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).

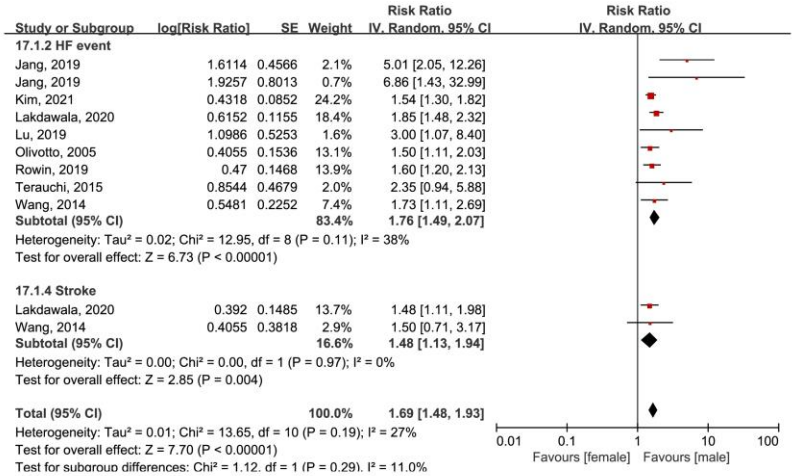
g. Assessment of outcome.

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

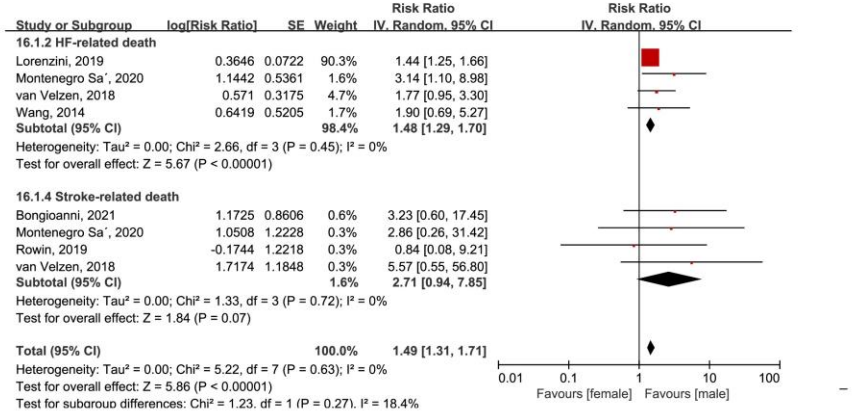


Figure S2. Egger's publication bias plot and Begg's funnel plot for main outcomes (HCM-related events, HCM-related death, all-cause mortality) of sex differences in HCM patients. a. Egger's publication bias plot for HCM-related events; b. Egger's publication bias plot for HCM-related death; c. Egger's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

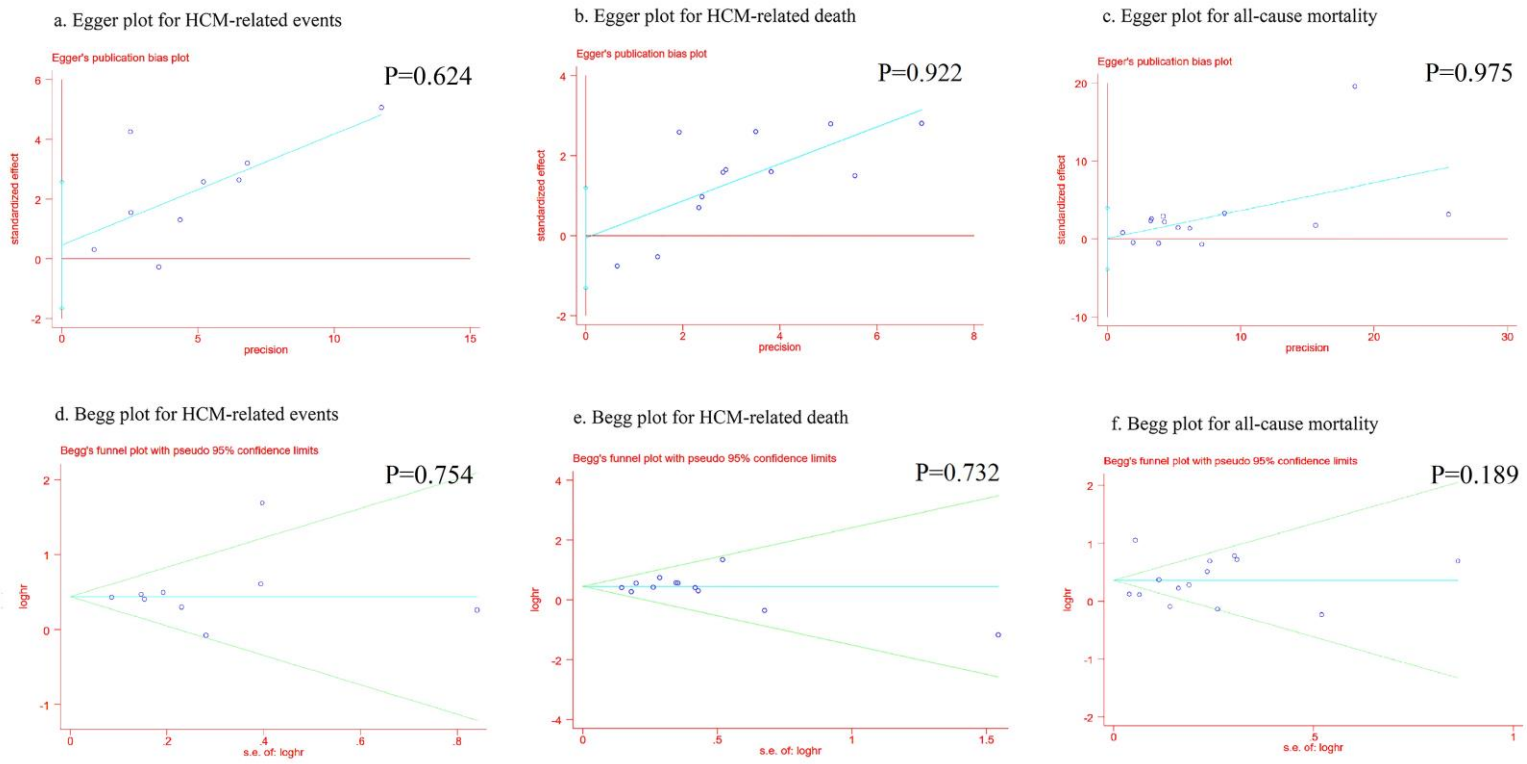
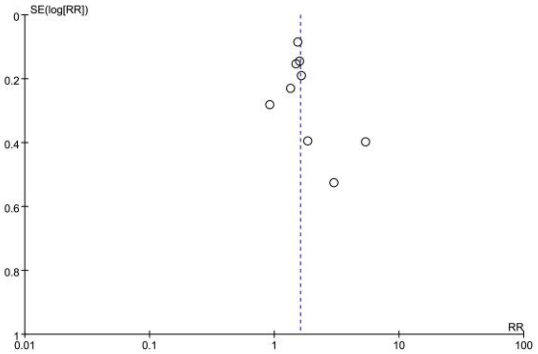
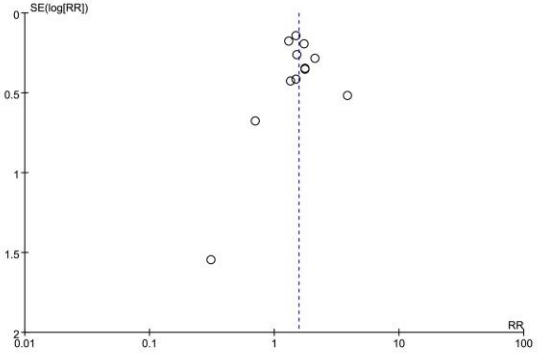


Figure S3. Funnel plot for main outcomes (HCM-related events, HCM-related death, all-cause mortality) of sex differences in HCM patients. a. HCM-related events; b. HCM-related death; c. all-cause mortality.

a. HCM-related events



b. HCM-related death



c. All-cause mortality

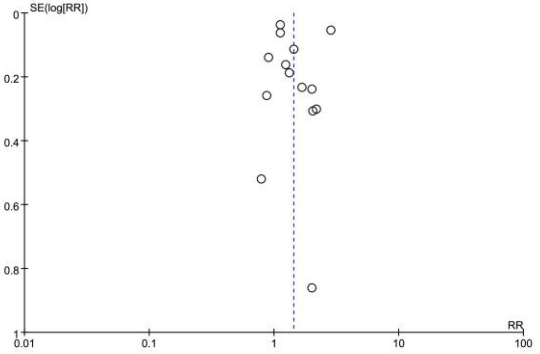


Figure S4. Sensitivity analysis of sex difference in HCM for HCM-related event, HCM-related death and all-cause mortality by omitting one study at once. a. HCM-related event; b. HCM-related death; c. All-cause mortality.

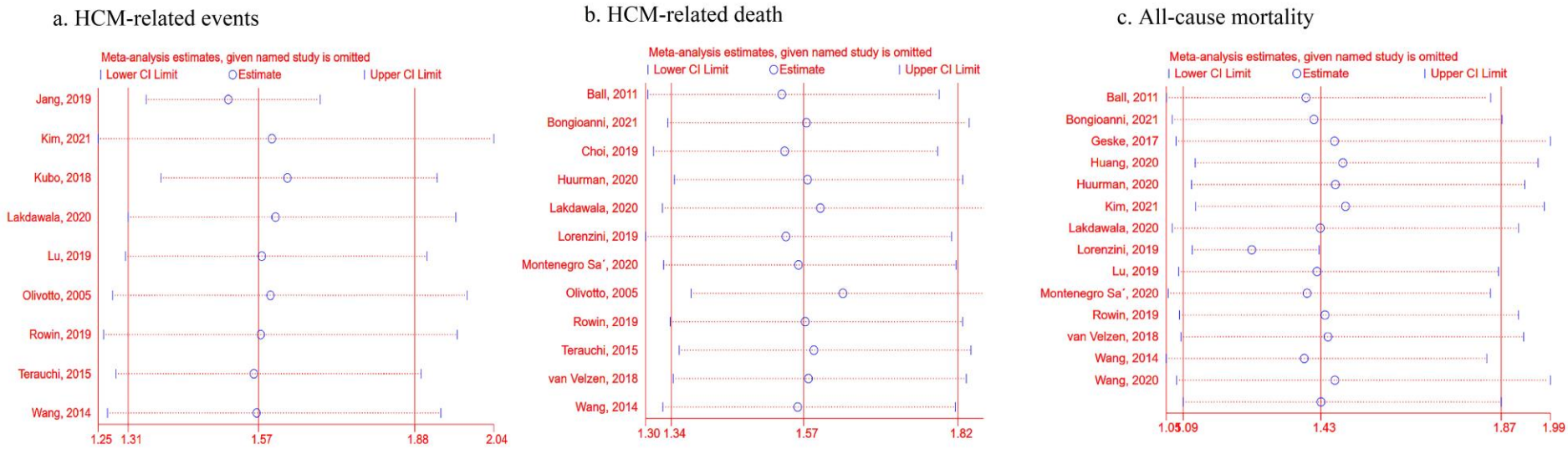
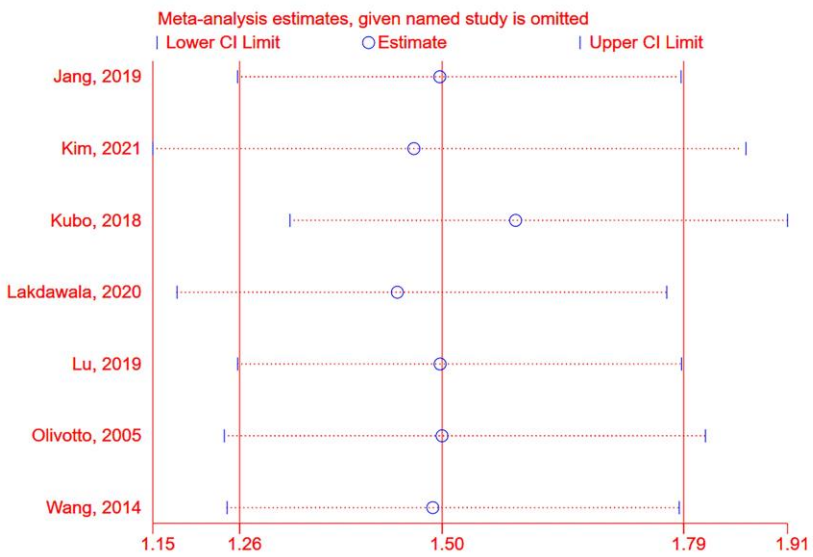


Figure S5. Sensitivity analysis of sex difference in HCM for HCM-related event and all-cause mortality by omitting one study at once after removing the univariate analysis. a. HCM-related event; b. All-cause mortality.

a. HCM-related events



b. All-cause mortality