Review

Association of erectile dysfunction and cardiovascular disease: an umbrella review of systematic reviews and meta-analyses

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Objectives

To present an overall picture of the evidence regarding the association of erectile dysfunction (ED) with cardiovascular disease (CVD).

Methods

Systematic reviews and meta-analyses that studied the association of ED with any CVD were included in this umbrella review. We did not restrict the population to a particular group or age. PubMed, Embase, the Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the PROSPERO register were searched to find relevant systematic reviews, with or without meta-analyses, from inception to April 2020. The JBI Checklist for Systematic Reviews and Research Syntheses was used for the critical appraisal. Only studies with acceptable quality were included. Two independent reviewers extracted the data using the JBI data extraction tool for qualitative and quantitative data extraction.

Results

The summary estimate showed a higher risk of CVD (relative risk [RR] 1.45, 95% confidence interval [CI] 1.36–1.54; $P <$ 0.001), coronary heart disease (RR 1.50, 95% CI 1.37–1.64; $P <$ 0.001), cardiovascular-related mortality (RR 1.50, 95% CI 1.37–1.64; $P <$ 0.001), all-cause mortality (RR 1.25, 95% CI 1.18–1.32; $P <$ 0.001), myocardial infarction (RR 1.55, 95% CI 1.33–1.80; $P <$ 0.001) and stroke (RR 1.36, 95% CI 1.26–1.46; $P <$ 0.001) in patients with ED than in other patients.

Conclusions

Our results confirm that ED is an independent predictor of CVD and their outcomes. ED and CVD are two presentations of the same physiological phenomenon. ED normally precedes symptomatic CVD, providing a window of opportunity for healthcare practitioners to screen and detect high-risk patients early to prevent avoidable morbidity and mortality.

Keywords

erectile dysfunction, umbrella review, cardiovascular disease, prevention, coroanary heart disease, myocardial infarction, cardiovascular disease, #erectiledysfunction

Introduction

Erectile dysfunction (ED) is defined as the recurrent or consistent inability to obtain and/or maintain a penile erection sufficient for satisfactory sexual performance [1]. It is a highly prevalent age-associated problem affecting a large proportion of men, and its prevalence increases with age [2]. In addition to the sexual distress it causes, ED has also been suggested to be a harbinger of cardiovascular disease (CVD) [3], the leading cause of death globally [4]. This is because both are vascular diseases with common risk factors [5]. In addition to aging, other cardiovascular (CV) risk factors including hypertension, diabetes, smoking, obesity and dyslipidaemia have also been shown to be significantly associated with ED [6,7]. ED has indeed been proposed as an early manifestation of a larger subclinical systemic pathology that subsequently results in full-blown CVD [8,9]. Several studies, including a number of meta-analyses, have aimed to calibrate the association between ED and CVD, with sometimes contradictory findings as a result of differences in study population and design. We aimed to perform an umbrella review to create an overview of the most high-quality evidence underlying the association of ED with CVD.

Methods

Umbrella Review Methods

An umbrella review is a comprehensive study to systematically search, evaluate and organize existing evidence from several systematic reviews, with or without meta-analysis, on health outcomes associated with an exposure [10]. We followed the instructions provided by the Joanna Briggs Institute (JBI) for performing the umbrella review. We performed a review of ED and multiple CV exposures of interest. We included systematic reviews, with or without meta-analysis, and presented the data in two quantitative and qualitative reports. We also performed a second meta-analysis by including the final effect estimate of multiple meta-analyses for specific outcomes when there were sufficient data. The proposal for this umbrella review was registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Literature Search

We searched PubMed, Embase, CINAHL, the JBI Database of Systematic Reviews and Implementation Reports, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the PROSPERO register to find relevant systematic reviews with or without meta-analyses that investigated the association between ED and CVD in all languages from inception to April 2020. We used the following search strategy: ("Erectile Dysfunction"[MeSH]) OR ("Erectile Dysfunction"[Text Word]) OR "Male Sexual Impotence"[Text Word]) OR "Male Impotence"[Text Word]) AND ("Cardiovascular Diseases"[MeSH]) OR ("Cardiovascular Disease"[Text Word]) OR "Cardiovascular Diseases"[Text Word]))) AND (systematic[sb] OR Meta-Analysis[ptyp]). Finally, we performed a manual search of the reference lists of relevant studies. Two authors independently screened the titles and abstracts and selected the full texts. The full text was evaluated for eligibility. In case of disagreement, a third author arbitrated.

Eligibility Criteria and Data Extraction

Only systematic reviews with or without meta-analysis were eligible for this review. We included meta-analyses of observational studies (cohort, case–control and cross-sectional) studies, together with qualitative systematic reviews. The inclusion of meta-analyses was not limited based on the method of data pooling (e.g. relative risk [RR] or odds ratio). No restrictions were imposed regarding the size, ethnicity, setting, race or country of origin of the sample population. However, we excluded aging populations or certain associated diseases, such as diabetes, hypertension, dyslipidaemia and obesity, to reduce potential bias. The studies generally compared the risk of developing CVD in two groups, those with ED and those without ED. If several CVD outcomes were evaluated in a study, we included each one separately in the analysis for the outcome of interest.

Two reviewers independently extracted the data from the included articles. Data extraction was carried out using the JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses [11]. Extraction list items included the name of the author, year of publication, objective, characteristics of the participants, number of studies/participants, sources/range searched, type of study, instrument and scoring of critical appraisal, estimates of the proportion of variance reflecting true differences in effect size (I^2) for publication bias, method of analysis, results, and conclusions. Differences between the two reviewers were resolved by consensus among the co-authors.

Assessment of Methodological Quality of Included Studies and Quality of Evidence

We used the JBI critical appraisal tools for systematic reviews to assess the methodological quality of systematic reviews [12]. The JBI critical appraisal tool was used to assess the methodological quality of the systematic reviews and the methods they have used to address and reduce bias. We did not review the studies included within the selected meta-analyses and we only used the summary estimate from each meta-analysis. Assessments with fewer than five 'yes' responses were excluded. The τ^2 statistic was used as a

measure of heterogeneity and we performed the Egger's test as a measure of publication bias where possible.

Data Synthesis

The findings of quantitative studies were presented in a table according to the JBI method for umbrella reviews. The table was stratified based on available CVD outcomes and each section included author, year of publication, number of studies/participants, results/findings and heterogeneity. A separate table was used to present the qualitative findings extracted from relevant reviews, including sections for phenomena of interest/context, synthesized findings and details of strategies.

Method of Analysis

We reanalysed each meta-analysis using the DerSimonian and Laird random-effects model [13]. We only performed the reanalysis when there was sufficient and detailed exposure and outcome data available. The summary data are presented in forest plots together with assessments of heterogeneity and publication bias and basic study characteristics.

Results

Figure 1 shows the systematic search and selection process of eligible studies for the umbrella review. The primary search resulted in 186 titles and, after removing the duplicates, we reviewed 112 titles and abstracts. Finally, 12 full texts were selected and, of these, seven (five meta-analyses and two qualitative systematic reviews) were eligible for the umbrella review. We reviewed six unique quantitative outcomes, and there was a median of 2.5 studies for each outcome. These outcomes included CVD events, all-cause mortality, CV-related mortality (CV mortality), myocardial infarction (MI), stroke and coronary heart disease (CHD).

The risk-of-bias assessment JBI questionnaire for critical appraisal of systematic reviews was used to evaluate the quality of the studies. All of the studies had more than five 'yes' answers, therefore, no study was excluded. A summary of the risk assessment of the seven eligible studies is shown in Table 1.

Quantitative findings are shown in Table 2, including the summary data for the reanalysis of the meta-analyses. The table shows some of the main characteristics of every study and the calculations for each outcome. The most commonly studied outcome was all-cause mortality, followed by CVD events. Except for CV mortality, the other summary outcomes showed statistically significant changes.

Cardiovascular Disease

The summary estimate shows that CVD is 45% more likely to occur in patients with ED than in those without ED (RR 1.45, 95% CI 1.36–1.54; $P < 0.001$). The results were similar to those of the most recent meta-analysis for this outcome by Zhao et al. [14] (RR 1.43, 95% CI 1.28–1.60; $P < 0.001$). However, the present review showed a higher level of heterogeneity for this outcome (Table 2).

Coronary Heart Disease

The summary estimate showed that CHD was 50% more likely to occur in patients with ED than in those without ED (RR 1.50, 95% CI 1.37–1.64; $P < 0.001$). However, this outcome analysis was performed only in two studies (Table 2).

Fig. 1 Flowchart of selection of studies for inclusion in the meta-analysis. CVD cardiovascular disease; ED, erectile dysfunction.
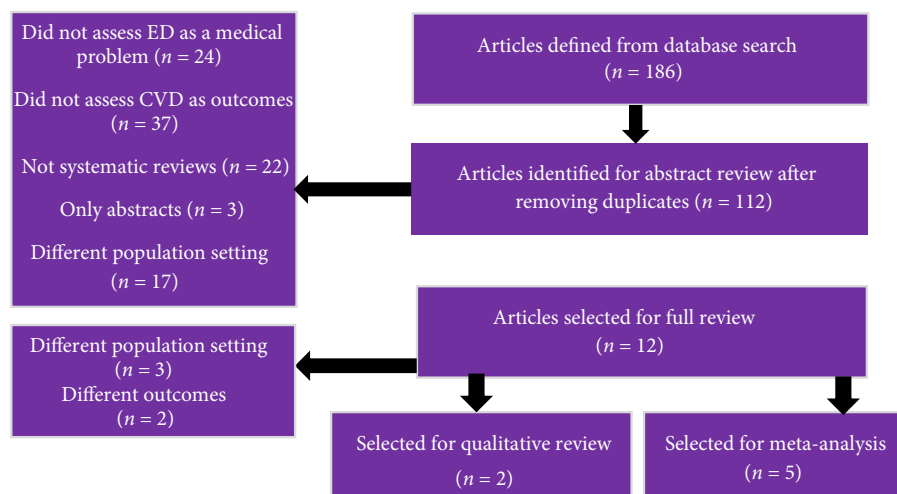
Table 1 Joanna Briggs Institute questionnaire for critical appraisal of systematic reviews.

Question*	Dong et al. 2011 [42]	Gandaglia et al. 2014 [15]	Guo et al. 2010 [40]	Raheem et al. 2017 [3]	Vlachopoulos et al. 2013 [23]	Fan et al. 2018 [41]	Zhao et al 2019 [14]
1. Is the review question clearly and explicitly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were the inclusion criteria appropriate for the review question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the search strategy appropriate?	No	Yes	Yes	Unclear	Yes	Yes	Yes
4. Were the sources and resources used for the study adequate?	No	Yes	Yes	Yes	Yes	No	Yes
5. Were the criteria for appraising studies appropriate?	Yes	No	Unclear	Unclear	Unclear	Yes	Yes
6. Was critical appraisal conducted by two or more reviewers independently?	Yes	No	Yes	Unclear	Yes	Yes	Yes
7. Were there methods to minimize errors in data extraction?	Yes	Unclear	Yes	No	Yes	Yes	Yes
8. Were the methods used to combine studies appropriate?	Yes	N/A	Yes	Unclear	Yes	Yes	Yes
9. Was the likelihood of publication bias assessed?	Yes	N/A	yes	N/A	Yes	Yes	Yes
10. Were recommendations for policy and/or practice supported by the reported data?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
11. Were the specific directives for new research appropriate?	Yes	Yes	Yes	Yes	No	Yes	No
Overall appraisal†	Include	Include	Include	Include	Include	Include	Include

*Possible responses: yes/no/unclear/not applicable. †Possible responses: include/exclude/seek further information.

Cardiovascular Mortality

The summary estimate showed that CV mortality was only 14% more likely to occur in patients with ED compared with those without ED; the difference was statistically significant (RR 1.50, 95% CI 1.37–1.64; $P < 0.001$ [Table 2]).

All-Cause Mortality

The summary estimate showed that all-cause mortality was 25% more likely to occur in patients with ED compared with those without ED (RR 1.25, 95% CI 1.18–1.32; $P < 0.001$). This outcome was assessed in all the included meta-analyses. Interestingly, the studies had a low level of heterogeneity for this outcome and the summary estimate had a narrow CI (Table 2).

Myocardial Infarction

The summary estimate showed that MI was 55% more likely to occur in patients with ED compared with those without ED (RR 1.55, 95% CI 1.33–1.80; $P < 0.001$); this was the biggest summary estimate measured among all outcomes. This estimate was based on only two studies, but both were of high quality and reported statistically significant findings (Table 2).

Stroke

The summary estimate shows that stroke was 36% more likely to occur in patients with ED compared with those without ED (RR 1.36, 95% CI 1.26–1.46; $P < 0.001$). We estimated this outcome in three meta-analyses; all were of high quality and had a low level of heterogeneity (Table 2).

Qualitative Summary Results

Erectile Dysfunction as a Predictor of Cardiovascular Disease

In a comprehensive critical systematic review, Gandaglia et al. [15] indicated that ED and CVD are different manifestations of the same pathophysiological disorder. They also hypothesized that using a validated questionnaire such as the International Index of Erectile Function can help identify patients with ED early, thereby also identifying the patients likely to experience CVD. The severity of ED can be a predictor of a higher prevalence of CVD, especially coronary artery disease [15]. Raheem et al. [3] concluded that ED could be a marker of the severity of CVD. However, ED did not improve risk assessments beyond more traditional previous measures (Table 3).

Pathophysiological Association of Erectile Dysfunction and Cardiovascular Disease

Gandaglia et al. [15] summarize and explain the pathophysiology of ED in three major mechanisms: the

Table 2 The summary estimates of six commonly reported outcomes in the meta-analysis.

Outcome	Author/year	Number of studies/ participants	Findings RR (95% CI): P value	Heterogeneity: I², %	τ²
CVD	Dong et al. 2011 [42]	8	1.48 (1.25–1.74); 0.001	72.9	0
	Guo et al. 2010 [40]	7	1.41 (1.22–1.64); < 0.001	20.1	
	Vlachopoulos et al. 2013 [23]	13/91 831	1.44 (1.27–1.63); < 0.001	66.4	
	Zhao et al. 2019 [14]	19	1.43 (1.28–1.60); < 0.001	72	
CHD	Dong et al. 2011	4	1.46 (1.31–1.63); 0.001	0	0
	Zhao et al. 2019 [14]	6	1.59 (1.36–1.85); < 0.001	35.8	
CV mortality	Vlachopoulos et al. 2013 [23]	4/34 761	1.19 (0.97–1.46); 0.089	58.5	0
	Fan et al. 2018 [41]	3	1.11 (0.92–1.35); 0.138	49.6	
All-cause mortality	Dong et al. 2011	3	1.19 (1.05–1.34); 0.005	0	0
	Guo et al. 2010 [40]	2	1.23 (1.02–1.48); 0.034	0	
	Vlachopoulos et al. 2013 [23]	5/17 869	RR 1.25 (1.12–1.39); < 0.001	31.9	
	Fan et al. 2018 [41]	6	RR 1.24 (1.11–1.39); 0.55	0	
	Zhao et al. 2019 [14]	7	1.33 (1.19–1.48); < 0.001	27.4	
MI	Guo et al. 2010 [40]	2	1.43 (1.10–1.85); 0.007	48.8	0
	Vlachopoulos et al. 2013 [23]	4	1.62 (1.34–1.96); < 0.001	0	
Stroke	Dong et al. 2011	3	1.35 (1.19–1.54); 0.001	0	0
	Vlachopoulos et al. 2013 [23]	6	1.39 (1.23–1.57); < 0.001	0	
	Zhao et al. 2019 [14]	4	1.34 (1.18–1.52); < 0.001	0	

Forest plot summaries of the meta-analysis of meta-analyses

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Dong et al. 2011	1.480	1.259	1.740	4.748	0.000
Guo et al. 2010	1.470	1.296	1.668	5.989	0.000
Vlachopoulos et al 2013	1.440	1.271	1.631	5.728	0.000
Zhao et al 2019	1.430	1.279	1.599	6.283	0.000
	1.450	1.361	1.546	11.424	0.000

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Dong et al. 2011	1.460	1.309	1.629	6.788	0.000
Zhao et al 2019	1.590	1.363	1.854	5.908	0.000
	1.502	1.374	1.642	8.955	0.000

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Vlachopoulos et al 2013	1.190	0.970	1.460	1.668	0.095
Yu Fan et al. 2018	1.110	0.916	1.345	1.067	0.286
	1.147	0.997	1.319	1.919	0.055

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Dong et al. 2011	1.190	1.053	1.344	2.796	0.005
Guo et al 2010	1.230	1.021	1.482	2.180	0.029
Vlachopoulos et al 2013	1.250	1.122	1.393	4.050	0.000
Yu Fan et al. 2018	1.240	1.108	1.388	3.749	0.000
Zhao et al 2019	1.330	1.193	1.483	5.126	0.000
	1.253	1.187	1.322	8.209	0.000

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Guo et al. 2010	1.430	1.103	1.854	2.697	0.007
Vlachopoulos et al 2013	1.620	1.339	1.959	4.973	0.000
	1.551	1.330	1.808	5.606	0.000

	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Dong et al. 2011	1.350	1.187	1.536	4.563	0.000
Vlachopoulos et al 2013	1.390	1.230	1.570	5.289	0.000
Zhao et al 2019	1.340	1.181	1.521	4.531	0.000
	1.361	1.265	1.463	8.315	0.000

CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; ED, erectile dysfunction; MI, myocardial infarction; RR, relative risk.

Table 3 Tabular presentation of qualitative findings for an umbrella review.

Phenomena of interest/ context	Synthesized finding	Details of strategies
ED and CVD should be considered two different manifestations of the same systemic disorder.	The link between these conditions resides in the interaction between CV risk factors, androgens and chronic inflammation that leads to atherosclerosis and flow-limiting stenosis. Macroscopically invisible alterations, such as endothelial dysfunction and autonomic hyperactivity, might partly explain the relationship between ED and CVD.	ED usually precedes CVD and its diagnosis offers a window of opportunity for risk reduction. Specific algorithms can help identify patient with ED that need further CV evaluations and need intensive treatments.
There is a paucity of clear clinical guidelines detailing when and how to evaluate for ED in patients with known CVD.	There is a strong consensus that men with ED should be considered at high risk of CVD. Coronary risk score should be evaluated by using risk assessment tools. The 2012 Princeton III Consensus Conference has defined possible approaches regarding management of patients with ED and no known CVD.	The similarities and differences of the existing clinical guidelines and recommendations regarding assessment and management of ED and CVD, as well as the pathophysiological linkage between ED and CVD, that may trigger opportunistic screenings and secondary prophylaxis considering the CV risk factors-mainly in young on-diabetic men with ED.

CV, cardiovascular.

artery size hypothesis; inflammation; and low androgen levels. Based on the artery size hypothesis, the diameter of the penile arteries is smaller than the coronary arteries, thus a systemic vascular pathology first presents as ED rather than coronary symptoms. Yet, studies show that this cannot explain all cases. Endothelial dysfunction and inflammation can also trigger the development of ED. Low androgen level can also be a factor underlying the complex pathophysiological link between ED and CVD [15] (Table 3).

Clinical Implications

Gandaglia et al. [15] concluded that patients with ED who have CV risk factors should be categorized as high risk and need further CV evaluations since this can lead to silent coronary artery disease. Testosterone replacement is an effective treatment for ED that might have a role in improving cardiac event rate over time. In addition, they highlighted the role of phosphodiesterase-5 (PDE5) inhibition in patients with ED at high risk for coronary artery disease, but recommended further prospective randomized controlled trials. Finally, they emphasized the need for a CV evaluation in patients complaining of ED to their physicians [15]. Raheem et al. [3] concluded that the role of the urologists, general practitioners and primary care physicians is to identify high-risk patients and refer them to cardiologists for further assessment (Table 3).

Discussion

A risk factor or determinant, which may be causal or non-causal, is strongly associated with increased rates of disease [16]. Hence, the identification of risk factors can be a screening strategy in medicine [17].

Since Graham Jackson introduced ED as an independent marker for undiagnosed CVD [18], the association of ED and CVD has been a matter of interest in many studies. Endothelial dysfunction leads to ED, which is a predominant vascular disease [19]. In both ED and CVD, there are low levels of testosterone; however, the relationship between testosterone and CVD is complex [20–22] and common risk factors coexist in both diseases. CVD can predict the risk of ED, or conversely, ED leads to CVD by triggering the associated CVD events [18]. The predictive role of ED for ischaemic heart disease is documented in a meta-analysis of 12 prospective cohort studies [23]. Others have highlighted increased CV risk in patients with ED and the potential prognostic importance of ED [24–26].

Several interacting risk factors contribute to the development of CVD [27]. In addition, different risk assessors have been developed as preventive treatment strategies. One of them is QRISK, which has been used in the general practice setting since 2007; it was then upgraded to QRISK2 [28]. QRISK2 is a widely used risk assessor, using UK patient data, to estimate the 10-year risk of experiencing a CVD event [29]. The incorporated risk factors in the algorithm include body mass index, ethnicity, type 2 diabetes mellitus, antihypertensive treatment status, family history of CVD, chronic kidney disease, atrial fibrillation and rheumatoid arthritis [28]. The most recent updated risk metric is QRISK3, which is also the most popular risk prediction model for CVD in the UK. Additional clinical variables in QRISK3 include migraine, corticosteroid use, systemic lupus erythematous, atypical antipsychotics, severe mental illness and ED. The other risk assessor is JBS3, which was developed from the QRISK2 lifetime CV risk algorithm in the Joint British Societies' CVD prevention guidelines in 2014. It provides novel lifetime risk

metrics including heart age and indicates the age of an individual of the same gender and ethnicity with an equivalent annual risk of a CV event but with an optimal risk factor profile [30]. The AUA guideline on testosterone replacement therapy stated that low level testosterone is a risk factor for CVD, and strongly recommended that clinicians should assess all testosterone-deficient patients for CVD risk factors including older age and male gender (as constant factors), as well as dyslipidaemia, hypertension, diabetes, current cigarette smoking (as justifiable factors) [31].

Meta-analyses of randomized, placebo-controlled trials to evaluate the efficacy and safety of PDE5 inhibitors with regard to cardiac function suggest that PDE5 inhibitor use contributes independently to improved cardiac function, with good safety profiles [32,33].

In a population-based study, the use of PDE5 inhibitors in patients with type 2 diabetes mellitus and ED was associated with a reduction in 7-year mortality as well as reduction of mortality in patients with a history of MI [34].

In addition, treatment for ED after a first MI was associated with reduced mortality, heart failure and hospitalization. Only men treated with PDE5 inhibitors had a reduced risk, which appeared to be dose-dependent [35]. Corona et al. [20], for the first time, evaluated systematically and comprehensively the available data on the association between testosterone and CVD in men, and concluded that low testosterone level was independently associated with overall CVD and CHD in cross-sectional surveys. In addition, low testosterone level predicts overall and CV mortality in longitudinal observational studies [20]. In addition, Pye et al. [36] showed that all-cause mortality in individuals with low-level testosterone (<8 nmol/L) was twice as high as in individuals with normal levels. Based on the population-based National Health and Nutrition Examination Survey, the risk of premature all-cause mortality is 70% higher in individuals with ED (hazard ratio 1.70, 95% CI 1.01–2.85; $P = 0.04$) [37].

Although, several studies have reported the role of ED as a potential predictor and risk factor for CVD, CV mortality, all-cause mortality and other CV morbidities [38], data in this regard are heterogeneous and often contradictory. When a topic is diverse and has a wide scope, umbrella reviews can provide ready summaries of the best evidence for decision-makers [11,39].

We used the JBI method for umbrella reviews since it is not limited to specific review types and it includes qualitative studies. Another feature of JBI umbrella reviews is its rigorous inclusion process, allowing only high-quality systematic reviews and meta-analyses [11]. We undertook an additional step in our study by performing a meta-analysis of meta-analyses for some of the outcomes when it was possible. Our results confirmed the results of previous meta-analyses,

showing a significant association of ED with CVD, CV mortality, all-cause mortality, MI, stroke and CHD [14,15,23,40,41]. The summary estimate for the association of ED with CV mortality was not statistically significant. Indeed, this estimate included only two studies without statistically significant outcomes. The study by Vlachopoulos et al. [23], which reported statistically insignificant results, did not have a strict risk-of-bias assessment for inclusion, and the other study included a small number of studies with high risks of bias, and most importantly, both of the studies had some levels of heterogeneity [23,41] (Table 2). ED and CVD have a similar pathophysiological disease process. They share risk factors but have different presentations. ED precedes CVD in most cases. This provides a crucial window of opportunity for clinicians to screen potential individuals for ED to identify CVD and prevent its exacerbation [15]. Raheem et al. [3] emphasize the roles of urologists and general practitioners in screening high-risk patients and referring them to cardiologists. This opportunistic screening is cost-beneficial and can improve patient quality of life and survival.

One of the strengths of this umbrella review was the inclusion of all available systematic reviews, regardless of country, language and type of CV outcome based on our review question. However, we only included systematic reviews with high quality and low risk of bias using the JBI risk-of-bias assessment tool. Another advantage was the inclusion of both qualitative and quantitative studies in the present review to provide a broad vision of the recent studies with the highest levels of evidence. One of the main limitations of this study was the limited number of high-quality studies, especially for some of the outcomes. The methods used for meta-analysis also varied among studies. Due to the limited number of studies and low heterogeneity, some studies used fixed models for the meta-analysis whereas the others used random-effect models. We partly attempted to solve this problem by using a random-effect model to perform the meta-analysis of meta-analyses: the summary estimates. Another limitation was the overlap in included studies for systematic reviews. Nevertheless, this umbrella review highlighted the importance of CV evaluations in patients with ED and it provides evidence of validated findings for researchers, clinical practitioners and policy-makers to fulfill their role in managing patients with ED and CVD.

In conclusion, our results confirm that ED is an independent predictor of CVD, MI, CHD, stroke, CV mortality and all-cause mortality. ED and CVD are different presentations of the same pathophysiological disorder. However, ED normally precedes CVD, giving the health practitioners a window opportunity for early detection and prevention in individuals who have increased risk of CVD exacerbations. PDE5 inhibitors and testosterone replacement can be effective treatments for CVD and ED and seem to have minimal CV

adverse events. However, there is a need for more high-quality prospective studies for more definitive recommendations.

Conflicts of Interest

None declared.

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JBI, Joanna Briggs Institute; MI, myocardial infarction; PDE5, phosphodiesterase-5; RR, relative risk.