REVIEW

# Sex differences in hypertrophic cardiomyopathy: new insights

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**Purpose of review**

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, diagnosed by left ventricular hypertrophy of at least 15 mm maximal wall thickness (MWT). Recent studies reported a sex difference in clinical presentation, progression and outcome of HCM. This review provides an overview of recent studies into sex differences in HCM.

**Recent findings**

A higher number of men (55–65% of total HCM patient group) with manifest HCM has been observed, whereas female patients are older at first evaluation and diagnosis, present more frequently with symptoms, and have worse survival. Additionally, ~~females~~ have relatively smaller hearts even when corrected for body surface area (BSA), but female HCM patients have a higher interventricular septum thickness after correction for BSA.

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**Summary**

Female HCM patients are possibly in a more advanced stage of disease at time of diagnosis because they require relatively more hypertrophy to reach the diagnostic threshold of at least 15 mm MWT. Additional studies are warranted to explore sex-specific diagnostic criteria for HCM.

**Keywords**

cardiomyopathy, hypertrophic, sex differences

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease, which is diagnosed by left ventricular (LV) hypertrophy in the absence of loading conditions, such as aortic valve stenosis or hypertension [1,2]. The diagnostic criterion for HCM diagnosis is a maximal wall thickness (MWT) at least 15 mm (≥13 mm in first-degree relatives) assessed by cardiac imaging. The prevalence of HCM is estimated to range between 1 : 500 and 1 : 200, which makes it the most common genetic cardiomyopathy [3]. Over 1400 different mutations (mostly missense mutations) have been identified in 11 genes encoding for various components of the sarcomere, such as the thick and thin filaments and the Z-disc [4–9]. The most commonly mutated genes are β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*), accounting for 70% of the mutations that cause HCM [4]. However, HCM mutations are incompletely penetrant as the genotype does not accurately predict severity of the disease. There is a large phenotypic heterogeneity in people who carry HCM-associated mutations; the clinical course of HCM includes normal life expectancy without or with mild symptoms, sudden cardiac death (SCD), atrial arrhythmias and progressive heart failure. Additionally, family members with the same mutation do not necessarily have the same symptoms or disease progression, and age of disease onset varies significantly [5,10]. Contributing to the phenotypic heterogeneity of HCM is a sex difference in clinical presentation, progression and outcome of the disease. Compared with other cardiac conditions, the description of sex differences in HCM is still in an early stage. This review provides an overview of recent studies on sex differences in HCM, which are schematically illustrated in Fig. 1.

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## KEY POINTS

- Numerous studies have observed a male predominance in HCM patients, whereas female HCM patients are older at first evaluation and diagnosis, and present more frequently with symptoms.
- Female HCM patients have lower 5-year and 10-year survival estimates than male HCM patients.
- HCM mutation carriers with a smaller heart (mostly women) requires relatively more hypertrophy to reach the diagnostic criterion of MWT at least 15 mm.
- ~~Females~~ could be in a more advanced stage of disease at the time of HCM diagnosis. Additional studies are warranted to investigate the need for sex-specific diagnostic HCM criteria.

## CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT AND PROGNOSIS

Clinicians may suspect HCM when a patient present with cardiac-related symptoms like dyspnea, chest pain, palpitations and syncope, or asymptomatic signs like a heart murmur or an abnormal electrocardiogram (ECG), especially when found during screening of first-degree relatives. Noninvasive cardiac imaging [echocardiography and/or cardiac magnetic resonance (CMR)] leads to the diagnosis of HCM when a MWT of at least 15 mm is measured. Genetic screening is recommended to confirm the diagnosis when patients exhibit signs and symptoms of disease suggestive of specific causes of HCM, and when it enables cascade genetic screening of family members [1]. When an HCM mutation is identified in the patient and certain family members, these family members will undergo regular screening with ECG and echocardiography to monitor presence or

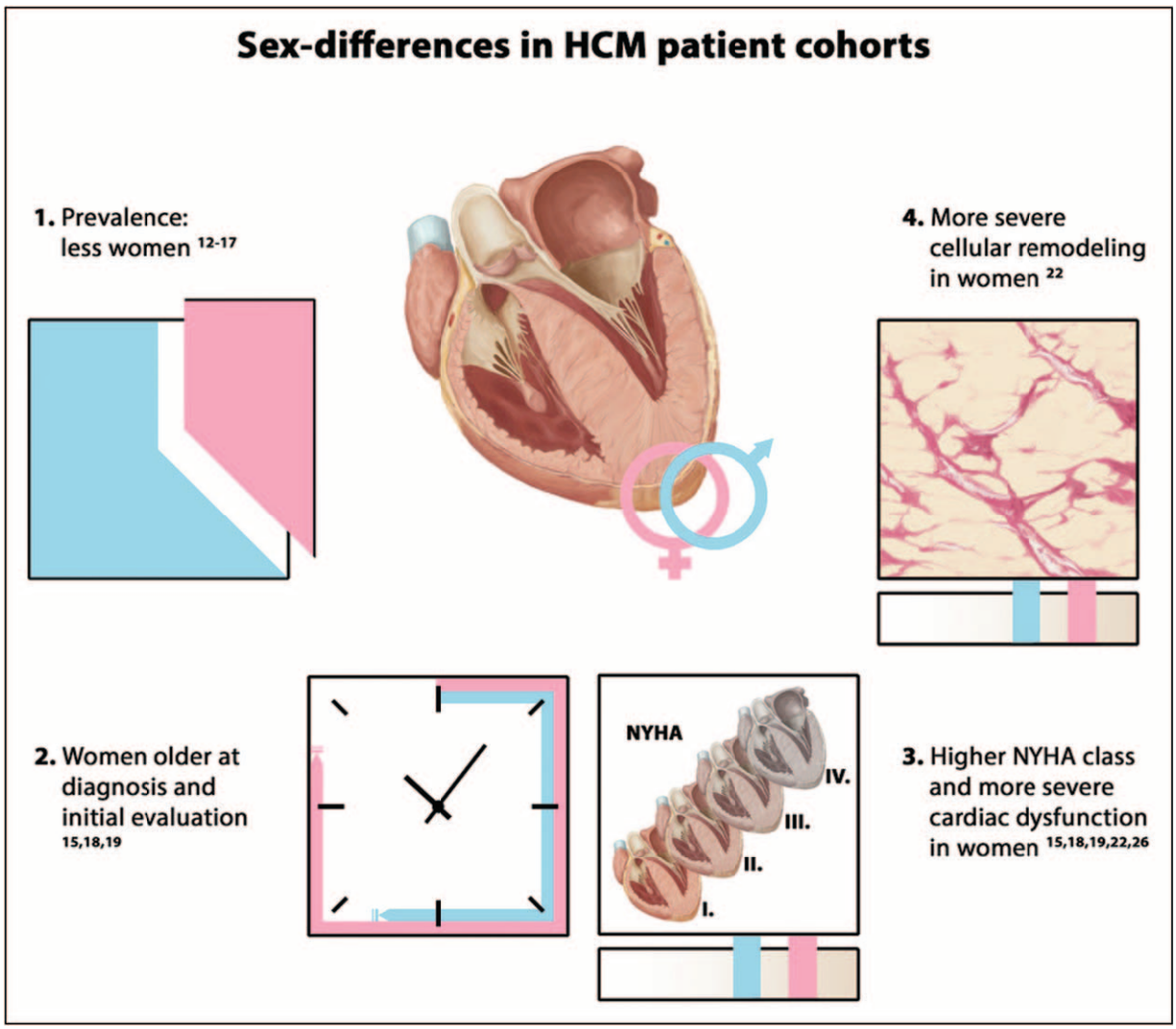


**FIGURE 1.** Schematic overview of reported sex-differences in hypertrophic cardiomyopathy. Point 4 adapted from [22▪].

progression of disease [11]. Presentation of HCM, either by symptoms or through screening of the mutation carriers, differs between sexes. A higher number of men (55–65% of total HCM patient group) with manifest HCM has been observed in several large patient cohorts [12–17], whereas ~~female patients~~ are older at first evaluation and diagnosis, and present more frequently with symptoms [15,18▪▪,19▪] (Fig. 1). It remains to be determined whether the sex-related age-difference in diagnosis is caused by inadequate clinical recognition in ~~females~~, slower disease progression because of protective sex hormones [20,21], or a lack of sex-specific diagnostic criteria. Female HCM patients are more likely to exhibit left-ventricular outflow tract obstruction (LVOTO) at rest and have higher gradients both at rest and during provocation [18▪▪,19▪]. At time of LV septal reduction therapy to reduce LVOTO gradients, ~~females~~ are on average 4–7 years older [18▪▪,22▪]. A survival analysis in 3569 HCM patients found that ~~females~~ have worse survival; female 5-year and 10-year survival estimates were significantly lower than survival estimates in men, even when corrected for age [18▪▪]. Lower female survival rates were not found in other studies [15,19▪,23], which can be explained by the fact that these studies had smaller cohorts with a relatively healthier patient population [18▪▪].

## CARDIAC FUNCTION

The clinical course of HCM is characterized by subtle asymptomatic impairments in diastolic function in

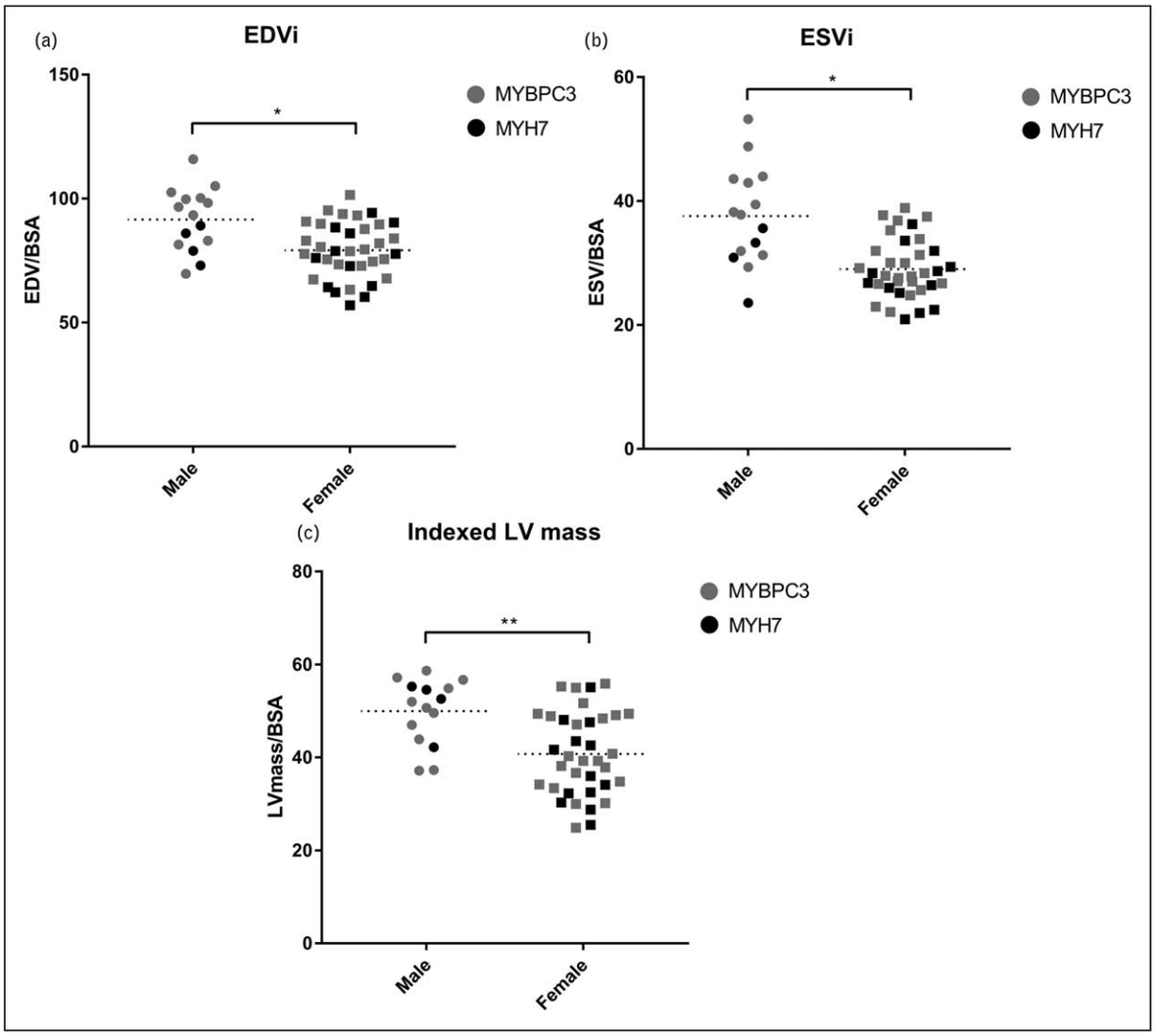


**FIGURE 2.** Sex-differences in cardiac dimensions of hypertrophic cardiomyopathy mutation carriers assessed by cardiac magnetic resonance imaging. Individuals with *MYH7* and *MYBPC3* mutations are indicated with black and gray symbols, respectively. ~~Females~~ have a lower end-diastolic volume (EDV; a), end-systolic volume (ESV; b) and LV mass (c), after correction for body surface area (BSA). $^{*}P < 0.05$; $^{**}P < 0.005$. CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy.

mutation carriers [24,25], which in some people progresses into diastolic dysfunction with normal or supernormal systolic function [LV ejection fraction (LVEF) >65%]. As the disease progresses, diastolic function decreases further accompanied by a decline in systolic function back to normal or reduced LVEF [11]. Female HCM patients showed more severe diastolic dysfunction than male patients evident from higher $E/e'$ and $E/A$ ratios, which are indicators for LV filling pressure [18▪▪,22▪]. In addition, a higher degree of systolic impairment was found in female compared with male HCM patients in a recent study [19▪]. These sex differences in cardiac function are in line with reports of decreased exercise capacity and higher NYHA classifications in female compared with male HCM patients [15,18▪▪,26].

## CARDIAC DIMENSIONS

Cardiac remodeling in HCM is characterized by asymmetric thickening of the LV wall, which most frequently affects the interventricular septum (IVS). IVS thickness may increase during progression of the disease, with a diagnostic criterion of MWT at least 15 mm and at least 13 mm for first-degree relatives of HCM patients. Our CMR studies of LV dimensions show sex differences in asymptomatic mutation carriers. Recurrent CMR scans were performed in 29 HCM mutation carriers (16 *MYBPC3*, 13 *MYH7* mutations) to measure LV end-diastolic volume (EDV), LV end-systolic volume (ESV) and LV mass. Data analysis was performed by a mixed model analysis with correction for repeated measures. After correction for body surface area (BSA), female mutation carriers on average have a 10.4 ml/m$^2$ smaller EDV ($P = 0.01$; Fig. 2a), a 6.2 ml/m$^2$ smaller ESV ($P = 0.007$; Fig. 2b) and a 9.6 g/m$^2$ lower LV mass ($P < 0.001$; Fig. 2c) than men. This analysis shows that the female heart is smaller than the male heart when normalized to BSA. These findings are in line with earlier studies that used CMR to analyze cardiac dimensions of healthy people, and found that the female heart is significantly smaller after correction for BSA or height [27–31]. Echocardiography performed in 51 manifest HCM patients (40 *MYBPC3*, 11 *MYH7* mutations) at the time of cardiac surgery showed that female patients have a significantly higher IVS after correction for BSA (Fig. 3). These cardiac imaging studies indicate that HCM mutation carriers with a smaller heart (mostly women) require relatively more hypertrophy to reach the diagnostic criterion of MWT at least 15 mm (Fig. 4). As this diagnostic criterion does not account for the relatively smaller female hearts, female patients could be in a more advanced stage of disease at time of diagnosis, causing a delay in treatment.

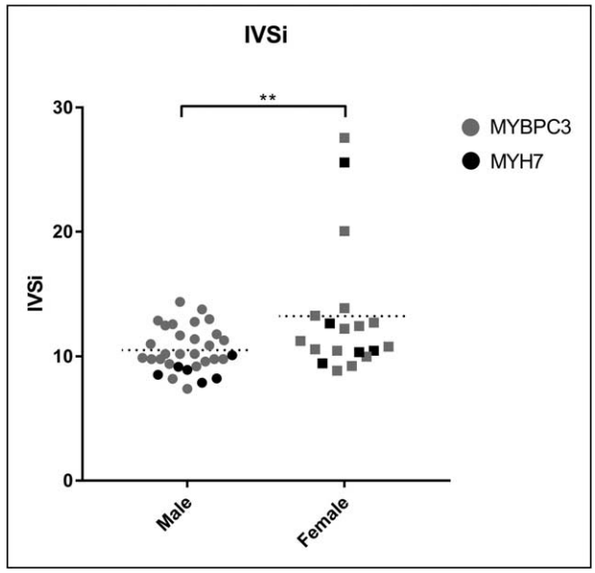


**FIGURE 3.** Analysis of echocardiographic analysis showed a higher interventricular septum thickness (corrected for BSA) in women than in men [22▪]. $^{**}P < 0.005$ (Reproduced with permission from reference 22). BSA, body surface area; IVS, interventricular septum.

## CELLULAR AND MOLECULAR CHANGES

The most recent report of the working group of myocardial function of the European Society of Cardiology describes that inefficient sarcomere contraction sets in motion a cascade of cellular changes, which can ultimately lead to HCM [32]. Inefficient sarcomere contraction has been proposed to lead to cellular energy depletion, impairing calcium homeostasis and mitochondrial function [32]. A study on myectomy samples of HCM patients did not find a sex difference in myofilament calcium sensitivity, but the expression of calcium-handling proteins was reduced in female patients compared with men [22▪]. Additionally, this study found a higher degree of fibrosis in female myectomy samples and observed more compliant titin isoform, which seems to be related to increased diastolic dysfunction in female patients as titin plays a role in regulating stiffness of the cardiomyocytes [33]. Overall, the latter study showed more advanced cardiac remodeling in female HCM patients compared with male HCM patients at the time of cardiac surgery (Fig. 1).

## MECHANISMS BEHIND SEX DIFFERENCES

The mechanisms behind sex differences in HCM are currently not well understood. Possible explanations are sought in female interaction with

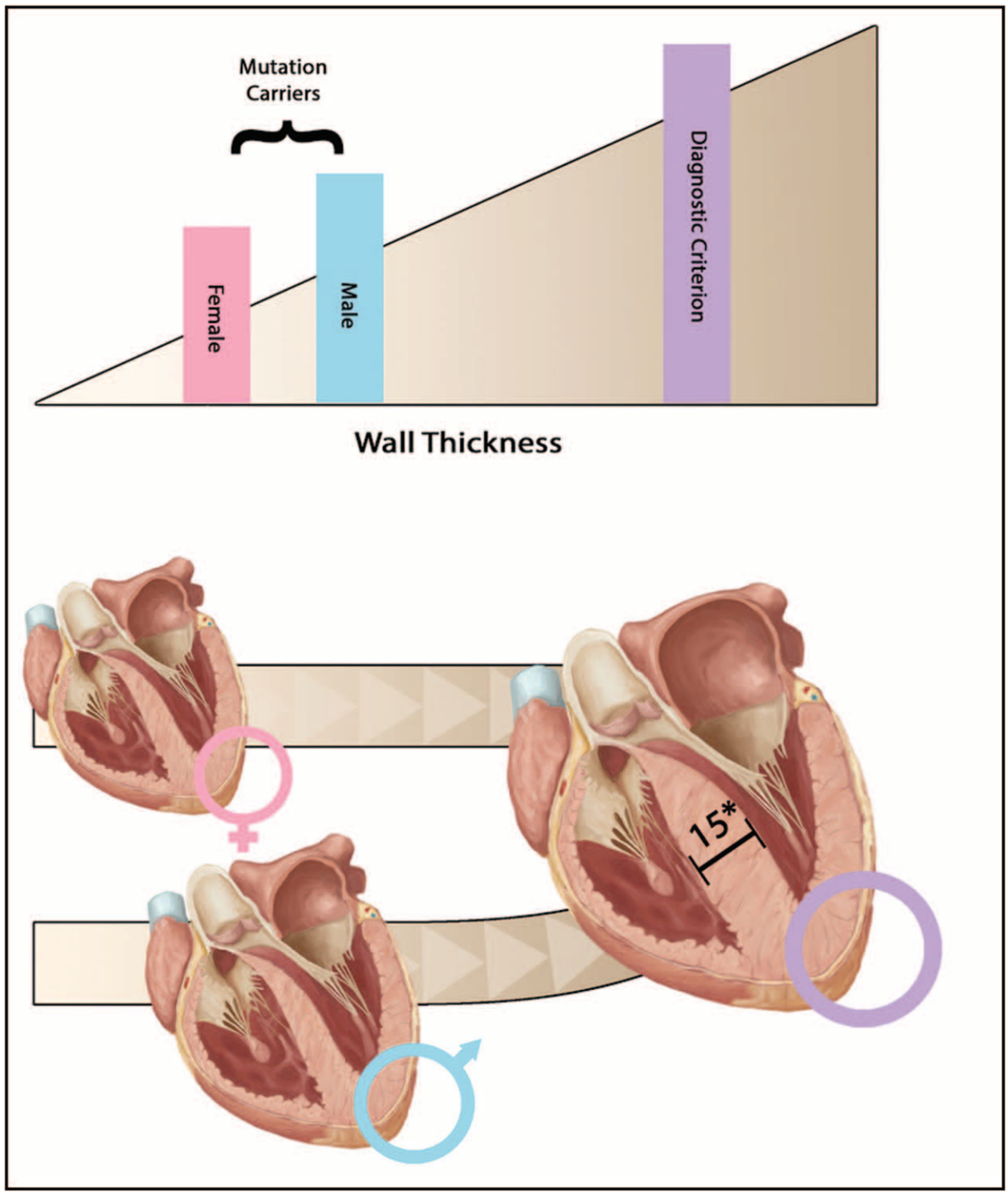


**FIGURE 4.** Schematic to illustrate that more cardiac hypertrophy is needed in female than in male hypertrophic cardiomyopathy mutation carriers. *In first degree relatives of HCM patients, the diagnostic criterion for hypertrophic cardiomyopathy is a maximal wall thickness at least 13 mm. HCM, maximal wall thickness.

healthcare: a decreased awareness and suspicion of disease, leading to under-recognition and delay in diagnosis. Reports of sex differences in hypertrophic response, fibrosis and gene expression suggest that physiological sex differences may also play a role [22▪,34]. Studies in HCM animal models have demonstrated cardioprotective effects of estrogen and estrogen receptor-deficient mice show increased cardiac remodeling by oxidative stress [35,36].

## CONCLUSION

Females with HCM are older when they are diagnosed and treated. Additionally, women have a higher degree of diastolic dysfunction, lower exercise capacity, are more symptomatic and have worse survival. There is a possibility that female HCM patients experience a delay in diagnosis and treatment because of a lack of diagnostic criteria that account for body size. Females have smaller hearts even after correction for BSA, which could mean they are in a more advanced stage of disease at the time of HCM diagnosis as they require more hypertrophy to reach the threshold of 15 mm MWT (Fig. 4). Additional studies are warranted to investigate the need for sex-specific diagnostic HCM criteria.

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### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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