC. 2024;■:■–■) © 2024 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AI = artificial intelligence

BSA = body surface area

CMR = cardiovascular magnetic resonance

GAMM = generalized additive mixed model

HCM = hypertrophic cardiomyopathy

LVH = left ventricular hypertrophy

MWT = maximum wall thickness

PI = prediction interval

Hypertrophic cardiomyopathy (HCM) affects as many as 1 in 200 individuals.[1] Current diagnostic methods for HCM rely heavily on a single measurement: the left ventricular maximum wall thickness (MWT) to identify unexplained left ventricular hypertrophy (LVH). The European Society of Cardiology[2] and the American Heart Association[3] use a "one size fits all" maximum wall thickness (MWT) threshold of ≥15 mm in adults (≥13 mm with a family history); a criterion that was established 50 years ago using M-mode echocardiographic methods.[4,5]

Although an HCM diagnosis typically involves a comprehensive assessment including clinical, imaging, genetic, and molecular markers,[6,7] the MWT measurement remains fundamental to both diagnosis and risk assessment.[8] Timely and accurate diagnosis of HCM has implications for the prevention of sudden cardiac death. However, it is equally important to avoid false positive diagnoses because they can have an adverse impact on an individual's life opportunities, including career choices, insurance eligibility, and exercise participation.

Whereas the 15-mm threshold is simple, it fails to account for the influence of age, sex, and body size on normal heart dimensions,[9,10] potentially introducing bias. In pediatric HCM diagnosis, MWT *z*-scores that consider age, height, and weight are already in use.[2,3,11] Many other adult cardiac measurements are similarly indexed, yet MWT remains an exception.[12] The limitations of a universal 15-mm threshold are evident in clinical practice: lower cutoffs have been proposed in Asia (≥10 mm for female individuals, ≥12 mm for male individuals).[13] HCM clinics globally report a 2:1 male-to-female prevalence ratio, despite HCM being primarily an autosomal dominant disease,[14] and female patients with HCM often receive their diagnoses later with more advanced disease characteristics, such as atrial dilatation and ventricular scarring,[15] with a worse prognosis.[16] Moreover, patients with HCM, particularly those without identified genetic mutations, tend to be predominantly male, older, and of larger body size.[17]

Recent advancements in data science and artificial intelligence (AI), combined with access to extensive data sets from biobanks, now enable us to determine normal measurement ranges for healthy populations with high precision. Together with the superior measurement precision of cardiovascular magnetic resonance (CMR), we aimed to better understand normal MWT values and their variability in healthy individuals. This approach allowed us to create demographic-adjusted LVH thresholds for MWT. We then explored LVH ascertainment both in a population cohort and in dedicated HCM clinics.

METHODS

Data were acquired from patients previously recruited to research studies that were studies approved by a National Health Service Research Ethics Committee (REC 21/EE/0037) and the Health Research Authority or local Institutional Review Board and conducted in accordance with the declaration of Helsinki.

SUBJECT COHORTS. Reference cohort. To define the standard parameters for normal myocardial MWT and thereby LVH, we collated source CMR images and demographics of healthy subjects (no comorbidities). We used 5 distinct studies to ensure generalizability: the UK Biobank,[18] the Framingham Heart Study Offspring Cohort,[19] and the MyoFit46 study.[20] In addition, healthy subjects from several other smaller independent studies based in London, United Kingdom, were included.[21-23]

Subjects were >18 years of age, with a body mass index between 18 and 35 kg/m^2. Subjects were considered healthy if free of hypertension, diabetes, hypercholesterolemia, peripheral vascular disease, coronary artery disease, and cerebrovascular disease. Additionally, they were not taking any cardioactive

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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medications, except for aspirin or statins for primary prevention. Health status was defined by subject self-reporting of no known comorbidities.

Population-based cohort. To compare potential biases of conventional ≥15 mm against a demographic-adjusted LVH threshold, we analyzed LVH ascertainment in the UK Biobank CMR substudy. This included population representative individuals, often with comorbidities and medication use. No subjects were excluded.

HCM cohort. To explore potential impacts within HCM global health care, we sourced original CMR images from global centers to analyze all patients with confirmed or suspected HCM who had undergone CMR. These were 6 specialized HCM centers in 5 countries: Italy, Spain, Portugal, United States, and the United Kingdom. A 15-mm MWT cutoff was not required for inclusion if the patients' conditions were managed as HCM. Exclusions were known phenocopies (ie, amyloidosis, Fabry disease), prior interventions (ie, myectomy, alcohol ablation). Across centers, genetic testing was performed by different sequencing technologies, using gene panels reflecting the standard practice at the time of diagnosis at each center, from a limited panel encompassing sarcomeric genes to broader ones.

For all recruited participants, we collected data relating to demographics (age, sex, ethnic background), comorbidities (hypertension, diabetes), and for the HCM cohort only, gene testing results, method of patient identification (proband or cascade screening) and the presence or absence of resting left ventricular outflow obstruction on echocardiography (defined as a peak instantaneous gradient ≥30 mm Hg).

Hypertension was a clinical diagnosis based on health care records and whether patients were treated by lifestyle measures or antihypertensive agents.

Patients with apical-predominant HCM were excluded from final analysis. A specific criterion for diagnosing apical-predominant HCM, based on a body surface area (BSA)-indexed MWT of >5.6 mm/m^2, has been proposed.[24] Patients were therefore classified as having apical-predominant HCM if their thickest segment was within the apex and they met this MWT criterion.

Patients who were identified by cascade screening because of first-degree familial diagnosis were also excluded from final analysis because they have a lower threshold for hypertrophy (≥13 mm) owing to their higher pretest probability.[3]

IMAGE ANALYSIS. All CMR images were analyzed with AI to measure smooth contours of the endocardium and epicardium of the left ventricle at end-diastole.[25,26] The maximum distance between the contours was used to derive MWT. This AI algorithm has been previously clinically validated with data from numerous institutions, including patients with HCM with a test-retest precision that is superior to that provided by clinical experts. Examples of this AI algorithm's segmentation performance are shown in Supplemental Figure 1. The largest diastolic wall thickness anywhere was recorded as the MWT. The MWTs for every point within the myocardium were transformed into Cartesian coordinates to align with the 16-segment American Heart Association model.

STATISTICAL ANALYSIS. Generalized additive mixed models (GAMMs) with integrated smoothness estimation via penalized regression splines modeled the distribution of MWT using age, sex, and BSA as covariates. We accounted for nonlinearities and cohort-specific effects in MWT related to age, sex, and BSA, using restricted maximum likelihood for unbiased results and specific constraints for data stability, constructing 95% and 99.7% prediction intervals (PIs) for MWT, adjusted for age, sex, and BSA, by bootstrapping GAMMS regression coefficients.

Each included cohort had its own specific characteristics, which could have influenced the MWT distribution (eg, geographic region, ethnic diversity, CMR sequence), giving rise to random effects. Moreover, the relationship between MWT and age, sex, and body size can be nonlinear. To flexibly capture nonlinear complex relationships and account for cohort-specific random effects, we used GAMMs to model the distribution of MWT using age, sex, and BSA as covariates.

Using a GAMM, we generated predicted normal MWT values based on age, sex, and BSA. Based on the uncertainty in the regression coefficients, we generated possible MWT distributions for a given age, sex, and BSA. From this, we constructed the 95% and 99.7% PIs, within which 95% and 99.7% of individuals with the same age, sex, and BSA are expected to fall, respectively. The upper limit of the 95% PI was used to define abnormal LVH, inasmuch as only 2.5% of individuals with a given sex, age, and BSA are expected to exceed this threshold.

Although PIs are not equivalent to SDs, the 95% PI may be interpreted similarly to the range within approximately 2 SDs from the mean (z-score ≥2) and the 99.7% PI similarly to approximately 3 SDs (z-score ≥3). For ease of communication, these thresholds will be referred to as the 2 SD and 3 SD cutoffs.

All analyses were performed in R 4.2.2. A 2-tailed P value <0.05 was considered statistically

TABLE 1 Demographics of Subject Cohorts

	Reference Cohort (n = 5,067)	Population Cohort (n = 43,239)	HCM Cohort (n = 2,424)	Proband, Nonapical Variant HCM Patients (n = 1,645)
Male	2,462 (48.6)	20,860 (48.2)	1,573 (64.9%)	1,116 (67.8%)
Age, y	59.9 ± 10.3	64.1 ± 7.7	56.4 ± 14.6	57.4 ± 14.5
Height, cm	170 ± 9	169 ± 9	170 ± 10	169 ± 11
Weight, kg	72.9 ± 13.1	76.0 ± 15.1	81.9 ± 18.0	82.4 ± 18.3
BSA, m^2	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
MWT, mm	10.6 ± 1.9	11.1 ± 2.5	18.5 ± 4.6	18.7 ± 4.6
Hypertension	0/5,067 (0.0)	9,786/43,239 (22.6)	1,152/2,306 (50.0)	877/1,626 (53.9)
Diabetes	0/5,067 (0.0)	2,444/43,239 (5.7)	377/2,307 (16.3)	284/1,628 (17.4)
LVOT obstruction	-	-	678/2,041 (33.2)	553/1,426 (38.9)
Sarcomere-positive (LP/P variants)	-	-	512/1,240 (41.3)	311/843 (36.9)

Values are n (%), mean ± SD, or n/N (%). Table compares the demographics and clinical features of the Reference Cohort, Population Cohort, HCM Cohort, and the subset of Proband, nonapical variant HCM patients. Key variables include sex, age, height, weight, body surface area (BSA), maximum wall thickness (MWT), hypertension, diabetes, and LVOT obstruction. Genetic data for sarcomere-positive variants (likely pathogenic/pathogenic) are shown where available for the HCM cohorts.

HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract.

significant. Full details of the statistical analysis are expanded in the Supplemental Methods.

RESULTS

REFERENCE RANGE GENERATION. The reference cohort comprised 5,067 healthy subjects sourced from the UK Biobank[18] (n = 3,902), the Framingham Heart Study Offspring Cohort[19] (n = 590), the MyoFit46 study[20] (n = 128), and multiple independent UK healthy volunteer studies[21] (n = 447). In all, 49% were male, and the mean age was 60 ± 10 years (range: 20-88 years) (**Table 1**).

Within the GAMM framework, age, sex, and BSA together explained 36% of MWT deviance. Linear univariate analysis of MWT against demographics demonstrated increased MWT in male individuals, older persons, and those with larger BSA (Supplemental Table 1).

Demographic-adjusted LVH threshold values for sex, age, and BSA are displayed in **Table 2** (male individuals) and **Table 3** (female individuals), using both the upper 95% PI and the upper 99.7% PI. Although the upper 95% PI can be interpreted similarly to approximately 2 SDs above the mean, and the upper 99.7% PI to approximately 3 SDs, it is important to note that these PIs are based on prediction models rather than direct SDs.

Using the 95% PI for common BSA values (1.7-2.3 m^2 for male individuals, 1.5-2.1 m^2 for female individuals), the LVH threshold ranged from 12 to 17 mm for male individuals and 10 to 15 mm for female individuals. When applying the higher 99.7% PI threshold, the LVH threshold increased to 13 to 18 mm for male individuals and 12 to 16 mm for female individuals. A 3D graph showing the results of the predicted MWT, upper 95% PI and upper 99.7% PI are shown in Supplemental Figure 2.

For the purposes of analysis, the upper limit of the 95% PI was used as the LVH threshold, which is approximately analogous to 2 SDs above the mean.

Applying the 16-segment American Heart Association model, the basal segments of the left ventricle were most commonly the thickest, as shown in Supplemental Figure 3. The basal anteroseptal segment was the thickest in 70% of cases (n = 3,566), followed by the basal anterior wall in 14% (n = 683), and the basal inferoseptal wall in 4% (n = 205). Together, these 3 basal segments accounted for 88% of the thickest segments observed. In the remaining 12% of cases where other segments were the thickest, the difference between the thickest segment and the basal septum was <1 mm.

WALL THICKNESS BIAS IN THE POPULATION-BASED COHORT. The Population Cohort from the UK Biobank (n = 43,239), which included individuals with comorbidities (22.6% hypertension, n = 9,786), comprised 48% male individuals with a mean age of 64 ± 8 years (range: 45-82 years), as shown in **Table 1**.

Using the traditional LVH criteria (≥15 mm), 4.3% (n = 1,854) of subjects were classified as having LVH. These were overwhelmingly male (89%, n = 1,642), representing an 8:1 male-to-female skew. These individuals were also significantly heavier (+15.3 kg; $P < 0.0001$), taller (+5.8 cm; $P < 0.0001$), and older (+3.3 years; $P < 0.0001$) in comparison with the population mean.

In contrast, applying the demographic-adjusted LVH threshold resulted in fewer subjects classified

TABLE 2 Predicted LVH Thresholds for Male Individuals

		Age, y												
BSA		20	25	30	35	40	45	50	55	60	65	70	75	80
1.7 m^2	95% PI (~2 SD)	12	12	12	13	13	13	13	13	14	14	14	14	15
	99.7% PI (~3 SD)	13	14	14	14	14	14	15	15	15	15	15	16	16
1.8 m^2	95% PI (~2 SD)	12	12	13	13	13	13	13	14	14	14	14	15	15
	99.7% PI (~3 SD)	14	14	14	14	14	15	15	15	15	15	16	16	16
1.9 m^2	95% PI (~2 SD)	13	13	13	13	13	14	14	14	14	14	15	15	15
	99.7% PI (~3 SD)	14	14	15	15	15	15	15	15	16	16	16	16	17
2.0 m^2	95% PI (~2 SD)	13	13	13	14	14	14	14	14	15	15	15	15	16
	99.7% PI (~3 SD)	14	15	15	15	15	16	16	16	16	17	17	17	17
2.1 m^2	95% PI (~2 SD)	13	14	14	14	14	14	15	15	15	15	16	16	16
	99.7% PI (~3 SD)	15	15	15	15	16	16	16	16	16	17	17	17	18
2.2 m^2	95% PI (~2 SD)	14	14	14	14	15	15	15	15	15	16	16	16	16
	99.7% PI (~3 SD)	15	15	16	16	16	16	16	17	17	17	17	18	18
2.3 m^2	95% PI (~2 SD)	14	14	15	15	15	15	15	16	16	16	16	17	17
	99.7% PI (~3 SD)	16	16	16	16	16	16	17	17	17	17	18	18	18

Predicted LVH thresholds for male individuals based on age and BSA. Derived from the healthy volunteer Reference Cohort, these thresholds are rounded to the nearest 1 mm. The table shows values at the upper 95% and 99.7% PI, corresponding to approximately 2 and 3 SDs above the mean. BSA values span the 5th to 95th percentile of male individuals in the Population Cohort.

BSA = body surface area; LVH = left ventricular hypertrophy; PI = prediction intervals.

as hypertrophic (2.2%; n = 945) while substantially normalizing the sex skew (56% male; n = 530). This approach also attenuated the differences between those classified as hypertrophic and the population mean in terms of weight (+4.8 kg; $P < 0.0001$), height (0 cm; $P = 0.06$), and age (+2.6 years; $P < 0.0001$).

Comparing the demographic-adjusted LVH thresholds to the traditional ≥15 mm definition revealed diagnostic concordance (within 1 mm) in 17% of cases (n = 6,680). The demographic-adjusted LVH threshold was <15 mm for 48% of subjects (n = 20,859), primarily affecting female individuals, younger individuals, and those with lower BSA. Conversely, it was higher for 36% (n = 15,700), predominantly affecting male individuals, older individuals, and those with higher BSA. Eighty-nine percent of individuals had a demographic-adjusted LVH threshold between 13 mm and 17 mm.

A comparison of sex skews using the ≥15 mm criterion and a demographic-adjusted LVH threshold in

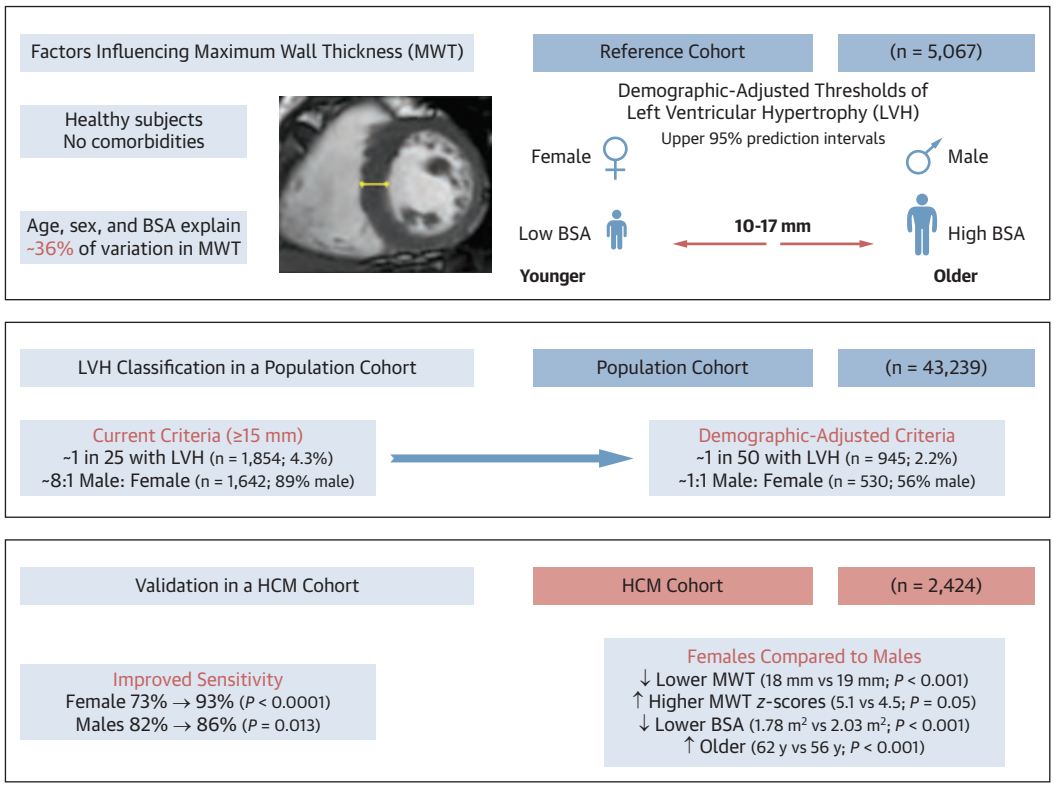
TABLE 3 Predicted LVH Thresholds for Female Individuals

		Age, y												
BSA		20	25	30	35	40	45	50	55	60	65	70	75	80
1.5 m^2	95% PI (~2 SD)	10	10	11	11	11	11	11	11	12	12	12	12	13
	99.7% PI (~3 SD)	12	12	12	12	12	13	13	13	13	13	14	14	14
1.6 m^2	95% PI (~2 SD)	10	11	11	11	11	11	12	12	12	12	12	13	13
	99.7% PI (~3 SD)	12	12	12	12	13	13	13	13	13	14	14	14	14
1.7 m^2	95% PI (~2 SD)	11	11	11	11	11	12	12	12	12	12	13	13	13
	99.7% PI (~3 SD)	12	12	12	13	13	13	13	13	14	14	14	14	15
1.8 m^2	95% PI (~2 SD)	11	11	11	11	12	12	12	12	13	13	13	13	14
	99.7% PI (~3 SD)	12	13	13	13	13	13	14	14	14	14	15	15	15
1.9 m^2	95% PI (~2 SD)	11	11	12	12	12	12	12	13	13	13	14	14	14
	99.7% PI (~3 SD)	13	13	13	13	13	14	14	14	14	15	15	15	15
2.0 m^2	95% PI (~2 SD)	12	12	12	12	12	13	13	13	13	14	14	14	14
	99.7% PI (~3 SD)	13	13	14	14	14	14	14	15	15	15	15	15	16
2.1 m^2	95% PI (~2 SD)	12	12	13	13	13	13	13	14	14	14	14	15	15
	99.7% PI (~3 SD)	14	14	14	14	14	15	15	15	15	15	16	16	16

Predicted LVH thresholds for female individuals based on age and BSA. Derived from the healthy volunteer Reference Cohort, these thresholds are rounded to the nearest 1 mm. The table shows values at the upper 95% and 99.7% PI, corresponding to approximately 2 and 3 SDs above the mean. BSA values span the 5th to 95th percentile of female individuals in the Population Cohort.

Abbreviations as in Table 2.

CENTRAL ILLUSTRATION **Demographic-Adjusted Left Ventricular Hypertrophy Thresholds for Hypertrophic Cardiomyopathy Diagnosis**



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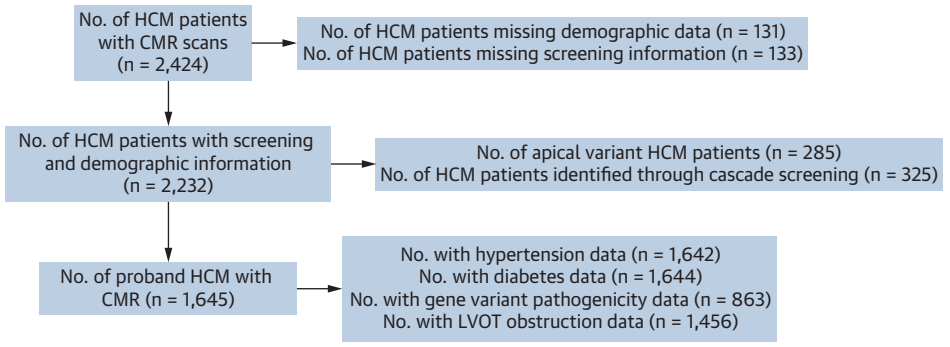
In healthy subjects, age, sex, and BSA collectively explain ~36% of the variation in MWT. Demographic-adjusted LVH thresholds show considerable range, varying with sex, BSA, and age. In a population cohort, demographic-adjusted criteria reduce LVH ascertainment, balance the male-to-female ratio, and attenuate demographic skews, compared with the current fixed threshold. Validation in an HCM cohort demonstrated improved diagnostic sensitivity for HCM, especially for female individuals. BSA = body surface area; HCM = hypertrophic cardiomyopathy.

the Population Cohort is displayed in the **Central Illustration**.

VALIDATION IN THE CLINICAL HCM COHORT. In all, 2,424 patients were enrolled from 6 specialized HCM centers across Italy, Spain, Portugal, the United States, and the United Kingdom, as illustrated in **Figure 1**. The demographic and disease characteristics are detailed in **Table 1**. In that cohort, 5.4% (n = 131) of patients lacked at least 1 key demographic data point, and 5.5% (n = 133) had no information about their method of identification (whether they were probands or identified through cascade screening), and these subjects were excluded from subsequent analyses. Additionally, 11.8% (n = 285) of patients who met the criteria for apical HCM, and 13.4% (n = 325) who were identified through cascade screening because of a first-degree familial diagnosis, were excluded from further analysis.

In total, 1,645 patients with HCM were included in the final analysis. This cohort had a mean age of 57 ± 14 years (range: 18-90 years) and an average BSA of 1.95 ± 0.24 m^2 (range: 1.21-2.94 m^2). The subjects were predominantly male (68%, n = 1,116), representing a 2:1 male-to-female ratio. The mean MWT was 19 ± 5 mm (range: 11-38 mm). Although a small proportion of patients (8.6%, n = 145) had severe hypertrophy with MWT >25 mm (8.6%; n = 145), a

FIGURE 1 Flowchart of Patients With HCM



Patients were recruited from 6 different international centers. CMR = cardiovascular magnetic resonance; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract.

substantial number (33%, n = 561) had MWT measurements between 13 mm and 17 mm (Figure 2).

A significant proportion of patients received diagnoses of HCM despite having MWT below the traditional LVH threshold (<15 mm): 27% of female individuals and 18% of male individuals. The demographic-adjusted threshold improved sensitivity in hypertrophy classification in female individuals, increasing detection from 73% to 93% ($P < 0.0001$) but also in male individuals, increasing detection from 82% to 85% ($P = 0.013$) (Figure 2).

Female patients, compared with male patients, had lower BSA (1.78 vs 2.03; $P < 0.001$), were older (62 years vs 56 years; $P < 0.001$) and had lower mean MWT (18 mm vs 19 mm; $P < 0.001$). However, despite the lower absolute MWT, female patients had higher mean z-scores for MWT (5.1 vs 4.5; $P = 0.05$).

Genetic data were available in 843 patients. Among gene-elusive patients (n = 532), female individuals had thinner MWT (18 mm vs 19 mm; $P = 0.049$) but higher z-scores for MWT (5.8 vs 5.1; $P = 0.014$). For patients with likely pathogenic/pathogenic gene variants (n = 311), female individuals compared with male individuals had thinner MWT (19 mm vs 20 mm; $P = 0.005$) but no significant difference in z-scores (6.5 vs 6.1; $P = 0.45$) (Supplemental Figure 4).

DISCUSSION

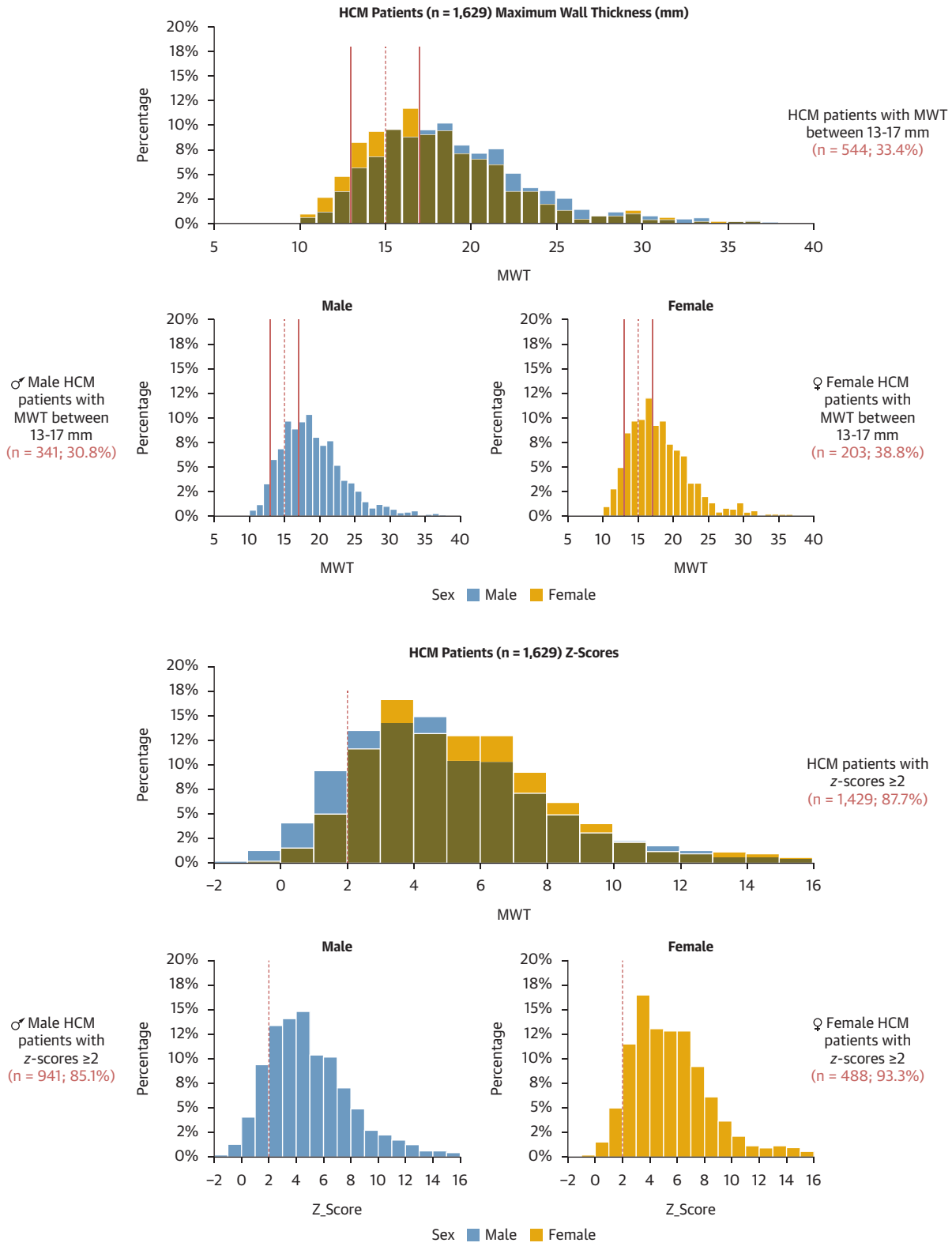
The current definition of LVH in HCM, using an MWT ≥15 mm, stems from studies conducted in the 1970s. This threshold was originally established as a highly specific measure to differentiate normal subjects from those with idiopathic hypertrophic subaortic stenosis, now known as HCM. Although the original authors recognized a strong correlation between BSA and MWT,[5] the ≥15-mm threshold has persisted as a static, binary standard in numerous past and current guidelines for diagnosing HCM with no consideration for demographic factors.

This study introduces a personalized approach to complement existing clinical and imaging criteria for diagnosing HCM. MWT was modeled in healthy subjects, accounting for the complex, nonlinear relationships between age, sex, BSA, and their collective impact on MWT. In healthy individuals, these demographic variables accounted for 36% of the variations observed in MWT measurements.

The model was then applied to the Population Cohort, which included subjects with various comorbidities with demographic-adjusted LVH thresholds ranging from 10 mm to 17 mm. The substantial variability in predicted MWT, and therefore LVH threshold values, across different demographic profiles is a nuance that is obscured when using a single, fixed cutoff value for all individuals.

The demographic-adjusted LVH threshold demonstrated different effects in the Population Cohort and the HCM Cohort. In the Population Cohort, it reduced the number of subjects classified as hypertrophic from 4.3% (n = 1,854) using the traditional ≥15-mm threshold to 2.2% (n = 945). Conversely, in the HCM Cohort, the demographic-adjusted threshold improved sensitivity in hypertrophy classification, particularly notable in female individuals, increasing detection from 73% to 93% ($P < 0.0001$) but also in male individuals, increasing detection from 82% to 85% ($P = 0.013$). A demographic-adjusted LVH

FIGURE 2 **Distribution of MWT and *z*-Scores of Patients in HCM Cohort**



HCM = hypertrophic cardiomyopathy; MWT = maximum wall thickness.

threshold may reduce overdiagnosis in the general population while also maintaining high sensitivity in the detection of HCM.

The demographic-adjusted LVH threshold led to improvements in demographic balance in the Population Cohort compared with the traditional ≥15-mm threshold. The sex distribution of subjects classified as having LVH was significantly normalized, reducing the male predominance from 89% to 56%. Furthermore, biases related to age, height, and weight were attenuated, bringing the characteristics of those classified as hypertrophic closer to the population mean. A demographic-adjusted LVH threshold therefore offers a more equitable approach to identifying LVH.

The observed sex skew with the ≥15-mm criterion may partially explain the 2:1 male-to-female ratio in HCM prevalence, which is unexpected for an autosomal-dominant condition. A demographic-adjusted LVH threshold, used alongside other diagnostic criteria, could provide a more accurate reflection of LVH prevalence across the population, with implications for clinical practice and epidemiologic understanding.

The presence of HCM patients with MWT <15 mm demonstrates that clinicians already use a comprehensive diagnostic approach beyond rigid MWT criteria. Demographic-adjusted LVH thresholds support this nuanced clinical judgment, particularly in cases with other HCM features but borderline MWT.

Female patients in the HCM cohort exhibited more severe relative hypertrophy than did to male patients, as evidenced by higher z-scores for MWT (5.6 vs 5.0; $P < 0.001$). This occurred even though female patients had a lower mean MWT (18 mm vs 19 mm; $P < 0.001$) and presented at an older age (61.9 years vs 55.2 years; $P < 0.001$). This aligns with prior studies indicating that women often present to clinics at a more advanced stage of disease. This is reflected in higher symptom burden, increased mortality risk, and a greater likelihood of requiring septal reduction therapy.[27]

These findings suggest a potential diagnostic gap. A subset of female, younger, and/or smaller individuals with HCM in the general population may not meet the current ≥15-mm MWT threshold but could be identified earlier using a predicted LVH threshold in conjunction with established clinical and imaging criteria. These patients are currently systematically being precluded from diagnosis.

As shown in **Figure 2**, a substantial proportion of HCM patients (33.4%, n = 544) have MWT between 13 mm and 17 mm, straddling the current 15-mm threshold. This distribution highlights how even a 1- to 2-mm threshold adjustment could significantly affect diagnostic rates.

Demographic-adjusted thresholds and z-scores offer crucial context for clinical decision making, particularly in borderline cases. To illustrate this, consider 2 hypothetical patients: a 64-year-old man (BSA 2.2, MWT 15 mm, predicted LVH threshold 15.6 mm, z-score 1.5) and a 30-year-old woman (BSA 1.7, MWT 14 mm, predicted LVH threshold 11.0 mm, z-score 4.0). The male patient meets the current ≥15-mm criterion yet shows only mild deviation from his predicted MWT. In contrast, the female patient falls below the 15-mm threshold but exhibits significant relative hypertrophy. Providing clinicians the continuum of z-scores enables more precise risk stratification and might influence decisions on the frequency of follow-up imaging or the threshold for initiating therapy.

Hypertension significantly contributes to LVH and often co-occurs in clinical settings with underlying HCM. However, distinguishing the hypertrophy caused by hypertension from that caused by cardiomyopathy is challenging. This complexity arises from the variability in hypertension control and its impact on myocardial remodeling. Examples include patients with consistently mild hypertension vs those with frequent severe spikes. In this study, hypertension was not included as a dependent variable for the prediction of normal MWT. Future research will focus on integrating hypertension into models for predicting MWT measurements and identifying abnormal values in patients with hypertension.

Other studies involving the UK Biobank have also examined the prevalence of HCM in the population cohort but have either excluded subjects with comorbidities likely to contribute to LVH, such as hypertension,[28] or focused on subjects with pathologic genetic variants.[29]

BSA is the predominant indexation method for cardiac metrics. However, this is controversial, with evidence for superiority of other methods of indexation using height and/or weight in different permutations. We cross-validated a separate height and weight model against the BSA model, and the results showed a negligible difference (<1 mm) in the predicted LVH threshold between the 2 models for 99.7% of the Population Cohort (Supplemental Figure 5). Given that the predicted MWT and LVH thresholds have been derived from individuals with a body mass index between 18 and 35, future work is needed to explore the nuances of how height and weight separately influence MWT in subjects with extremes of body type, including individuals with anorexia and obesity.

Future work will look at integrating our findings with other non-LVH diagnostic criteria, such as electrocardiograms and late gadolinium enhancement, to improve diagnostic criteria.

STUDY LIMITATIONS. Our analysis did not account for factors such as ethnicity, wall thickness asymmetry, and the level of physical activity. The ethnicity of the healthy reference range was primarily Caucasian. While in this study, both the Population Cohort and the HCM Cohort were also primarily Caucasian, future research must incorporate ethnically diverse normal ranges and account for athleticism. However, multiethnic and athlete data sets are scarce and are currently not available at the scale required to inform our modeling methods.

In the HCM Cohort, not all subjects had a measured MWT ≥15 mm on CMR when measured objectively with AI. Our approach intended to include all patients being actively treated in clinic as having HCM; in some patients it was as low as 11 mm. For some patients, their initial diagnoses were established based on echocardiographic measurements of MWT ≥15 mm before their inclusion in the clinic, and there are acknowledged variations in measurements between modalities.

Because of the lack of echocardiographic data from control subjects, we were not able to validate this method on echocardiography measurements, the first-line test used in the diagnosis of HCM. We used echocardiography to assess LVOT obstruction in our patient cohort but were not able to integrate echo wall thickness measurements, potentially missing potential insights.

The composition of our HCM cohort, predominantly consisting of patients with suspected HCM being monitored in specialized clinics, may not fully represent the broader HCM population. On the continuum of HCM, some patients may have left ventricular dilatation and wall thinning at end-stage HCM. However, we believe there is already an underlying selection bias within HCM clinics. Despite our patient cohort exhibiting a lower prevalence of LVOT obstruction and the reduced proportion of patients with sarcomere mutations than in previously described populations, there may still be ongoing selection bias.

CONCLUSIONS

HCM diagnosis is complex, involving multiple clinical, imaging, and genetic markers beyond MWT. The current ≥15-mm MWT threshold for LVH results in an 8:1 male:female skew in population cohorts, potentially biasing HCM diagnosis.

Our study introduces a demographic-adjusted LVH threshold and individualized z-score approach as an adjunct to existing criteria. This method shows promise in mitigating demographic biases and potentially may have a role in improving early detection and risk stratification. By providing a nuanced context for MWT interpretation, especially in borderline cases, this approach supports comprehensive clinical judgment in HCM diagnosis.

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APPENDIX For supplemental figures, table, and methods, please see the online version of this paper.