Journal of the American Heart Association

ORIGINAL RESEARCH

Is There a Sex Difference in the Prognosis of Hypertrophic Cardiomyopathy? A Systematic Review and Meta-Analysis

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BACKGROUND: It is still unclear whether there is a sex difference in the prognosis of patients with hypertrophic cardiomyopathy (HCM). Therefore, we performed a meta-analysis to elucidate the association between sex and adverse outcomes in patients with HCM.

METHODS AND RESULTS: The PubMed, Cochrane Library, and Embase databases were used to search for studies on sex differences in prognosis in patients with HCM up to August 17, 2021. Summary effect sizes were calculated using a random effects model. The protocol was registered in PROSPERO (International prospective register of systematic reviews) (registration number- CRD42021262053). A total of 27 cohorts involving 42 365 patients with HCM were included. Compared with male subjects, female subjects had a higher age at onset (mean difference=5.61 [95% CI, 4.03–7.19]), a higher left ventricular ejection fraction (standard mean difference=0.09 [95% CI, 0.02–0.15]) and a higher left ventricular outflow tract gradient (standard mean difference=0.23 [95% CI, 0.18–0.29]). The results showed that compared with male subjects with HCM, female subjects had higher risks of HCM-related events (risk ratio [RR]=1.61 [95% CI, 1.33–1.94], I^2=49%), major cardiovascular events (RR=3.59 [95% CI, 2.26–5.71], I^2=0%), HCM-related death (RR=1.57 [95% CI, 1.34–1.82], I^2=0%), cardiovascular death (RR=1.55 [95% CI, 1.05–2.28], I^2=58%), noncardiovascular death (RR=1.77 [95% CI, 1.46–2.13], I^2=0%) and all-cause mortality (RR=1.43 [95% CI, 1.09–1.87], I^2=95%), but not atrial fibrillation (RR=1.13 [95% CI, 0.95–1.35], I^2=5%), ventricular arrhythmia (RR=0.88 [95% CI, 0.71–1.10], I^2=0%), sudden cardiac death (RR=1.04 [95% CI, 0.75–1.42], I^2=38%) or composite end point (RR=1.24 [95% CI, 0.96–1.60], I^2=85%).

CONCLUSIONS: Based on current evidence, our results show significant sex-specific differences in the prognosis of HCM. Future guidelines may emphasize the use of a sex-specific risk assessment for the diagnosis and management of HCM.

Key Words: hypertrophic cardiomyopathy ■ meta-analysis ■ prognosis ■ sex

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited cardiovascular diseases, with a prevalence of 0.2%.[1] According to the global burden of disease, the mortality rate caused by cardiomyopathy was 0.42 in 2019. Sex-based differences in the clinical presentation of HCM are becoming increasingly recognized. Evidence from earlier epidemiological studies showed that female subjects are underrepresented among patients with HCM; however, those diagnosed at an older age have a higher symptom burden than male subjects.[2–4]

Subsequently, several reports showed that female subjects with HCM have a high risk of cardiovascular

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This manuscript was sent to Mark W. Russell, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026270

For Sources of Funding and Disclosures, see page 19.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Based on observational studies, female patients with hypertrophic cardiomyopathy have higher age onset, higher left ventricular ejection fraction, and higher left ventricular outflow tract gradient.
- Female sex is associated with a worse prognosis in patients with hypertrophic cardiomyopathy.
- There is no significant statistical association between sex and atrial fibrillation, ventricular arrhythmia, or sudden cardiac death in patients with hypertrophic cardiomyopathy.

What Are the Clinical Implications?

- Future guideline may emphasize the sex-specific risk assessment, diagnosis, or management for hypertrophic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

ASA	alcohol septal ablation
HCM	hypertrophic cardiomyopathy
MD	mean difference
MYBPC3	myosin-binding protein C3 gene
NOS	Newcastle-Ottawa Scale
SCD	sudden cardiac death

death and all-cause mortality.[5–9] For example, an analysis by the Mayo Clinic comprising 3673 patients with 10.9 years of follow-up showed that female sex was associated with poorer overall survival.[10] These results strongly suggest a potential sex difference in the prognosis of HCM, although several cohorts have shown no sex-based difference in all-cause mortality outcomes.[11–13] Notably, the 2020 American College of Cardiology/American Heart Association guidelines for the management of HCM have yet to provide specific comments about sex differences in prognosis.[14] Clarifying this point is important for the management and treatment of HCM. Given this background, we performed a meta-analysis to elucidate the association between sex and outcomes of HCM.

METHODS

The data sets used and analyzed in the current study are available from the corresponding author on reasonable request.

This present study reported the results by the guidelines of the Preferred Reporting Item for Systematic Review and Meta-Analysis 2020 (Table S1). The protocol was registered with PROSPERO (http: www.york.ac.uk/inst/crd) registration number- CRD42021262053.

Literature Search

The PubMed, Cochrane Library, and Embase databases were used as search libraries. In addition, we searched other sources, such as the American College of Cardiology website (https://www.acc.org/) and the *Circulation* website (https://www.ahajournals.org/journal/circ). Without language restriction, we used the following Medical Subject Headings to retrieve advanced articles up to August 17, 2021: (1) for patients: "hypertrophic cardiomyopathy," "hypertrophic cardiomyopathies," and "hypertrophic obstructive cardiomyopathies," and for exposure: "sex," and "gender." Table S2 shows the detailed statement of the search strategies.

Study Selection

We used the Endnote X9 database, a reference management software, to organize all the studies. All the titles and abstracts were reviewed to consider eligibility for inclusion. Then, the full-text evaluation was performed after initial identification.

The inclusion criteria were as follows: (1) cohort studies on the association between sex and prognosis in HCM. Sex is the state of being either male or female at the biological level; HCM is an inherited cardiomyopathy characterized by asymmetric hypertrophy of the ventricles. According to the 2020 American Heart Association/American College of Cardiology guidelines for the management of hypertrophic cardiomyopathy, HCM refers specifically to a group of cardiac diseases characterized by left ventricular hypertrophy attributable to variants in the genes encoding myosin or of unknown pathogenesis. HCM in adults is diagnosed when a 2-dimensional echocardiogram or cardiac magnetic resonance imaging shows a maximum end-diastolic thickness of ≥15 mm anywhere in the left ventricle and there is no other cause of myocardial hypertrophy, and 13–14 mm of myocardial hypertrophy can also be diagnosed as HCM if there is a positive genetic test or if there is a family member with HCM; (2) patients in the study were adults (aged >18 years) who were diagnosed with HCM by echocardiography; and (3) studies showing odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) and their corresponding 95% CIs or providing data to calculate these risk estimates.

We excluded studies with the following conditions: (1) reviews and studies with insufficient data; and (2) articles with data on postoperative in-hospital mortality, considering the influence of postoperative complications. Accordingly, if the same population was used in

multiple studies, then we included the most informative article.

Outcome Definitions

Atrial fibrillation (AF) was defined as an irregular heart rhythm without distinct P-waves documented on ECG. Ventricular arrhythmia involved the ventricular arrhythmia composite end point, appropriate implantable cardioverter defibrillator (ICD) therapy, ventricular tachycardia, and/or fibrillation. HCM-related events were defined as (1) heart failure (HF) presentation, HF admission, HF worsening or progression; (2) stroke; and (3) HCM-related composite events (related to all the above events). HCM-related death involved (1) HF-related death and (2) stroke death. Major cardiovascular events were defined as cardiovascular-related death, HCM-related cardiovascular complications, fatal arrhythmias, stroke, receiving implantable cardioverter defibrillator treatment, or undergoing heart transplantation. The details of the composite end point and noncardiovascular death of each included study are shown in Table S3.

Data Extraction and Quality Assessment

Two researchers (X.L. and Z.T.) independently extracted the information from the included literature, including author, publication year, country, sample size, duration of follow-up, participants' information (mean age, sex, age at diagnosis, left ventricular ejection fraction [LVEF]), outcomes, and adjusted variables.

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of observational studies. The scores range from 0 to 9 to evaluate the selection, comparability, and outcome of articles. Studies with NOS scores >7 were considered high quality.[15]

Statistical Analysis

Age expressed as quartiles and medians are converted to the mean and SD to explore age differences between sexes.[16] To elucidate the baseline differences between sexes in patients with HCM, we pooled the mean age of male subjects and female subjects using the inverse-variance method and random model, respectively.

OR is approximately equivalent to RR in retrospective studies when the incidence of the study outcome is equal to the population prevalence or the outcome is rare.[17] In addition, HR and RR have approximately the same meaning in prospective studies and can approximate each other in the same conduction.[18] Therefore, the RRs and 95% CIs were pooled by a random-effects model. We estimated the effect size by calculating the natural logarithm of the RR (log [RR]) and its standard error (SElog [RR]). For those studies that did not provide effect size, we calculated them by events and total numbers of patients in female groups and male groups. Considering that age was the most important confounding factor, additional sensitivity analyses were performed by excluding studies without adjustment for age. In addition, we removed the univariate analysis and then performed a sensitivity analysis by removing the literature 1 by 1.

Predefined subgroup analyses included mean age (<50 years old and ≥50 years old), follow-up time (<5 years and ≥5 years), region (America, Europe, and Asia), sample size (<1000 and ≥1000), study design (retrospective and prospective cohort), population (the methods of treatment patients involved septal myectomy or alcohol septal ablation), and NOS quality assessment (≤7 and >7).

Review Manager (RevMan) version 5.40 (The Cochrane Collaboration 2014; Nordic Cochrane Center Copenhagen, Denmark) was used for the statistical analysis. A P value of <0.05 was considered statistically significant.

Heterogeneity Test and Publication Bias

We calculated statistical P values using the Q-test, with a P value<0.1 representing a significant difference between the 2 groups. We applied I^2 statistics to estimate the total variability due to heterogeneity.[19] Funnel plots and Egger's and Begg's tests were used to test for the presence of publication bias. Egger's and Begg's tests with a P value <0.05 were considered statistically significant.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, implementation, reporting, or dissemination plans of our research.

RESULTS

Study Selection

As shown in Figure 1, 1525 publications and 13 conference abstracts were identified in the initial literature search (PubMed=684; Cochrane Library=3; Embase=838; other source=13). After excluding duplicates and screening the titles and abstracts, 83 remained for full-text assessment. Thirty-one studies were excluded for the following reasons: (1) studies without data of interest (n=4); (2) certain publication types with no data (n=7); (3) studies without appropriate methods (n=3); (4) studies that did not focus on HCM (n=6); (5) studies that did not target certain populations (n=2) or outcomes (n=8); and (6) duplicated cohorts (n=1). All the excluded studies with the corresponding reasons are shown in Table S4. Ultimately, 27 studies with

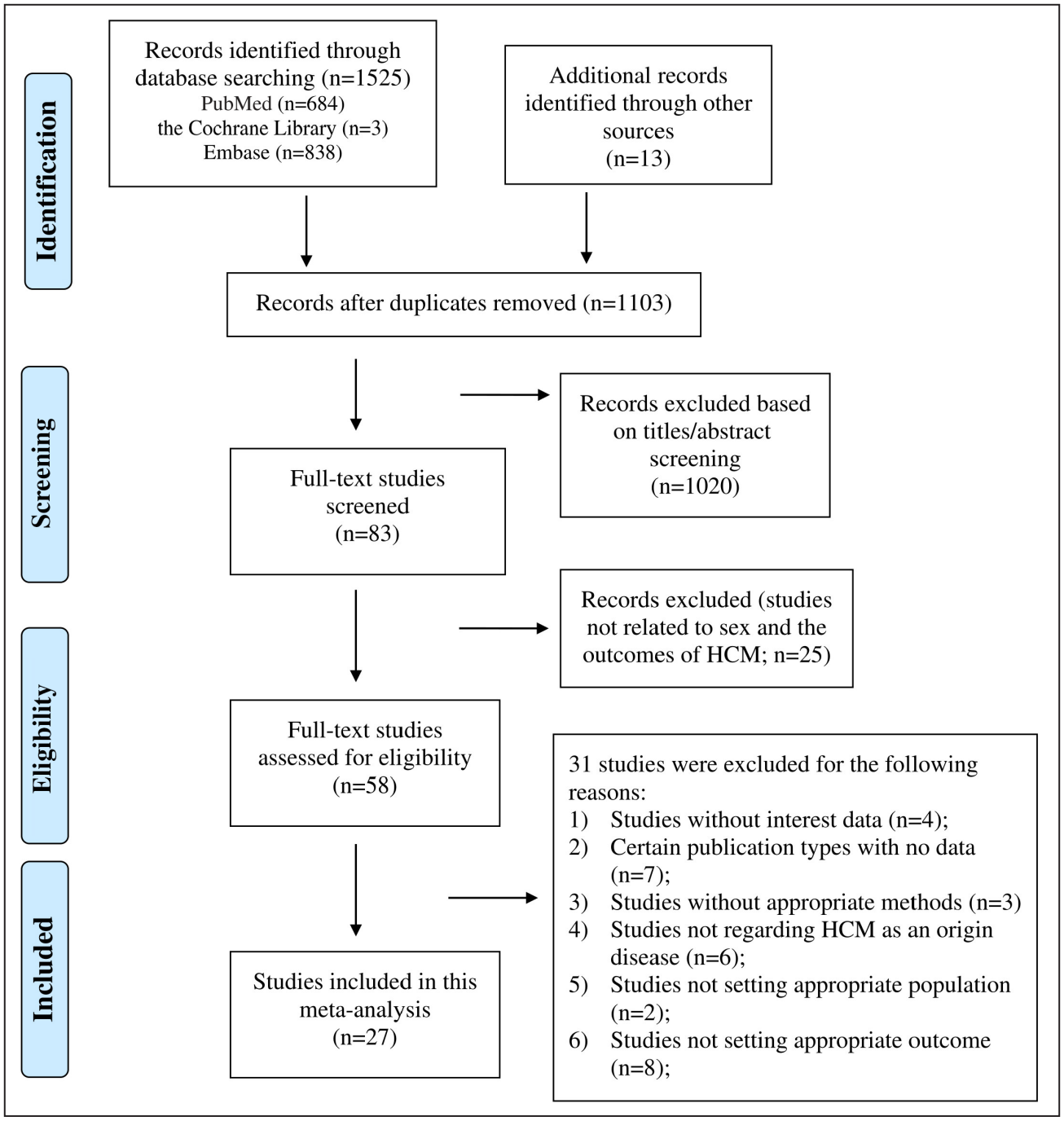

Figure 1. Flowchart of study selection in the systematic review and meta-analysis of sex difference in the prognosis of hypertrophic cardiomyopathy.
Other sources include the American College of Cardiology website and *Circulation* website. HCM indicates hypertrophic cardiomyopathy.

42 365 individuals (27 471 male subjects and 14 894 female subjects) were included.[2,5–7,9–11,13,20–38]

Study Characteristics

The basic characteristics of the included studies are presented in Table 1. These studies were published from 2001 to 2021, and the sample sizes varied from 50 to 9524 patients. The mean age of the patients ranged from 42 to 63 years, and the follow-up ranged from 2.1 to 13.0 years. Eleven of them were retrospective cohort studies, and the others were prospective cohort studies. Eight studies were from North America (6 from the United States and 2 from Canada), 9 were

Table 1. Basic Characteristics of the Articles Included in the Meta-Analysis of Sex Difference in the Prognosis of Hypertrophic Cardiomyopathy

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Olivotto et al, 2001, Italy[36]	PC	Azienda Ospedaliera Careggi; and Minneapolis Heart Institute, patients with HCM	9.1 y; 107	50.0; 57.0	NA	NA	NA	NA	AF	1.11 (0.70–1.70), male	Univariate analysis
Ho et al, 2004, China[25]	RC	Queen Mary Hospital, patients with HCM	5.8 y; 118	54.0; 52.5	NA	14.0/14.0	68.0/72.0	NA	Major cardiovascular events	5.86 (1.77–7.21)	Age at presentation, family history of HCM, NYHA class III/IV, ECG features at presentation, types of HCM
Woo et al, 2005, Canada[7]	PC	Toronto General Hospital Obstructive HCM population after septal myectomy	7.7 y; 338	47.0; 60.1	NA	NA	NA	NA	HF (HF worsening)	3.60 (2.00–6.70)	Age, history of preoperative AF, LA diameter, septal/posterior thickness ratio, concomitant CABG
									Major cardiovascular events	3.30 (2.00–5.40)	
Olivotto et al, 2005, Italy[2]	PC	Azienda Ospedaliera Careggi; Minneapolis Heart Institute; Tufts-New England Medical Center, patients with HCM	6.2 y; 969	42.0; 59.4	18.0/6.0	NA	NA	62.0/58.0	HF (HF progression)	1.50 (1.11–2.00)	Age
									HCM-related death	52/58	
									SCD	26/33	
									Noncardiac death	36/22	
Lee et al, 2007, China[6]	RC	A tertiary referral center in Taiwan, patients with HCM	5.3 y; 163	60.9; 51.5	NA	NA	NA	NA	All-cause mortality	2.99 (1.13–9.87)	LVOT obstruction, AF
Ball et al, 2011, Canada[8]	PC	Toronto General Hospital, patients with obstructive HCM	7.2 y; 649	51.0; 56.2	NA	NA	NA	NA	HCM-related death	2.10 (1.20–3.60)	Age, septal thickness, resting LVOT gradient, invasive treatment
									All-cause mortality	2.00 (1.30–3.20)	
Wang et al, 2014, China[9]	PC	Fuwai Hospital, patients with HCM	4.0 y; 621	47.5; 74.1	NA	0.6/0.7	67.1/67.5	81.9/71.9	All-cause mortality	2.19 (1.21–3.95)	Age, syncope (without any invasive treatment, including ICD and septal reduction therapy), SCD family history, maximum LV wall thickness, LA diameter, AF, LVOT obstruction (without septal reduction therapy) and NYHA class at enrollment.
									Cardiovascular death HF (chronic HF/HF progression)	2.19 (1.17–4.09) 1.73 (1.12–2.69)	
									SCD	7/12	
									HF-related death	6/9	
									Ventricular arrhythmia	1/3	
									AF	12/28	
									Stroke	10/19	

(*Continued*)

Table 1. Continued

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Terauchi et al, 2015, Japan[37]	PC	Kochi Medical School Hospital, patients with HCM	13.0 y; 50	47.0; 54.0	17.0/0	NA	67.0/65.0	NA	HCM-related death	3/5	Univariate analysis
									HCM-related events	11/7	
									HF	10/5	
Debonnaire et al, 2017, Netherlands[22]	PC	Leiden University Medical Center, patients with HCM	4.8 y; 242	53.0; 64.5	NA	NA	NA	NA	AF (new-onset AF)	1.41 (0.75–2.63), male	Univariate analysis
Geske et al, 2017, United States[10]	RC	Mayo Clinic, patients with HCM	12.7 y; 3673	55.0; 54.8	45.0/35.0	6.0/7.0	71.0/69.0	36.0/23.0	All-cause mortality	1.13 (1.03–1.22)	Age, NYHA Class III/IV symptoms, and history of AF, CAD, hypertension, ICD implantation, and beta receptor antagonist use
Ho et al, 2018, United States[5]	RC	SHARE registry, patients with HCM	5.4 y; 4591	44.3; 62.9	NA	NA	NA	NA	Composite end point	0.88 (0.77–1.01)	Family proband status, SARC+, SARC VUS and race
Kubo et al, 2018, Japan[30]	PC	Kochi Cardiomyopathy Network, patients with HCM	6.1 y; 293	56.0; 67.2	NA	NA	NA	NA	HCM-related events	0.93 (0.54–1.60), male	Age at registration, NYHA class III, presence of AF, maximum LV wall thickness, LVFS, and presence of LVOT obstruction
Van Velzen et al, 2018, Netherlands[13]	RC	Erasmus Medical Center in Rotterdam, patients with HCM	6.8 y; 1007	52.0; 61.6	NA	6.0/4.0	NA	NA	All-cause mortality	1.25 (0.91–1.73)	Family relatedness
									Cardiovascular death	1.22 (0.83–1.79)	
									SCD	0.75 (0.44–1.30)	
									HF-related death	1.77 (0.95–3.27)	
									Stroke- related death	5.57 (0.55–56.8)	
									Noncardiac death	2.11 (1.21–3.69)	
Choi et al, 2019, Korea[21]	PC	Two tertiary referral centers, patients with HCM	4288 person-years; 730	57.1; 75.5	NA	NA	NA	NA	SCD	3.83 (1.39–10.60)	HCM SCD-risk score

(*Continued*)

Table 1. Continued

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Lorenzini et al, 2019, Italy[32]	RC	7 European centers, patients with HCM	6.1 y; 4893	49.2; 63.9	17.1/7.5	15.9/17.1	66.0/65.0	10.0/8.0	Composite end point	1.19 (1.06–1.30)	Age at presentation, previous VF/VT, NYHA class, EF ≤50%, MWT, LA diameter, LVOT max, AF, NSVT on Holter, family history of sudden death, syncope, septal myectomy, ASA
									HF-related death	1.44 (1.25–1.59)	
									SCD	0.80 (0.40–1.10)	
									All-cause mortality	2.87 (2.57–3.19)	
									HCM-related death	51/52	
									Noncardiac death	96/114	
Ghiselli et al, 2019, Italy[23]	RC	IRCCS Sacro Cuore Don Calabria Hospital, patients with HCM	5.9 y; 292	46.0; 72.3	11.0/6.0	NA	67.0/67.0	14.0/18.0	Composite end point	2.32 (1.04–5.22)	Univariate analysis
Jang et al, 2019, Korea[28]	PC	Inha University Hospital, patients with nonobstructive HCM	34.0 mo; 202	63.0; 69.8	14.8/2.1	NA	65.1/64.9	NA	HF (HF presentation)	5.01 (2.05–12.26)	Age
									Cardiovascular death	5.18 (1.32–20.34)	
									HF (HF hospitalization)	6.86 (1.43–32.99)	
Lu et al, 2019, United States[33]	RC	Johns Hopkins HCM Registry, patients with HCM	2.1 y; 728	53.3; 62.0	21.0/7.0	NA	67.0/65.0	35.0/26.0	HF	3.00 (1.10–8.40)	Age, NYHA III-IV, LA diameter, and LV global longitudinal peak systolic strain
									Composited end point	1.90 (1.20–2.90)	
									AF	18/12	
									Ventricular arrhythmia	5/9	
									All-cause mortality	4/2	

(*Continued*)

Table 1. Continued

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Meghji et al, 2019, United States[34]	RC	Mayo Clinic HCM population after septal myectomy	8.2 y; 2506	55.1; 55.0	90.8/84.8	12.8/14.2	73.0/70.0	67.0/50.0	All-cause mortality	0.98 (0.76–1.26)	Age, year of surgery, BMI, diabetes, NYHA class, amiodarone, pacemaker using, NSVT, hypertension, disopyramide, use of ACEi or angiotensin receptor blockers, presyncope, dyslipidemia, prior septal reduction, syncope, mitral valve regurgitation grade, race, β-blocker, calcium-channel blocker, family history of HCM and SCD, ethnicity, anteroseptal wall thickness, ICD.
Rowin et al, 2019, United States[11]	PC	Tufts HCM Institution, patients with HCM	4.7 y; 2123	47.2; 62.6	39.0/23.0	24.0/25.0	64.0/63.0	NA	SCD	0.92 (0.60–1.50)	Age
									All-cause mortality	1.32 (0.92–1.91)	
									Noncardiac death	55/46	
									Cardiovascular death	4/3	
									HCM-related death	1.50 (0.70–3.40)	
									HF	1.60 (1.20–2.10)	
									Stroke-related death	1/2	

(*Continued*)

Table 1. Continued

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Huurman et al, 2020, Netherlands[27]	PC	Erasmus Medical Center HCM population after septal myectomy	5.9 y; 162	52.1; 61.1	79.0/78.0	11.0/15.0	NA	93.0/82.0	Composite end point	2.32 (0.79–6.83), male	Age, NYHA class ≥III, AF, hypertension, hypercholesterolemia, diabetes, pathogenic gene variant, negative inotropic therapy, HF therapy, ICD, time from symptom onset, time from diagnosis, preoperative peak LVOT gradient, maximal wall thickness, LA diameter, LV end-diastolic diameter, impaired systolic function, diastolic function, systolic anterior motion of the mitral valve, mitral regurgitation
									SCD	0/2	
									All-cause mortality	5/10	
Huang et al, 2020, China[26]	PC	West China Hospital, patients from HCM database with HCM	3.2 y; 576	54.9; 54.9	46.9/30.7	4.2/6.0	66.9/66.4	33.0/24.0	Cardiovascular death	0.64 (0.32–1.30)	Univariate analysis
									All-cause mortality	23/32	
Lakdawala et al, 2020, United States[31]	RC	Patients from SHARE registry with HCM	7.7 y; 5873	46.7; 62.1	21.6/9.3	22.1/20.6	66.0/64.6	35.5/26.6	HF (HF composite)	1.85 (1.48–2.32)	Age, hypertension, and history of AF
									All-cause mortality	1.45 (1.16–1.82)	
									Ventricular arrhythmia composite	111/202	
									AF (incident AF)	1.21 (1.01–1.46)	
									Stroke	1.48 (1.11–1.98)	
									HCM-related death	1.50 (1.13–1.99)	

(*Continued*)

Table 1. Continued

Author, year, country	Study design	Data source, study populations	Follow-up time; sample size	Mean age, y; male, %	Baseline comorbidities or echo, female/male				End Point	Estimate effect (95% CI) or case, female/male case	Adjusted covariates
					NYHA III/IV %	ICD %	LVEF	LVOT gradient			
Montenegro Sa´ et al, 2020, Portugal[35]	RC	Portuguese Registry of patients with HCM	65.0 mo; 1042	53.3; 58.8	16.1/10.8	10.9/15.6	65.6/64.3	16.9/14.6	All-cause mortality	2.05 (1.11–3.75)	Age, symptoms, HF, mitral regurgitation, diastolic dysfunction, CAD.
									Cardiovascular death	3.16 (1.25–7.99)	
									HF-related death	11/5	
									Stroke-related death	2/1	
									SCD	15/18	
Wang et al, 2020, China[38]	RC	A large tertiary hospital in North-eastern China. HCM population after alcohol septal ablation	7.5 y; 320	51.6; 49.4	67.3/56.3	6.8/5.7	62.0/60.0	NA	All-cause mortality	1.12 (1.08–1.27)	Age, NYHA III/IV, AF, CAD, hypertension, diabetes, beta receptor antagonist use, CCB use, alcohol dose, LVEF, residual LVWT >3 mo postprocedure, reduction in LVOT gradient >3 mo postprocedure, persistent complete AVB.
Kim et al, 2021, Korea[29]	PC	Korea National Health Insurance Service claims database patients with HCM	4.4 y; 9524	51.7; 77.6	NA	NA	NA	NA	Composite end point	1.43 (1.22–1.68)	Propensity score-matched (age, income, underlying disease, current medication, Charlson comorbidity index)
									Cardiovascular death	1.27 (0.91–1.78)	
									HF (new-onset HF admission)	1.54 (1.30–1.82)	
									All-cause mortality	0.91 (0.69–1.21)	
Bongioanni et al, 2021, Italy[39]	RC	Mauriziano Hospital, patients with HCM	86.5 mo; 573	53.0; 61.4	7.9/3.0	8.0/7.0	63.0/65.0	34.0/24.0	HCM-related death	1.52 (0.91–2.52)	Univariate analysis
									All-cause mortality	32/31	
									SCD	3/13	
									Stroke-related death	4/2	
									Noncardiac death	5/6	

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ASA, alcohol septal ablation; AVB, atrioventricular block; CABG, concomitant coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, internal cardiac defibrillator; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness; MWT, left ventricular maximum wall thickness; NA, not applicable; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PC, prospective cohort; RC, retrospective cohort; SARC VUS, sarcomere variant of unknown significance present; SARC, sarcomere mutation; SARC+, at least 1 pathogenic or likely pathogenic variant in any of the above sarcomere genes; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

from Europe (5 from Italy, 3 from the Netherlands, and 1 from Portugal), and 10 were from Asia (5 from China, 3 from Korea, and 2 from Japan).

Study Quality

Of the 27 included articles, 2 had an NOS score of 6.[22,26] They were univariate analyses and had a short follow-up period (<5 years). The remaining studies were high-quality studies with NOS scores >7 (Table S5).

Baseline Differences Between Sexes

For age and cardiac function analysis, our meta-analysis included 11 219 female subjects and 21 672 male subjects.[2,6,9–11,13,23,25–29,31–33,35,37–39] Overall, female subjects were older at the initial diagnosis (mean difference [MD]=5.61; 95% CI: 4.03–7.19; I^2=94%; P<0.00001) (Figure 2A) and had higher LVEFs (standard MD=0.09; 95% CI: 0.02–0.15; I^2=74%; P<0.00001) and higher left ventricular outflow tract (LVOT) gradients (standard MD=0.23; 95% CI: 0.18–0.29; I^2=63%; P=0.003) (Figure 2B and 2C).

Meta-Analysis of Sex Differences in Adverse Outcomes

Atrial Fibrillation and Ventricular Arrhythmia

Five articles (7453 individuals with 4713 male subjects and 2740 female subjects) showed an association between sex and AF.[9,22,31,33,36] There was no significant difference between female and male subjects in terms of AF risk (RR=1.13 [95% CI, 0.95–1.35], I^2=5%; P=0.38), with no evidence of heterogeneity (Figure 3A). The heterogeneity did not significantly change after excluding each study one by one.

Three studies involving 7222 patients, including 4558 male subjects and 2664 female subjects, showed that female sex was not associated with a higher risk of ventricular arrhythmias (RR=0.88 [95% CI, 0.71–1.10], I^2=0%; P=0.69) (Figure 3B).

Cardiovascular Events

Our meta-analysis included HCM-related events and major cardiovascular events.

Nine studies on HCM-related events involved 20 383 participants (14 216 male subjects and 6167 female subjects).[2,9,11,28–31,33,37] Female sex was associated with an increased risk of HCM-related events (RR=1.61 [95% CI, 1.33–1.94]), with evidence of heterogeneity (I^2=49%, P=0.05). In addition, a study by Woo et al supported this result (OR=3.60 [95% CI, 1.93–6.70]).[7] The leave-one-out method did not significantly change the heterogeneity (I^2: 0%–55%) (Figure 3C). Further analysis showed that female sex was associated with an increased risk of HF events (RR=1.76 [95% CI, 1.49–2.07], I^2=38%; P=0.11) and stroke (RR=1.48 [95% CI, 1.13–1.94], I^2=0%; P=0.97) (Figure S1).

Two studies involving 456 patients (265 male subjects and 191 female subjects) showed the relationship between sex and major cardiovascular events.[7,25] Female subjects were associated with a higher risk of major cardiovascular events (RR=3.59 [95% CI, 2.26–5.71]; P=0.39) (Figure 3D), with no evidence of heterogeneity (I^2=0%).

Death

Sudden Cardiac Death

Nine studies involving 12 120 individuals with 7726 male subjects/4394 female subjects were included in the meta-analysis of sudden cardiac death (SCD).[1,2,9,11,13,21,27,32,35,39] Female sex was not associated with an increased risk of SCD (RR=1.04 [95% CI, 0.75–1.42]; P=0.11), with no evidence of heterogeneity (I^2=38%, P=0.11) (Figure 4A).

HCM-Related Death

Twelve studies with 18 692 participants (11 765 male subjects and 6927 female subjects) were included in the analysis of the relationship between sex and HCM-related death.[2,8,9,11,13,20,21,27,31,32,35,37] There was a positive association between female sex and HCM-related death (RR=1.57 [95% CI, 1.34–1.82]; P=0.69), with low evidence of heterogeneity (I^2=0%) (Figure 4B). Further analysis showed that female sex was associated with an increased risk of HF-related death (RR=1.48 [95% CI, 1.29–1.70], I^2=0%; P=0.45). However, no difference was found in stroke-related death (RR=2.71 [95% CI, 0.94–7.85], I^2=0%; P=0.72) between the sexes (Figure S1).

Cardiovascular Death

Seven studies involving 15 095 participants with 10 867 male subjects/4228 female subjects were included in the meta-analysis of cardiovascular death.[9,11,13,26,28,29,35] The pooled results showed that female sex was associated with an increased risk of cardiovascular death in patients with HCM (RR=1.55 [95% CI, 1.05–2.28]), with evidence of heterogeneity (I^2=58%, P=0.03) (Figure 4C). The I^2 was reduced to 46% when the study by Huang et al[26] was excluded, and the results were stable (RR: 1.72 [95% CI, 1.20–2.48]; P=0.10).

Noncardiovascular Death

Five studies involving 9565 individuals with 6003 male subjects/3562 female subjects[2,11,13,32,39] were included in the meta-analysis of noncardiovascular death. Female sex was associated with an increased risk of noncardiovascular death (RR: 1.77 [95% CI, 1.46–2.13]) (Figure 4D), with no evidence of heterogeneity (I^2=0%, P=0.42).

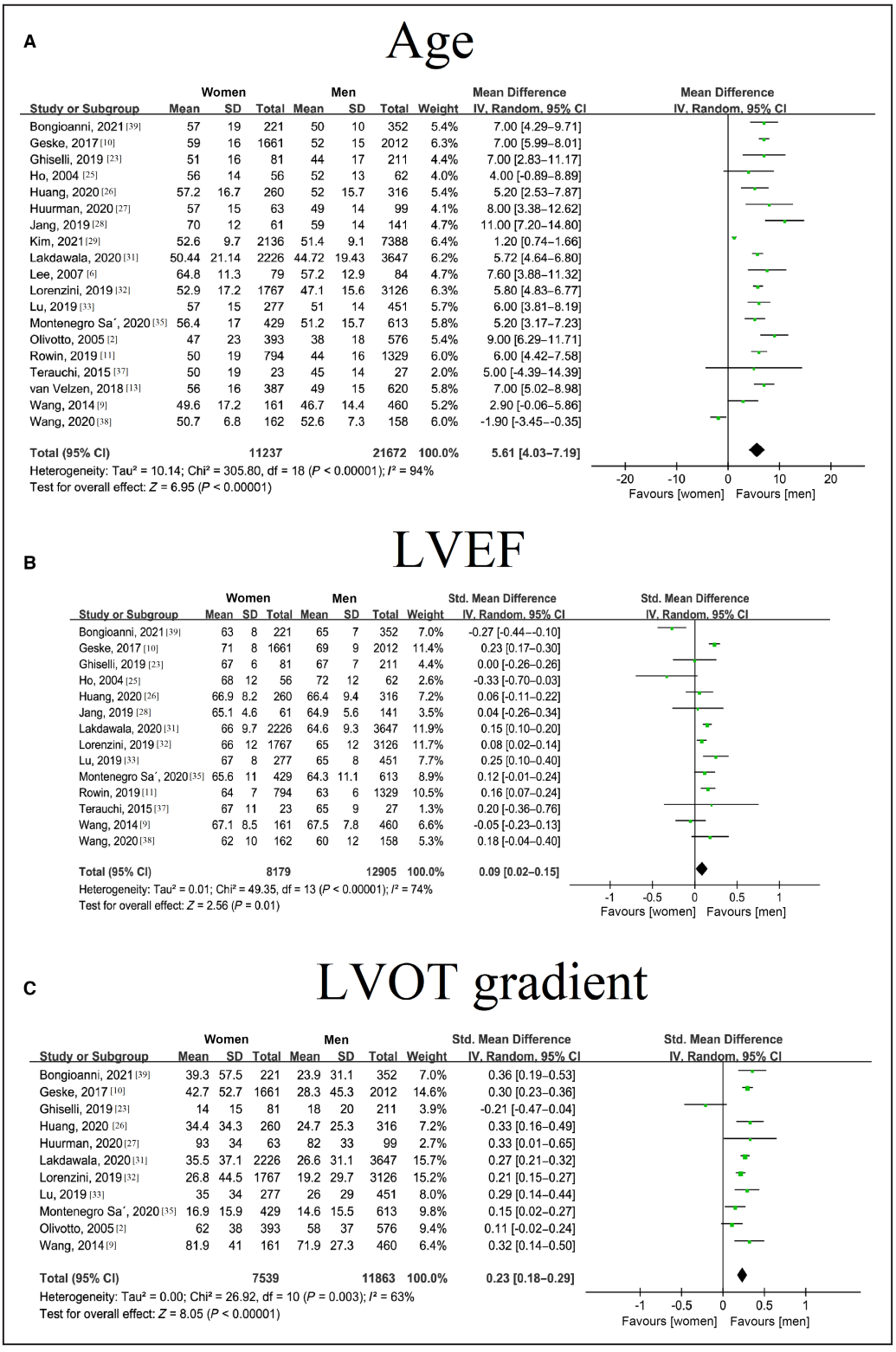

Figure 2. Forest plot showing the differences in age and cardiac function at diagnosis between sexes in patients with hypertrophic cardiomyopathy.

A, Diagnosis age in women and men with hypertrophic cardiomyopathy; **B**, Left ventricular ejection fraction in women and men with hypertrophic cardiomyopathy; **C**, Left ventricular outflow tract gradient in women and men with hypertrophic cardiomyopathy. HCM indicates hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; and LVOT, left ventricular outflow tract.

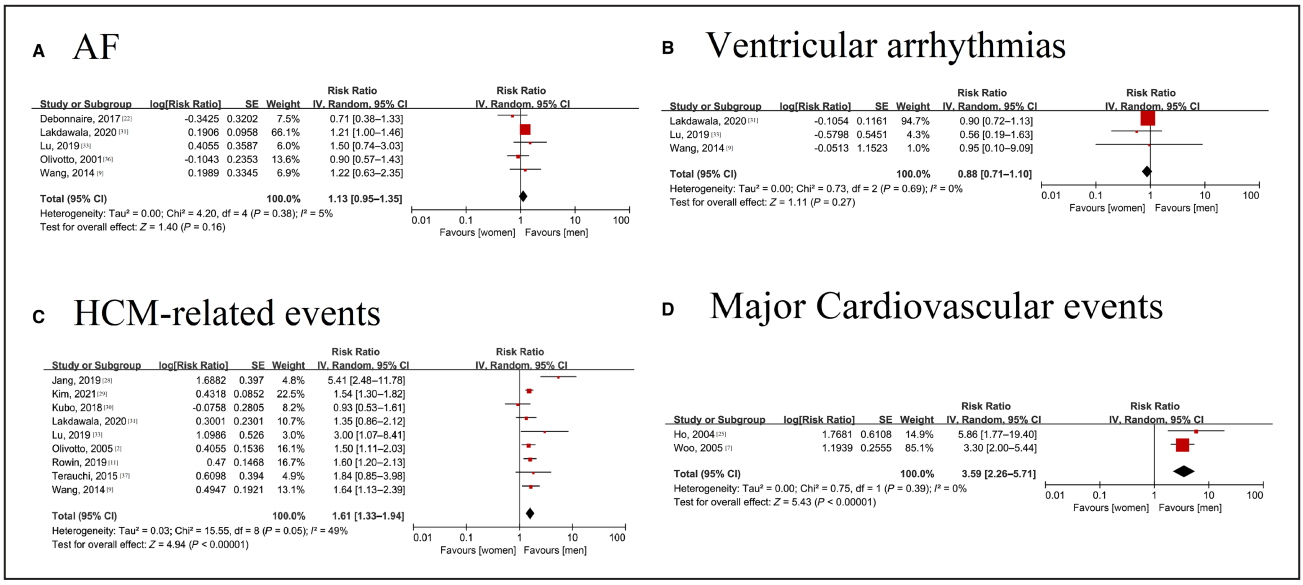

Figure 3. Forest plot for the association between sex and cardiovascular diseases in patients with hypertrophic cardiomyopathy.

A, Forest plot for the association between sex and atrial fibrillation in patients with HCM; **B**, Forest plot for the association between sex and ventricular arrhythmia in patients with HCM; **C**, Forest plot for the association between sex and HCM-related events in patients with HCM; **D**, Forest plot for the association between sex and major cardiovascular events in patients with HCM. AF indicates atrial fibrillation; and HCM, hypertrophic cardiomyopathy.

All-cause Death

Fourteen articles with 31 764 individuals (20 935 male subjects/10 829 female subjects) reported all-cause mortality.[8,9–11,13,20,26,27,29,31–33,35,38] Female sex was assoc iated with an increased risk of all-cause mortality (RR=1.43 [95% CI, 1.09–1.87], I^2=95%; P<0.00001) (Figure 4E). A study by Lee et al also reported a positive relationship between sex and all-cause mortality (OR=2.99 [95% CI, 1.13–7.91]).[6] Excluding the study by Lorenzini[32] reduced the I^2 from 95% to 53%, and the RR became 1.26 (95% CI, 1.11–1.42; P=0.01).

Composite End Point

Six studies involving 20 190 participants with 14 162 male subjects/6028 female subjects showed the composite end point.[5,23,27,29,32,33] The definition of the composite end point was not uniform across studies, with most being HF hospitalization or HCM-related events, SCD, and death. There was no significant sex difference in the composite end point (RR=1.24 [95% CI, 0.96–1.60], I^2=85%; P<0.00001) (Figure 4F). By excluding the study by Ho et al[5] the heterogeneity was reduced to 68%.

Publication Bias

Publication bias tests were performed for the outcomes, with >10 studies according to the guidelines.[40] The results showed no evidence of publication bias detected by the funnel plot, Egger test, or Begg test (Egger test: HCM-related events P=0.624; HCM-related death P=0.922; all-cause mortality P=0.975; Begg test: HCM-related events P=0.754; HCM-related death P=0.732; all-cause mortality P=0.189) (Figures S2 and S3).

Sensitivity Analyses

We performed sensitivity analysis for HCM-related events, HCM-related death, and all-cause mortality. Sensitivity analyses by excluding studies in which a univariate analysis was performed, excluding studies without age adjustment and the leave-one-out method generated confirmed results (Figure S4 and S5).

Subgroup Analyses

Considering the statistical power, subgroup analysis was performed only for those outcomes that were reported in >10 studies (HCM-related events, HCM-related death, and all-cause mortality).

As shown in Table 2, female sex was still associated with an increased risk of worse outcomes in almost all subgroups stratified by mean age, follow-up period, sample size, study design, population, region, and NOS quality assessment, and there was little evidence of heterogeneity between these subgroups in the meta-regression analyses (P>0.05).

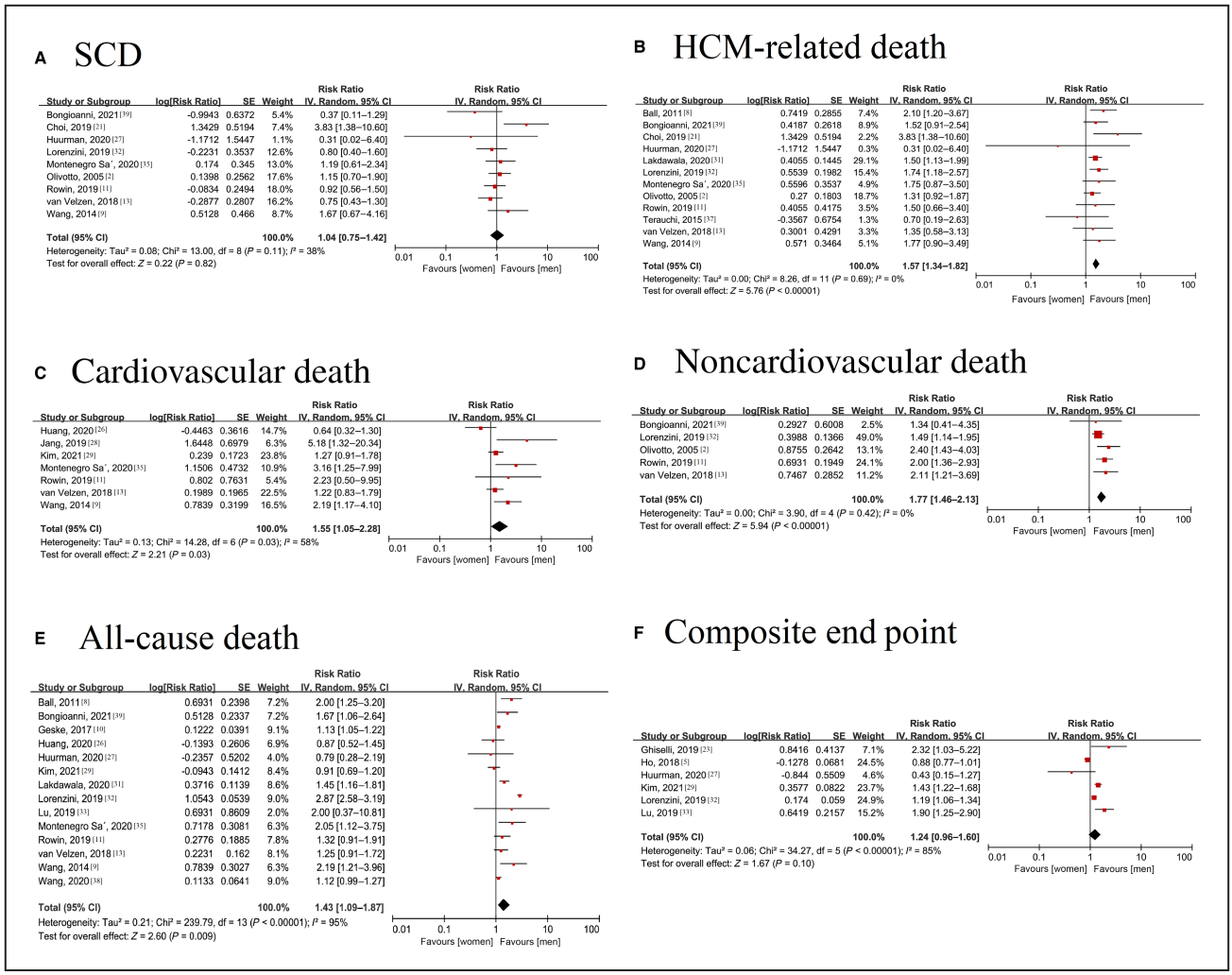

Figure 4. Forest plot for the association between sex and death or composite end point in patients with hypertrophic cardiomyopathy.

A, Forest plot for the association between sex and sudden cardiac death in patients with HCM; **B**, Forest plot for the association between sex and HCM-related death in patients with HCM; **C**, Forest plot for the association between sex and cardiovascular death in patients with HCM; **D**, Forest plot for the association between sex and noncardiac death in patients with HCM; **E**, Forest plot for the association between sex and all-cause mortality in HCM; **F**, Forest plot for the association between sex and composite end point in patients with HCM. HCM indicates hypertrophic cardiomyopathy; and SCD, sudden cardiac death.

DISCUSSION

Main Findings

Based on the pooled analysis from 27 cohorts with 42 365 patients with HCM, the present meta-analysis showed that (1) female subjects with HCM were older and had higher LVEFs and higher LVOT gradients at diagnosis; (2) female sex was associated with worse outcomes in patients with HCM, including cardiovascular events, but not AF or SCD; and (3) the subgroup analyses and sensitivity analyses confirmed the above results. Overall, our study showed a significant sex difference in the prognosis of HCM.

Sex-Based Differences at Diagnosis of HCM

Our results showed that female subjects were underrepresented in our pooled cohorts, representing <40%, which was consistent with some prior findings.[2,10] The underlying reason for this skew is still unknown. In the HCM population, >50 sarcomere contractile protein gene mutations have been identified.[41] Some researchers have attributed it to decreased disease penetrance in female subjects, predominantly in individuals with cardiac myosin-binding protein C3 gene (*MYBPC3*) variants.[37,42–44] A study showed sex differences in the clinical features of HCM caused by *MYBPC3* mutation.

Table 2. Subgroup Analysis for the Meta-Analysis of Sex Difference in the Prognosis of Hypertrophic Cardiomyopathy

Items		No. of cohorts	RR (95% CI)	I^2%	*P* Within subgroup	*P* Between subgroup
HCM-related events		9	1.61 (1.33–1.94)	57		
Mean age	<50 y	5	1.47 (1.19–1.82)	65	<0.001	0.49
	≥50 y	4	1.81 (1.04–3.14)	73	0.03	
Follow-up time	<5 y	5	1.75 (1.34–2.27)	47	<0.001	0.19
	≥5 y	4	1.35 (1.01–1.80)	78	0.04	
Sample size	<1000	6	1.68 (1.20–2.35)	53	0.003	0.45
	≥1000	3	1.43 (1.12–1.83)	82	0.004	
Study design	PC	7	1.61 (1.33–1.93)	36	<0.001	0.44
	RC	2	1.34 (0.89–2.04)	84	0.16	
Region	America	2	1.40 (1.00–1.97)	87	0.01	0.68
	Europe	2	1.41 (0.69–2.86)	60	0.35	
	Asia	5	1.71 (1.25–2.33)	50	<0.001	
NOS quality assessment	≤7	2	1.63 (1.24–2.13)	0	<0.001	0.83
	>7	7	1.56 (1.23–1.99)	57	<0.001	
Excluding univariate analysis	Multivariate analysis	7	1.67 (1.38–2.20)	53	<0.001	0.53
Excluding without age adjustments	Adjust age	8	1.56 (1.29–1.89)	49	<0.001	0.69
All-cause mortality		14	1.43(1.09–1.87)	94		
Mean age	<50 y	4	1.58 (0.91–2.77)	98	0.11	0.59
	≥50 y	11	1.35 (1.10–1.64)	60	0.004	
Follow-up time	<5 y	5	1,20 (0.86–1.67)	57	0.29	0.32
	≥5 y	9	1.52 (1.09–2.13)	96	0.01	
Sample size	<1000	7	1.38 (1.03–1.84)	58	0.03	0.83
	≥1000	7	1.46 (0.97–2.19)	97	0.07	
Study design	PC	7	1.21 (0.98–1.50)	60	0.08	0.20
	RC	7	1.65 (1.07–2.55)	96	0.02	
Population	Without treatment	10	1.51 (1.10–2.07)	95	0.01	0.33
	After treatment	4	1.21 (0.89–1.65)	70	0.22	
Region	America	5	1.36 (1,10-1,67)	88	0.03	0.24
	Europe	5	1.70 (1.05–2.75)	66	0.22	
	Asia	4	1.11 (0.85–1.43)	62	0.45	
NOS quality assessment	≤7	3	1.27 (0.90–1.78)	43	0.17	0.50
	>7	11	1.48 (1.09–2.03)	96	0.01	
Excluding univariate analysis	Multivariate analysis	10	1.50 (1.11–2.04)	96	0.009	0.38
Excluding without age adjustments	Adjust age	11	1.49 (1.09–2.05)	96	0.01	
HCM-related death		12	1.33 (1.14–1.55)	34		
Mean age	<50 y	6	1.49 (1.25–1.78)	0	<0.001	0.62
	≥50 y	6	1.65 (1.16–2.35)	43	0.006	
Follow-up time	<5 y	2	1.65 (0.98–2.79)	0	0.06	0.77
	≥5 y	10	1.52 (1.24–1.85)	29	<0.001	
Sample size	<1000	7	1.58 (1.22–2.04)	9	0.0004	0.72
	≥1000	5	1.48 (1.16–1.89)	26	0.001	
Study design	PC	7	1.59 (1.21–2.10)	9	0.001	0.71
	RC	5	1.49 (1.18–1.87)	26	0.0007	

(*Continued*)

Table 2. Continued

Items		No. of cohorts	RR (95% CI)	I^2%	*P* Within subgroup	*P* Between subgroup
Population	Without treatment	11	1.55 (1.29–1.86)	18	<0.001	0.30
	After treatment	1	0.31 (0.02–6.40)	17	0.45	
Region	America	3	1.60 (1.25–2.03)	0	0.0001	0.67
	Europe	6	1.43 (1.12–1.82)	25	0.004	
	Asia	3	1.84 (1.00–3.40)	27	0.05	
NOS quality assessment	≤7	4	1.64 (0.99–2.72)	32	0.06	0.85
	>7	8	1.56 (1.32–1.84)	0	<0.001	
Excluding univariate analysis	Multivariate analysis	4	1.59 (1.06–2.38)	64	0.03	0.83
Excluding without age adjustments	Adjust age	9	1.60 (1.36–1.88)	0	<0.001	

ASA indicates alcohol septal ablation; HCM, hypertrophic cardiomyopathy; NOS, Newcastle-Ottawa Scale; PC, prospective cohort; RC, retrospective cohort; RR, risk ratio; and SM, septal myectomy.

The higher cardiac disease penetrance of *MYBPC3* mutation carriers in male subjects than in female subjects was confirmed.[37] Other genetic factors, such as modifier genes on the sex chromosome, may also influence the penetrance in female subjects. This high penetrance caused by mutation allows male subjects to exhibit the disease earlier. Therefore, female subjects are older and have more serious symptoms at the time of illness onset, which affects the prognosis of HCM in women. Notably, recent results from Lakdawala et al provided novel insight into this hypothesis.[31] They showed that the sex-based difference in the age at diagnosis was more pronounced in genetically tested patients with sarcomere-mutated HCM (female subjects were 7.1 years older at diagnosis) than in those without sarcomere-mutated HCM (female subjects were 3.6 years older at diagnosis). This may be related to differences in LVOT obstruction and diastolic function. However, sarcomere mutation may not be associated with systolic dysfunction (female subjects with *MYBPC3* variants are 35% less likely to develop systolic dysfunction than male subjects).[31] The increased frequency and severity of LVOT obstruction in female subjects may be associated with a smaller left ventricular chamber,[45] which is consistent with our findings. The incidence of HF events was also 87% higher in female subjects when controlling for obstruction, systolic dysfunction, hypertension, and age, suggesting that diastolic dysfunction contributes to the poor prognosis of women with HCM. Indeed, sarcomere variants that cause HCM have been shown to impair relaxation in model systems spanning the spectrum from isolated sarcomere filaments to human sarcomere mutation carriers without overt HCM.[46] However, previous studies of sex-based differences in HCM diastolic function in *MYBPC3* sarcomere mutants are limited, and more research is needed to confirm this. Moreover, the disease appears to develop at similar ages in female subjects and male subjects with HCM when caused by *beta myosin heavy chain 7* (*MYH7*) variants. Therefore, whether there is incomplete penetrance among female subjects might be a more complicated question. On the other hand, social bias, such as poor recognition of the condition by health care providers because of bias, might also be responsible, caused by lower awareness of women's diseases by their physicians.

Several large longitudinal cohorts showed worse clinical presentations in female subjects at diagnosis. Unexpectedly, the results showed that LVEFs were higher in female subjects and that LVOT gradients were lower than those in male subjects (LVEF standard MD: 0.10 [95% CI, 0.04–0.17]; LVOT gradient standard MD: 0.25 [95% CI, 0.19–0.30]). The reason for this result may be related to the small sample size of female subjects, and the exact data still need to be studied more extensively. In addition, 73% of female subjects had New York Heart Association class II to IV symptoms at the time of diagnosis compared with 53% of male subjects. Therefore, female subjects were significantly more likely to have advanced drug-refractory HF (New York Heart Association class III/IV) than male subjects (53% and 35%, respectively).[11] Female subjects are known to have a higher prevalence of obstructive phenotypes, poorer diastolic function, and more severe HF symptoms.[2,10] At the same time, these results are supported by the suggestion by Abraham et al that diastolic dysfunction, not left ventricular systolic dysfunction, contributes to the worsening of symptoms in female patients with HCM.[33]

Sex-Based Differences in HCM Outcomes

Evidence from longitudinal studies showed that there might be a sex difference in the prognosis of patients with HCM, but the results were inconsistent.[47]

In our results, compared with those in male subjects, the risk of HCM-related events, HCM-related death, cardiovascular-related events, major cardiovascular death, noncardiovascular death, and all-cause mortality in female patients with HCM increased by 61%, 57%, 259%, 55%, 77%, and 43%, respectively. Moreover, these results were stable in the sensitivity analysis, which confirmed the robustness of our results. Notably, there was no statistically significant difference in the composite end point. This might be because the composite end point comprised SCD and ventricular arrhythmia, which did not have a sex difference and thus might have reduced the statistical power.

It is worth noting that our meta-analysis showed that there was no difference between sexes in SCD or ventricular arrhythmia. Considering that malignant ventricular arrhythmia is a major cause of SCD, these results are not surprising. The results reinforce the current guidelines of established clinical risk factors for HCM sudden death risk stratification, which do not include a component of sex. Based on the Sarcomeric Human Cardiomyopathy Registry study, the results in genotyped patients and full cohorts were inconsistent. Ho et al showed that female sex was associated with a decreased risk of ventricular arrhythmia composite events in genotyped cohorts (patients with HCM with a sarcomere mutation) after adjustment.[5] However, this association was not found in the overall cohort.[31] As previously reported, patients with genotyped HCM have a significantly higher composite risk of ventricular arrhythmia than patients without a sarcomere mutation, which might be attributable to the greater number of cases in the genotyped HCM cohort, higher statistical power, or other confounding factors. Considering the limited evidence from current studies, more studies are needed to verify the association between sex and ventricular arrhythmia in patients with genotyped HCM.

In patients undergoing septal myectomy, our results showed that female subjects experienced more HCM events than death (HCM-related death or all-cause death) (Table 2). We should interpret this result with caution considering the limited number of studies (n=1 for HCM-related death, n=4 for all-cause death). The conclusion that the death rate is significantly different will be more solid if larger cohorts show consistent results. In fact, the sex discrepancy is a controversial topic in contemporary literature on patients with HCM receiving surgery. Recently, Wang et al reported significantly increased mortality in female patients with HCM undergoing alcohol septal ablation based on a Chinese cohort after 10 years of follow-up.[38] Woo showed that female subjects who underwent treatment were more likely to develop HCM-related events,[7] and Huurman showed that the composite end point was more likely to occur in female subjects undergoing surgical treatment.[27] However, a cohort in the Netherlands showed a similar survival rate among male subjects and female subjects after surgical treatment.[27] In general, female subjects with HCM are older and have more severe symptoms, and whether female subjects, independent of the above clinical characteristics, have worse outcomes of HCM after surgical treatment remains unclear.

Age is one of the most important confounding factors in HCM outcome. In most of the included studies, female subjects were significantly older than male subjects at diagnosis. Even after age adjustment, female sex was still an independent factor for cardiovascular death,[28] all-cause mortality,[33] and HF.[2,31] It has also been reported that there was no sex difference in mortality after age adjustment.[26] Our results showed that even after the removal of age-unadjusted studies, female sex was still associated with worse prognosis.

Genotype is another vital confounding factor. Survival analysis showed that compared with patients with sarcomeric variant-negative, patients with sarcomeric variant-positive had an earlier onset of events and higher incidences of the overall composite outcome, HF, and AF.[5] After genotype adjustment, female subjects still had a higher risk of mortality (RR=1.45) and the HF composite end point (RR=1.85).[31] However, different variants might have different influences on sex. For example, on the 2 most common genes, *MYH7* and *MYBPC3*, the sex-based difference in the age of diagnosis was found predominantly in individuals with *MYBPC3* variants,[37,42–44] rather than in patients with *MYH7* variants.[31] Therefore, there remains considerable heterogeneity within the sarcomeric variants. The interaction between sex and sarcomeric variants still needs to be clarified.

Underlying Mechanism

Although the potential mechanisms behind sex differences in patients with HCM remain unknown, several hypotheses have been proposed. Constantine and coworkers showed that there is a significant sex difference in cardiovascular physiology and morphology.[48,49] Compared with male subjects, female subjects have a smaller left ventricular chamber size and mass index (up to 40%).[50] Age-related cardiac remodeling is also more pronounced in female subjects, who are initially protected from adverse cardiovascular outcomes but experience more frequent adverse outcomes after the age of 60 years. Myocardial remodeling in response to different types of ventricular overload also differs between the sexes. Female subjects experience more left ventricular hypertrophy in response to aortic stenosis, while male subjects experience more severe left ventricular dilatation following aortic regurgitation. Age-dependent changes in diastolic ventricular function and arterial stiffness

were greater in female subjects than in male subjects. Although the mechanisms behind sexual dimorphism are unclear, differences in endogenous hormones may contribute to cardiac remodeling and lifelong risk of cardiovascular disease.[48] In addition, female subjects usually have a smaller left ventricular chamber, and female patients with HCM have greater changes in the left ventricle, such as ventricular thickness and left ventricular systolic function, than male patients, which largely influences the risk of HF and LVOT obstruction between sexes.[51,52] On the other hand, different likelihoods of events are associated with wall thinning and cardiac remodeling.[53] There is evidence that female patients with HCM have a significantly larger degree of left ventricular remodeling.[54] The effects of left ventricle remodeling and fibrosis may cause diastolic dysfunction, which is more likely to lead to worse clinical outcomes in female subjects. Moreover, because of the bias of clinicians, more women delay their HCM diagnosis and treatment,[31,41,55] which may influence the prognosis of HCM.

Clinical Implications

The updated 2020 American Heart Association/American College Cardiology HCM Guideline for the Diagnosis and Management of HCM did not specifically comment on sex-specific prognosis or approaches to HCM.[56] Our study can be used to help clarify the sex differences in diagnosis and prognosis in patients with HCM, highlighting the clinical importance of sex-based differences. Further guideline updates or clinical trials may emphasize this sex difference for prognosis. In the context of SCD, our results are consistent with the current guidelines; that is, the inclusion of sex as a risk assessment factor for HCM-SCD is not supported.

Comparison With Prior Meta-Analyses

Sex-related differences in patients with HCM have been reported in previous studies.[35,48] However, the difference in prognosis was still unclear. Consistent with our research results, a meta-analysis shows clinical outcome differences between female subjects and male subjects.[57] Our study extends these findings. We demonstrate a sex-specific difference in diagnosis, cardiac function, LVOT, and more comprehensive HCM outcomes, such as noncardiac death, cardiovascular death, arrhythmia, sudden death, and composite end points. Moreover, our study includes 16 more high-quality cohorts and various subgroup analyses, which makes the results robust.

Strengths and Study Limitations

Our study systematically assessed the sex-related prognosis of patients with HCM, adding valuable knowledge that may go into guidelines. Several limitations should be noted. First, relatively high heterogeneity was observed in the major end point; however, the heterogeneity was somewhat reduced by excluding some articles, while the results were still significant. Second, few included studies report on some outcomes (eg, major cardiovascular events), so more prospective cohorts are needed to confirm these results. Then, the component of composite end points varied across studies, which may be responsible for the inconsistent results from other outcomes. In addition, this is attributable to a lack of data, and to keep smaller heterogeneity, we select the age at diagnosis instead of age at onset for each HCM population, which may have some slight effect on the analysis of age. Finally, the meta-analysis is based on observational studies, so causality cannot be deduced from our study.

CONCLUSIONS

Based on current evidence, our results suggest that female sex is associated with a higher risk of HCM-related events, HCM-related death, major cardiovascular events, cardiovascular death, noncardiovascular death, and all-cause mortality. There is no association between sex and AF or SCD. Future guidelines may emphasize sex-specific risk assessment, diagnosis, or management for HCM.

ARTICLE INFORMATION

Received March 28, 2022; accepted March 20, 2023.

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Acknowledgments

We acknowledge the grant support from Guangzhou Science Technology Bureau (202102010007).

Author contributions: Guarantor of the article, X. Liu; X. Liu contributed to the study concept and design and revised the draft. Z. Tan and X. Liu performed the search strategy and contributed to database research, acquisition of data, and statistical analyses. All the authors participated in data analysis and reviewed and approved the final manuscript.

Sources of Funding

This work was supported by a grant from the Natural Science Foundation of Jiangxi Province (Nos. 20192ACBL21037, 202004BCJL23049, 202002BAB216022, and 20212BAB216051 to J.Z.; Nos. 20212BAB216047 and 202004BCJL23049 to P.Y.) and the National Natural Science Foundation of China (Nos. 82160371 and 82160371 to J.Z.; and Nos. 82100869 and 82100869 to P.Y.; No. 21866019 to J.M.; No. 82100347 to X.L.),

China Postdoctoral Science Foundation (2021M703724 to X.L.), National High Technology Research and Development Program of Guangzhou (20180304001 and 2019GZR110406004 to J.W.), Natural Science Foundation of Guangdong Province (2022A1515010582 to X.L.), and Natural Science Foundation of Guangzhou (202201011395 to X.L.).

Disclosures

None.

Supplemental Material

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Supplemental Material

Table S1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6-7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6-7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in	7-8

Section and Topic	Item #	Checklist item	Location where item is reported
		the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-13
	23b	Discuss any limitations of the evidence included in the review.	13
	23c	Discuss any limitations of the review processes used.	13
	23d	Discuss implications of the results for practice, policy, and future research.	14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	16
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	16
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	16
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	16

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S2. Detailed description of the search strategy

PubMed	
#1	(Sex [MeSH Terms]) OR (Genotypic Sex) OR (Phenotypic Sex)
#2	(Hypertrophic cardiomyopathy [MeSH Terms]) OR (HCM) OR (Hypertrophic Cardiomyopathies) OR (Hypertrophic Cardiomyopathy) OR (Hypertrophic Obstructive Cardiomyopathies) OR (Hypertrophic Obstructive Cardiomyopathy)
#3	#1 AND #2
Embase	
#1	'Hypertrophic cardiomyopathy':ab,ti OR 'HCM' OR 'Hypertrophic Cardiomyopathies' OR 'Hypertrophic Cardiomyopathy' OR 'Hypertrophic Obstructive Cardiomyopathies' OR 'Hypertrophic Obstructive Cardiomyopathy'
#2	'sex':ab.ti OR 'genotypic sex' OR 'phenotypic sec'
#3	#1 AND #2
Cochrane	
#1	MeSH descriptor: [Sex] explode all trees
#2	Phenotypic Sex
#3	Genotypic Sex
#4	MeSH descriptor: [Cardiomyopathy, Hypertrophic] explode all trees
#5	HCM
#6	Hypertrophic cardiomyopathy
#7	Hypertrophic Cardiomyopathies
#8	Cardiomyopathy, Hypertrophic Obstructive
#9	Cardiomyopathies, Hypertrophic Obstructive
#10	Hypertrophic Obstructive Cardiomyopathies
#11	Hypertrophic Obstructive Cardiomyopathy
#12	Obstructive Cardiomyopathies, Hypertrophic
#13	Obstructive Cardiomyopathy, Hypertrophic
#14	#1 OR #2 OR #3
#15	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR # 13
#16	#14 AND #15

Table S3. The definition of composite endpoint, major CV events and other outcomes

Study	Definition
	Composite endpoint
Ho, 2018 [5]	First occurrence of any component of the ventricular arrhythmic or heart failure composite end point (without inclusion of LV ejection fraction), all-cause mortality, atrial fibrillation (AF), stroke, or death.
Lorenzini, 2019 [32]	All-cause mortality, transplantation, aborted SCD, appropriate ICD shock.
Ghiselli, 2019 [23]	Combination of cardiac death, heart failure requiring hospitalization, sustained ventricular tachycardia, appropriate implantable cardioverter defibrillator dis charge or resuscitated sudden cardiac death and cardiac embolic stroke.
Lu, 2019 [33]	Including new onset AFib, new sustained VT (VT rate ⩾130 bpm, >30 sec duration) or VF, new onset or worsening HF to New York Heart Association functional class III or IV requiring hospitalization, and all-cause mortality.
Huurman, 2020 [27]	Repeat septal reduction therapy, absorbed SCD, all-cause mortality and cardiac transplantation.
Kim, 2021 [29]	Composite of cardiovascular death or new-onset heart failure (HF) admission.
	Major CV death
Ho, 2004 [25]	Major cardiovascular events related to hypertrophic cardiomyopathy were defined as sudden death or death due to cardiac arrhythmias, heart failure, or stroke associated with atrial fibrillation; potentially fatal cardiac arrhythmias in which patients were successfully resuscitated from cardiac arrest or received appropriate shocks from an implanted defibrillator; cardiac transplantation in patients with intractable heart failure; or percutaneous alcohol septal ablation in patients with symptomatic obstructive hypertrophic cardiomyopathy refractory to medical therapy. Cardiovascular complications related to hypertrophic cardiomyopathy included the occurrence of atrial fibrillation, heart failure, nonfatal ventricular arrhythmia, nonfatal stroke associated with atrial fibrillation, and infective endocarditis.
Woo, 2005 [7]	Late major cardiovascular events included in the model were any of the following events: (1) CHF that required hospitalization, (2) stroke, (3) arterial thromboembolic event, (4) subsequent cardiac surgical procedure (repeat myectomy, repair of ventricular septal defect, valve surgery, or pericardiectomy), (5) cardiac transplantation, or (6) cardiovascular cause of death.

	Non-CV death
Bongioanni, 2021 [39]	Non-cardiac death.
Lorenzini, 2019 [32]	Died from non-CV causes.
Olivotto, 2005 [2]	Not HCM-related death (sudden death and heart failure/stroke-related death).
Rowin, 2019 [11]	Most commonly, pulmonary disease, cancer, and multiorgan noncardiac comorbidities often associated with advanced age.
Van Velzen, 2018 [13]	Non-cardiac mortality.
	Other outcomes
Wang, 2014 [9]	Chronic HF: Chronic heart failure was diagnosed on the basis of shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as ankle swelling; and objective evidence of an abnormality in the heart structure or function at rest.
Jang, 2019 [28]	HF presentation: HF presentation was defined based on clinical symptoms (e.g., breathlessness, ankle swelling and fatigue) and signs which had elevated jugular venous pressure, peripheral edema, pulmonary edema on chest X-ray, or elevated N-terminal prohormone of brain natriuretic peptide (NTproBNP)>125 pg/mL if available.

Table S4. Studies excluded (n=31) with reasons

Studies excluded	Reasons
Constantine, 2019 [52]	Review
van Driel, 2019 [62]	Review
Pelliccia, 2018 [42]	Review
Nijenkamp, 2015 [63]	Review
Dimitrow, 2004 [64]	Editorial
Siontis, 2019 [50]	Editorial
Nogales-Romo, 2020 [65]	Cross-section study
Maron, 2003 [57]	Not the target outcome: thickness of left ventricular
Zhang, 2016 [66]	Not the target outcome: serum uric acid (SUA) level
Frielingsdorf, 2004 [67]	Not the target outcome: systolic function of the left ventricle (wall thickness and wall stress)
Aurigenmma, 1995 [68]	Not the target outcome: left ventricular structure and hypertension
Bos, 2008 [69]	Not the target outcome: genetically and morphologically classified HCM
Lind, 2008 [70]	Not the target outcome: genetic variation in sex hormone receptors and the development of left ventricular hypertrophy in HCM
Dimitrow, 2001 [71]	Not the target outcome: left ventricular cavity size, contractility and left ventricular outflow tract obstruction
Ohmoto-Sekine, 2007 [72]	Not the target outcome: prevalence of deep Q waves in HCM and in the morphologic and electrocardiographic features of HCM with deep Q waves
Movahed, 2010 [73]	Not the target population: teenagers
O¨ stman-Smith, 2008 [74]	Not the target population: childhood
Sreenivasan, 2021 [75]	Not the target exposure: postoperative in-hospital mortality
Carnlöf, 2018 [76]	Not the target exposure: atrio-ventricular junction ablation (AVJ)
Condon, 2008 [77]	Not the target exposure: cardiovascular disease/ acute myocardial infarction
Schulz-Menger, 2008 [78]	Not the target exposure: fibrosis in HCM
Takigawa, 2013 [79]	Not the target exposure: catheter ablation of paroxysmal atrial fibrillation
Frankel, 2016 [80]	Not the target exposure: ventricular tachycardia
Schuldt, 2021 [81]	Molecular level: protein detection
Luckey, 2007 [82]	Animal experiment
Brimacombe, 2008 [83]	Not interest data
Lin, 1999 [55]	Not interest data
Dimitrow, 1997 [59]	Not interest data
Nijenkamp, 2020 [84]	Not interest data
Giorfiriddo, 2019 [24]	Repeated population
Marstrand, 2019 [85]	Repeated population

Table S5. Quality assessment of included studies

Author (Publication Year)	Newcastle-Ottawa Scale									Total
	Selection			Comparability			Outcome			
	a	b	c	d	e	f	g	h	i	
Jang, 2019 [28]	1	1	1	1	1	1	1	1	0	8
Kim, 2021 [29]	1	1	1	1	1	1	1	1	0	8
Wang, 2020 [38]	1	1	1	1	1	1	1	1	1	9
van Velzen, 2018 [13]	1	1	1	1	0	1	1	1	1	8
Ghiselli, 2019 [23]	1	1	1	1	1	1	1	1	1	9
Lakdawala, 2020 [31]	1	1	1	1	1	1	1	1	1	9
Montenegro Sa´, 2020 [35]	1	1	1	1	1	1	1	1	1	9
Geske, 2017 [10]	1	1	1	1	1	1	1	1	1	9
Rowin, 2019 [11]	1	1	1	1	1	0	1	1	0	7
Olivotto, 2005 [2]	1	1	1	1	1	1	1	1	1	9
Lu, 2019 [33]	1	1	1	1	1	1	1	1	0	8
Huang, 2020 [26]	1	1	1	1	0	0	1	1	0	6
Wang, 2014 [9]	1	1	1	1	1	1	1	1	0	8
Ball, 2011 [8]	1	1	1	1	1	1	1	1	1	9
Bongioanni, 2021 [39]	1	1	1	1	0	0	1	1	1	7
Choi, 2019 [21]	0	1	1	1	0	1	1	1	1	7
Debonnaire, 2017 [22]	1	1	1	1	0	0	1	1	0	6
Ho, 2004 [25]	1	1	1	1	1	1	1	1	1	9
Ho, 2018 [5]	1	1	1	1	1	1	1	1	1	9
Huurman, 2020 [27]	1	1	1	1	1	1	1	1	1	9
Kubo, 2018 [30]	1	1	1	1	1	1	1	1	1	9
Lee, 2007 [6]	1	1	1	1	0	1	1	1	1	8
Lorenzini, 2019 [32]	1	1	1	1	1	1	1	1	1	9
Olivotto, 2001 [36]	1	1	1	1	0	0	1	1	1	7
Terauchi, 2015 [37]	1	1	1	1	0	0	1	1	1	7
Woo, 2015 [7]	1	1	1	1	1	1	1	1	1	9
Meghji, 2019 [34]	1	1	1	1	1	1	1	1	1	9

a. Representativeness of the exposed cohort.

b. Selection of the non-exposed cohort.

c. Ascertainment of exposure.

d. Demonstration that outcome of interest was not present at start of study.

e. Comparability of cohorts on the basis of the design or analysis (adjusted for age).

f. Comparability of cohorts on the basis of the design or analysis (adjusted for any other factor).

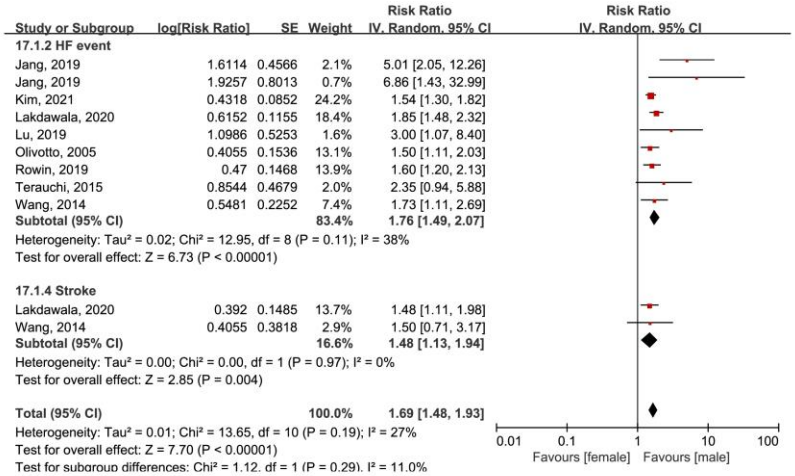
g. Assessment of outcome.

h. Was follow-up long enough for outcomes to occur (>1 year).

i. Adequacy of follow-up of cohorts (>5 years).

Figure S1. Forest plot for subgroup analysis of HCM-related events and HCM-related death. a. HCM-related events type (ventricular arrhythmia, heart failure event, stroke) subgroup. b. HCM-related death (sudden cardiac death, heart failure-related death, stroke-related death) type subgroup.

a.Subgroup of HCM-related events



b.Subgroup of HCM-related death

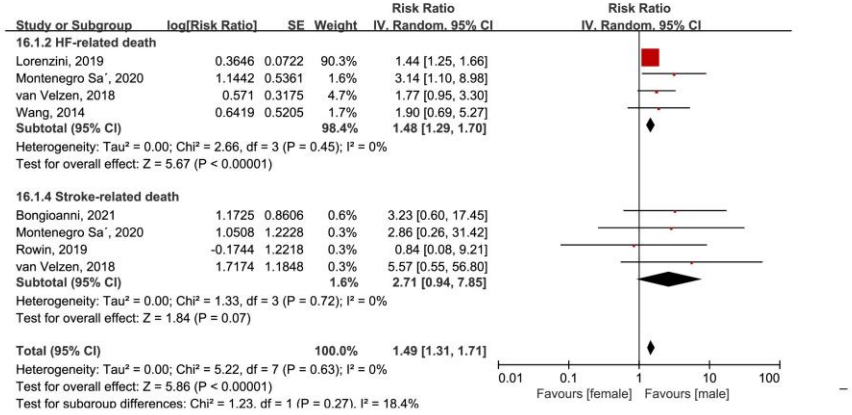


Figure S2. Egger's publication bias plot and Begg's funnel plot for main outcomes (HCM-related events, HCM-related death, all-cause mortality) of sex differences in HCM patients. a. Egger's publication bias plot for HCM-related events; b. Egger's publication bias plot for HCM-related death; c. Egger's publication bias plot for all-cause mortality; e. Begg's funnel plot for HCM-related events; b. Begg's funnel plot for HCM-related death; c. Begg's funnel plot for all-cause mortality.

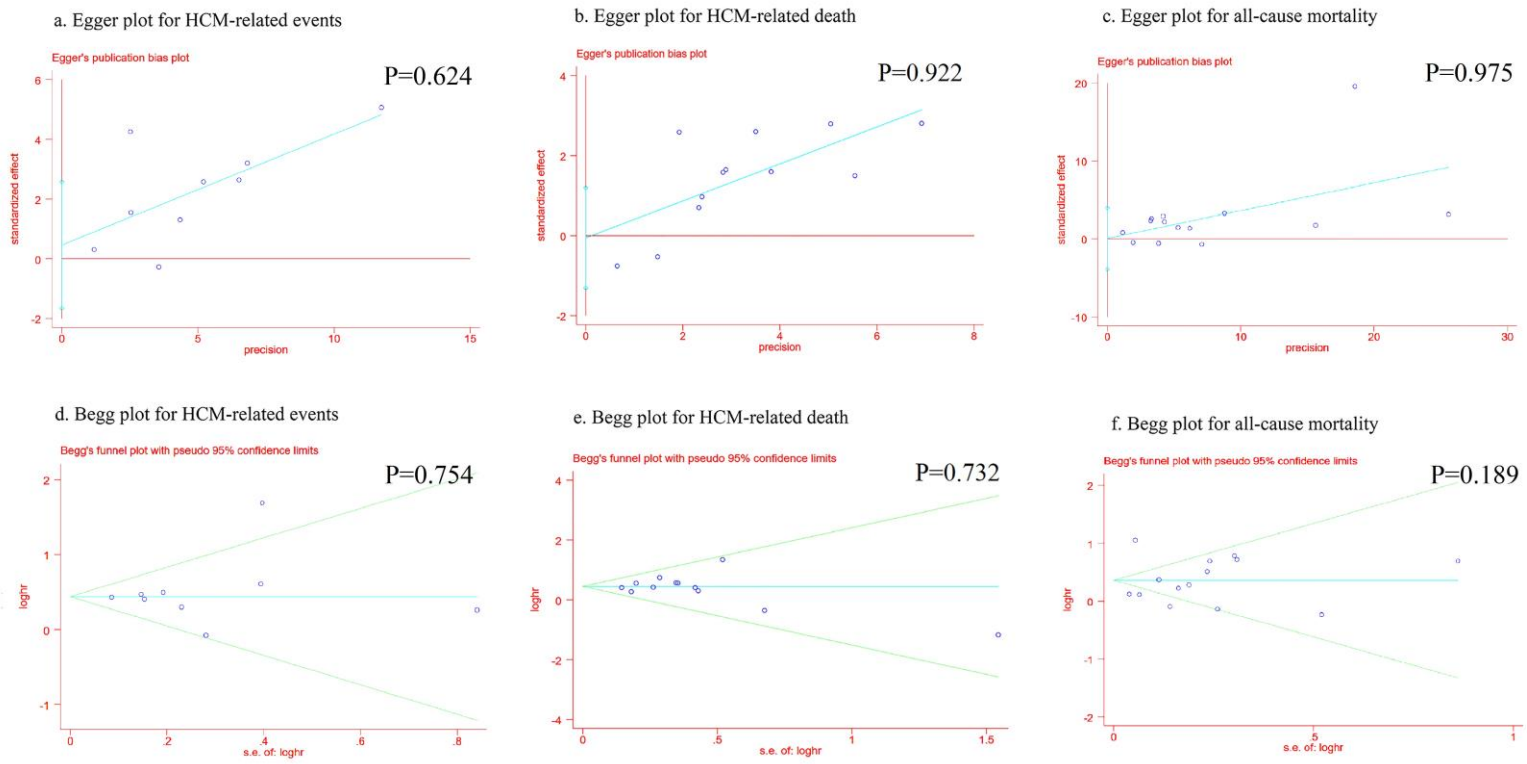
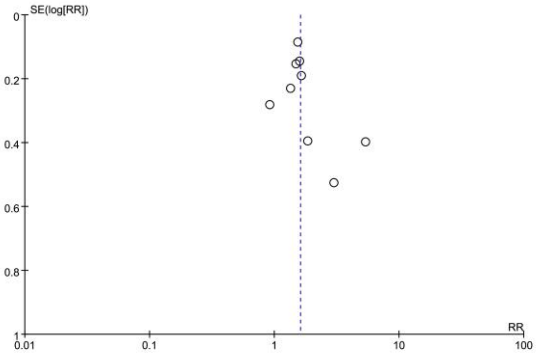
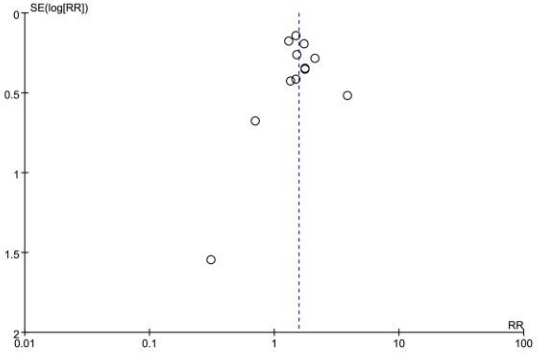


Figure S3. Funnel plot for main outcomes (HCM-related events, HCM-related death, all-cause mortality) of sex differences in HCM patients. a. HCM-related events; b. HCM-related death; c. all-cause mortality.

a. HCM-related events



b. HCM-related death



c. All-cause mortality

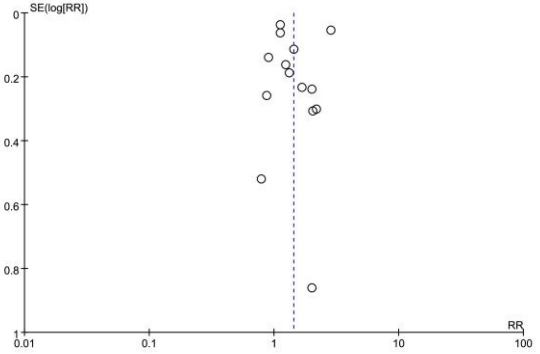


Figure S4. Sensitivity analysis of sex difference in HCM for HCM-related event, HCM-related death and all-cause mortality by omitting one study at once. a. HCM-related event; b. HCM-related death; c. All-cause mortality.

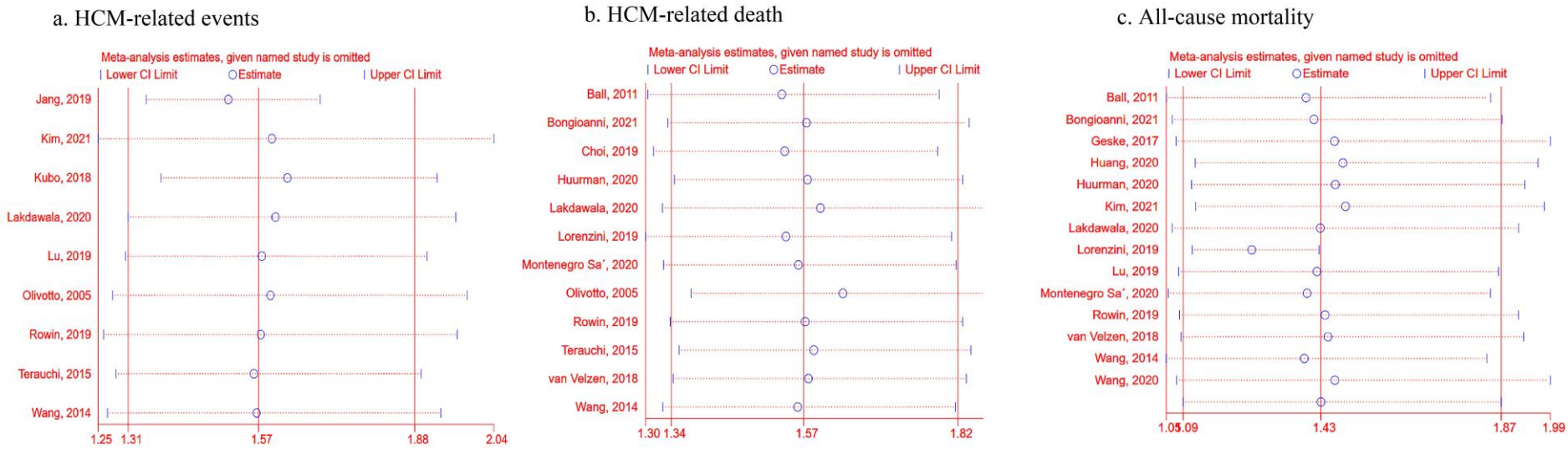
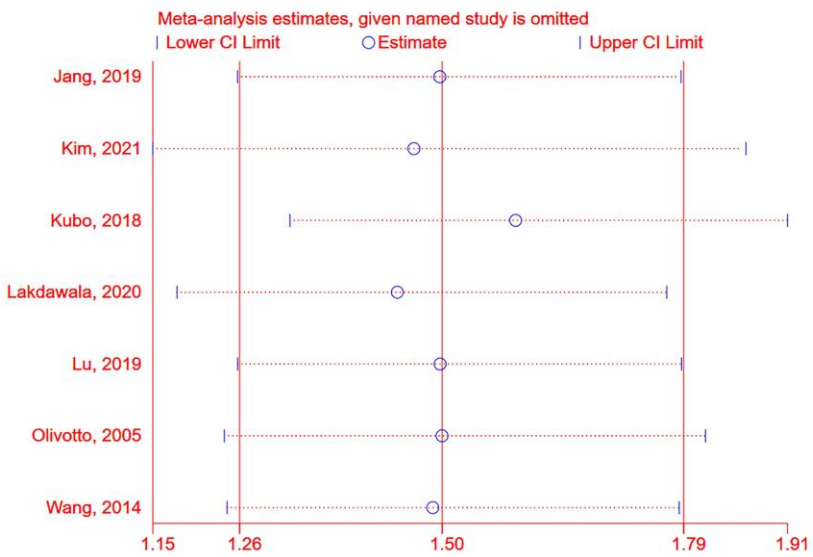


Figure S5. Sensitivity analysis of sex difference in HCM for HCM-related event and all-cause mortality by omitting one study at once after removing the univariate analysis. a. HCM-related event; b. All-cause mortality.

a. HCM-related events



b. All-cause mortality