

Erectile Dysfunction and Risk of Cardiovascular Disease

Meta-Analysis of Prospective Cohort Studies

Jia-Yi Dong, BSC,* Yong-Hong Zhang, MD, PhD,† Li-Qiang Qin, MD, PhD*

Suzhou, China

Objectives

Our goal was to evaluate the association between erectile dysfunction (ED) and risk of cardiovascular disease (CVD) and all-cause mortality by conducting a meta-analysis of prospective cohort studies.

Background

Observational studies suggest an association between ED and the incidence of CVD. However, whether ED is an independent risk factor of CVD remains controversial.

Methods

The PubMed database was searched through January 2011 to identify studies that met pre-stated inclusion criteria. Reference lists of retrieved articles were also reviewed. Two authors independently extracted information on the designs of the studies, the characteristics of the study participants, exposure and outcome assessments, and control for potential confounding factors. Either a fixed- or a random-effects model was used to calculate the overall combined risk estimates.

Results

Twelve prospective cohort studies involving 36,744 participants were included in the meta-analysis. The overall combined relative risks for men with ED compared with the reference group were 1.48 (95% confidence interval [CI]: 1.25 to 1.74) for CVD, 1.46 (95% CI: 1.31 to 1.63) for coronary heart disease, 1.35 (95% CI: 1.19 to 1.54) for stroke, and 1.19 (95% CI: 1.05 to 1.34) for all-cause mortality. Sensitivity analysis restricted to studies with control for conventional cardiovascular risk factors yielded similar results. No evidence of publication bias was observed.

Conclusions

This meta-analysis of prospective cohort studies suggests that ED significantly increases the risk of CVD, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors. (J Am Coll Cardiol 2011;58:1378–85) © 2011 by the American College of Cardiology Foundation

Erectile dysfunction (ED) is common and increases as men age. It is estimated that approximately 18 million men in United States currently experience ED (1). Meanwhile, cardiovascular disease (CVD) remains the leading cause of death in the United States (2). It is well accepted that CVD predicts incidence of ED, largely because both conditions share the same risk factors, including age, hypertension, dyslipidemia, smoking, obesity, and diabetes (3). Conversely, it has also been hypothesized that ED may be a marker of further cardiovascular events (4).

The past few years have seen a rapidly growing interest in testing this hypothesis. Many epidemiologic studies (5–21) have investigated the link between ED and risk of CVD, and most found a positive association. However, the magnitudes of the association varied between studies. Although a previous meta-analysis (22) combined several cohort studies and re-

ported a statistically significant relation of ED to cardiovascular risk, evidence was limited because only 7 cohort studies were available at that time. Of note, 2 of the 7 cohort studies used a retrospective cohort design, which suffers more confounding and biases than a prospective cohort design. Furthermore, whether ED is an independent risk factor or merely a silent marker of CVD remains unclear. An improved understanding of this issue may have important public health and clinical implications given the possibility that prevention and treatment of ED might reduce the incidence of cardiovascular events. With recently accumulating evidence, our goal, therefore, was to evaluate the association between ED and risk of CVD and all-cause mortality by conducting a meta-analysis of prospective cohort studies.

Methods

Search strategy. We attempted to follow the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) (23) guidelines to report the present meta-analysis. We conducted a PubMed database search through January 2011 for relevant studies that tested the association between ED and risk of CVD, coronary heart disease

From the *Department of Nutrition and Food Hygiene, School of Radiation Medicine and Public Health, Soochow University, Suzhou, China; and the †Department of Epidemiology, School of Radiation Medicine and Public Health, Soochow University, Suzhou, China. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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(CHD), stroke, or all-cause mortality. The following search terms were used: 1) cardiovascular diseases, coronary disease, coronary thrombosis, myocardial ischemia, myocardial infarction, coronary stenosis, coronary restenosis, cerebrovascular disorders, stroke, death, mortality, and all-cause mortality; 2) erectile dysfunction, sexual dysfunction, and impotence; and 3) cohort studies, prospective studies, and follow-up studies. No restrictions were imposed. In addition, we reviewed the reference lists of retrieved papers and recent reviews.

Study selection. We first performed an initial screening of titles or abstracts. A second screening was based on full-text review. Studies were considered eligible if they met the following criteria: 1) the study design was a prospective cohort study; 2) the exposure of interest was ED; 3) the outcome of interest was CVD, CHD, stroke, or all-cause mortality; and 4) relative risk (RR) and the corresponding 95% confidence interval (CI) (or data to calculate them) were reported.

Data extraction. The key exposure variable was the presence or absence of ED at baseline. In most studies, men without ED served as the reference group, although in 3 studies (12,18,20), men with minimal or mild ED served as the reference group. We included all these studies for meta-analysis and performed a sensitivity analysis that only included studies with a reference group defined as strictly non-ED men.

Outcomes of interest in this study included major CVD (fatal and nonfatal), CHD (fatal and nonfatal), stroke (fatal and nonfatal), and all-cause mortality. CVD were defined as CHD, stroke, cardiac arrest, heart failure, peripheral artery disease, and sudden death. CHD was defined as acute myocardial infarction, angina pectoris, and other ischemic heart disease.

Data extraction was then performed using a standardized data-collection form. We extracted any reported RRs, hazard ratios, or incidence density ratios of outcomes for patients with ED compared with the reference group. We also extracted study characteristics for each trial. Data were recorded as follows: first author's last name; year of publication; country of origin; study period and duration of follow-up; characteristics of study population and age at baseline; number of CVD, CHD, stroke, or all-cause mortality events and total participants; ascertainment of ED; assessments of outcomes; and statistical adjustments for confounding factors. Two authors (J.-Y.D. and L.-Q.Q.) independently conducted the studies selection and data extraction. Any disagreements were resolved by discussion.

Statistical analyses. RR was used as a common measure of the association between ED and risk of CVD, CHD, stroke, or all-cause mortality across studies. The hazard ratios and incidence density ratios were directly considered as RRs. We calculated RRs for one study (19) in which only age-adjusted incidence rates for each group were reported. For another study (11) that reported hazard ratios separately

for reduced erectile rigidity and severely reduced erectile rigidity, we combined these 2 groups into a single group and calculated a combined hazard ratio using a fixed-effects model for the main analysis. RRs and corresponding SEs, which were derived from 95% CIs or p values, were logarithmically transformed to stabilize variance and normalize the distribution (24).

Homogeneity of RRs across studies was tested by using the Q statistic (significance level at $p < 0.10$). The I^2 statistic, which is a quantitative measure of inconsistency across studies (25), was also calculated. The combined risk estimates were computed using either fixed-effects models or, in the presence of heterogeneity, random-effects models (26). Because characteristics of populations, ascertainment of ED, and adjustments for confounding factors were not consistent between studies, we further conducted a sensitivity analysis to explore possible explanations for heterogeneity and to examine the influence of various exclusion criteria on the overall risk estimate. We also investigated the influence of a single study on the overall risk estimate by omitting 1 study in each turn. The sensitivity analysis was only performed for CVD because of rather small numbers of studies for other outcomes.

Potential publication bias was assessed by visual inspection of the Begg funnel plots in which the log RRs were plotted against their SEs. We also performed the Begg rank correlation test and Egger linear regression test at the $p < 0.10$ level of significance (27,28). All analyses were performed using STATA version 11.0 (StataCorp LP, College Station, Texas). A p value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Literature search. We initially retrieved 633 unique citations from the PubMed database. Of these, the majority were excluded after the first screening based on abstracts or titles, mainly because they were reviews, case-control studies, cross-sectional studies, or not relevant to our analysis. After full-text review of 19 papers, 4 studies (5,6,8,17) were excluded because they used a retrospective cohort design. An additional 3 studies (29–31) in which the association of interest was not evaluated were excluded. Finally, 12 studies (7,9–13,15,16,18–21) were included in our meta-analysis. A flow chart showing the study selection is presented in Figure 1.

Study characteristics. The characteristics of the 12 prospective cohort studies are presented in Table 1. These studies were published between 2005 and 2011. Five studies were conducted in the United States, 4 in Europe, 2 in China, and 1 was a multicountry study. The mean length of follow-up ranged from 4 to 16.2 years. Three studies were

Abbreviations and Acronyms

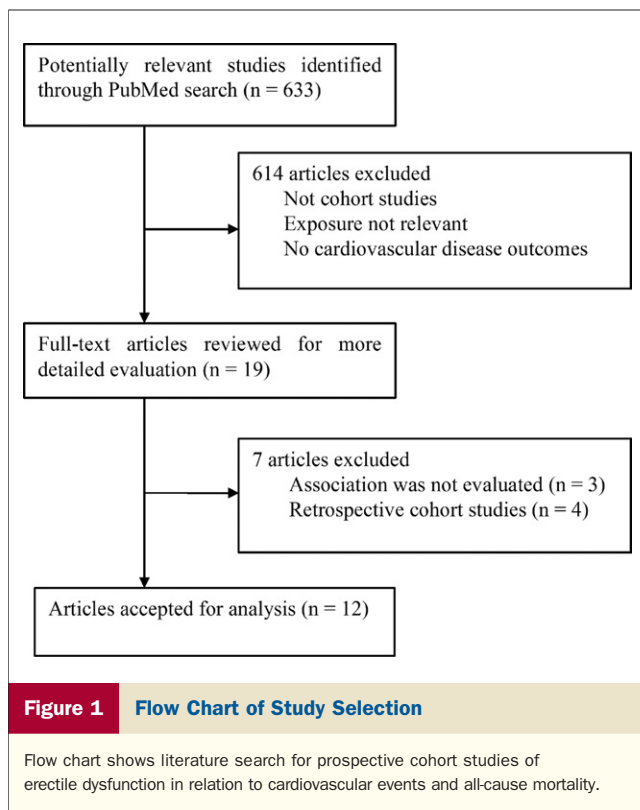
CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

ED = erectile dysfunction

RR = relative risk



conducted in patients with diabetes. The sizes of the cohorts ranged from 291 to 9,006 (total 36,744). The ascertainment of ED varied across studies, with most based on self-report or interviewer-administered questionnaires. Among the 12 studies included here, 8 reported CVD events, 4 reported CHD events, 3 reported stroke events, and 3 reported all-cause mortality. Outcome assessments were from a variety of sources, including medical record, self-report, and hospital database. Two studies adjusted for age only, whereas others controlled a group of conventional risk factors for CVD, including age, body mass index, blood pressure, diabetes, cholesterol, and smoking.

ED and risk of CVD. Figure 2 shows the results from the random-effects model combining the RRs for CVD. Among the 8 studies, 7 showed a significantly positive relation between ED and risk of CVD. However, the RRs for the association varied from 0.92 to 2.10 across studies. Overall, men with ED compared with the reference group experienced a significantly increased risk for developing CVD (RR: 1.48 [95% CI: 1.25 to 1.74]; $p < 0.001$). Substantial heterogeneity was observed ($p = 0.001$, $I^2 = 72.9\%$).

ED and risk of CHD, stroke, and all-cause mortality. Figure 3 presents the results from fixed-effects models combining the RRs for CHD, stroke, and all-cause mortality. Although there were fewer studies for these outcomes than CVD, the results were relatively consistent. The overall combined RRs in relation to ED were 1.46 (95% CI: 1.31 to 1.63; $p < 0.001$) for CHD, 1.35 (95% CI: 1.19 to 1.54; $p < 0.001$) for stroke, and 1.19 (95% CI: 1.05 to 1.34; $p =$

0.005) for all-cause mortality. There was no evidence of heterogeneity for these outcomes (all p values > 0.40 , all I^2 values = 0%). Further analyses using the random-effects model yielded identical results.

Sensitivity analyses. Sensitivity analyses were conducted to explore potential sources of heterogeneity in the association between ED and CVD and to examine the influence of various exclusion criteria on the overall risk estimate. Exclusion of 2 studies (18,19) in which men with minimal or mild ED served as the reference group yielded similar results (RR: 1.46 [95% CI: 1.20 to 1.78]; $p < 0.001$), with substantial evidence of heterogeneity ($p < 0.001$, $I^2 = 79.6\%$). Exclusion of 2 studies (19,20) that adjusted only for age showed a somewhat greater risk (RR: 1.54 [95% CI: 1.28 to 1.87]; $p < 0.001$), yet heterogeneity was still present ($p < 0.001$, $I^2 = 79\%$). Exclusion of 2 studies (9,16) that enrolled patients with diabetes changed the overall risk estimate little (RR: 1.47 [95% CI: 1.32 to 1.64]; $p < 0.001$), but no evidence of heterogeneity was observed among the remaining studies ($p = 0.45$, $I^2 = 0\%$). Further exclusion of any single study did not materially alter the overall combined RR, with a range from 1.38 (95% CI: 1.21 to 1.59; $p < 0.001$) to 1.56 (95% CI: 1.34 to 1.83; $p < 0.001$).

Publication bias. Visual inspection of the Begg funnel plot did not identify substantial asymmetry. The Begg rank correlation test and Egger linear regression test also indicated no evidence of publication bias among studies of ED and CVD risk (Begg, $p = 0.81$; Egger, $p = 0.24$).

Discussion

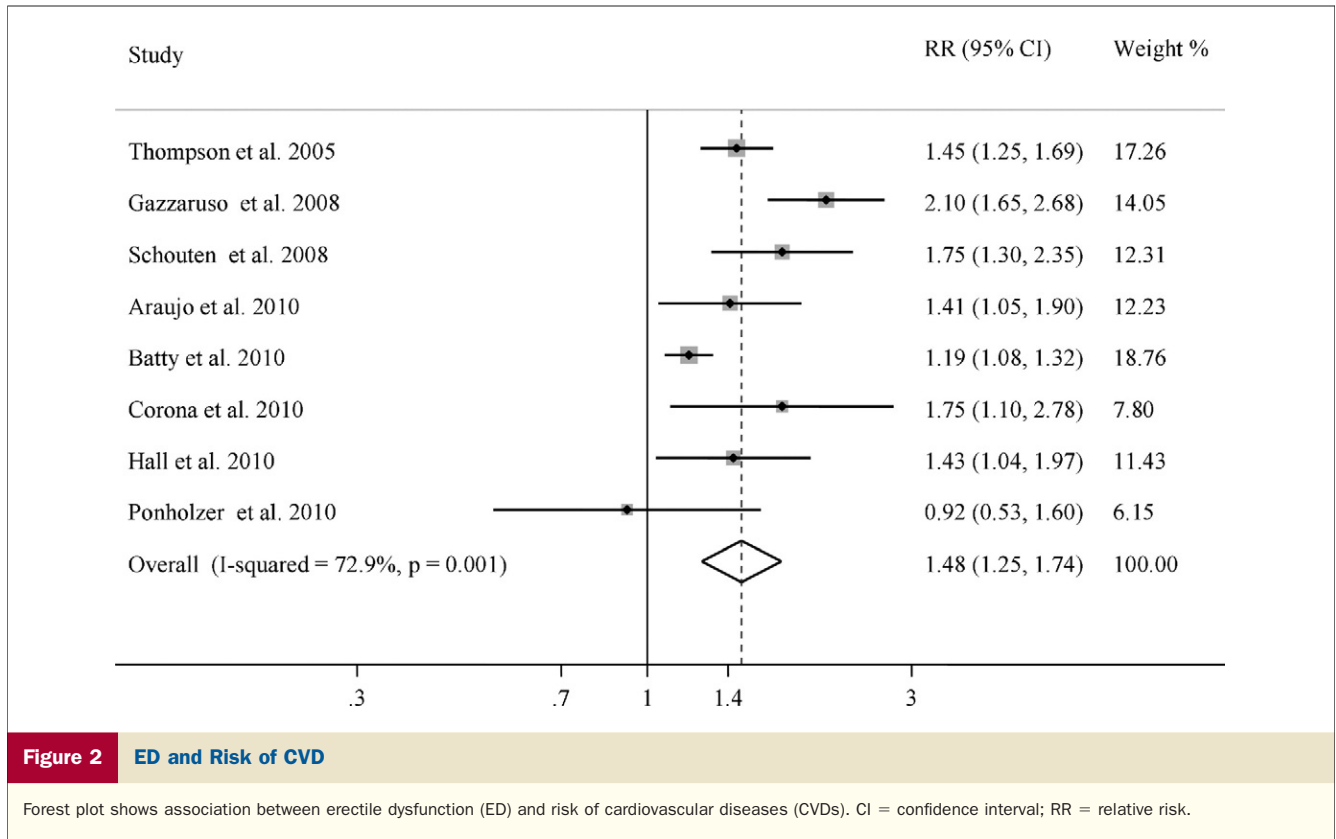
There is rapidly growing interest in the association between ED and risk of CVD. Our meta-analysis of 12 prospective cohort studies provides evidence that ED is significantly and independently associated with an increased risk of CVD, CHD, stroke, and all-cause mortality. Men with ED, compared with the reference group, experienced a significantly increased risk of 48% for CVD, 46% for CHD, 35% for stroke, and 19% for all-cause mortality.

ED as an independent risk factor of CVD. At present, the association between ED and CVD is not fully understood. It is well accepted that CVD is a risk factor of ED (3). It is also recognized that ED is a marker of further vascular diseases (32). However, whether ED is independently associated with incidence of CVD remains controversial. Results from our sensitivity analysis restricted to studies (7,9,11,15,16,18) with control for conventional cardiovascular risk factors, including age, body mass index, blood pressure, diabetes, cholesterol, and smoking, suggest that ED is probably an independent risk factor of CVD. Moreover, if ED was merely an early marker, it would be more likely to occur near the time of onset of cardiovascular events. In fact, the mean length of follow-up in primary studies ranged from 4 to 16 years. Such a large interval between the 2 diseases further supports the hypothesis that ED is an independent risk factor.

Table 1 Characteristics of 12 Prospective Cohort Studies of ED and Cardiovascular Events and All-Cause Mortality

First Author, Year (Ref. #)	Location/Period	Duration (yrs)	Population	Assessment of ED	Outcomes	Adjustment for Covariates
Thompson et al., 2005 (7)	United States, 1994–2003	7.0	8,063 men; age \geq 55 yrs	Self-report questionnaire	CVD, CHD, stroke, and all-cause mortality	Age, BMI, blood pressure, TC, HDL-C, diabetes, family history of myocardial infarction, race, current smoking, current use of antihypertensive medication, physical activity, and global and self-reported health status
Gazzaruso et al., 2008 (9)	Italy, 1998–2006	4.0	291 diabetic patients; mean age 54.8 yrs	IIEF-5 questionnaire	CVD	Age, diabetes duration, hypertension, family history of CHD, smoking, microalbuminuria, glycated hemoglobin, BMI, TC, TG, LDL-C, HDL-C, and autonomic dysfunction
Ma et al., 2008 (10)	Hong Kong of China, 1995–2005	4.0	2,306 diabetic patients; mean age 54.2 yrs	Interview	CHD	Age, duration of diabetes, albuminuria, and use of antihypertensive medications
Schouten et al., 2008 (11)	the Netherlands, 1994–2003	6.3	1,248 men; age 50–75 yrs	Self-report questionnaire	CVD	Age, smoking, HDL-C, cholesterol, SBP, and diabetes
Araujo et al., 2009 (12)	United States, 1989–2004	15.0	1,709 men; age 40–70 yrs	Interviewer-administered questionnaire	All-cause mortality	Age, smoking, HDL-C, SBP, race, waist circumference, alcohol consumption, physical activity, self-assessed health, and self-reported chronic disease
Inman et al., 2009 (13)	United States, 1996–2005	10.0	1,402 men; age 40–79 yrs	Self-report questionnaire	CHD	Age, BMI, diabetes, hypertension, and history of smoking
Araujo et al., 2010 (15)	United States, 1989–2004	11.7	1,057 men; age 40–70 yrs	Interviewer-administered questionnaire	CVD	Age, BMI, HDL-C, TC, smoking, and hypertension
Batty et al., 2010 (16)	Multiple countries, 2001–2007	5.0	6,304 diabetic patients; age 55–88 yrs	Interview	CVD, CHD, stroke, and all-cause mortality	Age, BMI, use of metformin or beta-blockers, history of macrovascular or microvascular disease, diabetes duration, smoking, alcohol intake, physical activity, glycated hemoglobin, creatinine, TC, HDL-C, resting heart rate, blood pressure, and education
Corona et al., 2010 (18)	Italy, 2000–2007	4.3	1,687 men; age 17–88 yrs	Structured interview	CVD	Age and Chronic Diseases Score
Hall et al., 2010 (19)	United States, 1987–2004	16.2	1,165 men; age 40–70 yrs	Self-report questionnaire	CVD	Age
Ponholzer et al., 2010 (20)	Austria, 2001–2008	6.5	2,506 men; age 20–80 yrs	IIEF-5 questionnaire	CVD	Age
Chung et al., 2011 (21)	Taiwan of China, 1996–2006	5.0	9,006 men; age \geq 40 yrs	Clinical diagnosis	Stroke	Age, income, geographical location, hypertension, peripheral vascular disease, diabetes, CHD, atrial fibrillation, and hyperlipidemia

BMI = body mass index (calculated as weight in kilograms divided by height in meters squared); CHD = coronary heart disease; CVD = cardiovascular disease; ED = erectile dysfunction; HDL-C = high-density lipoprotein cholesterol; IIEF-5 = 5 item version of the International Index of Erectile Function; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = total triglycerides.

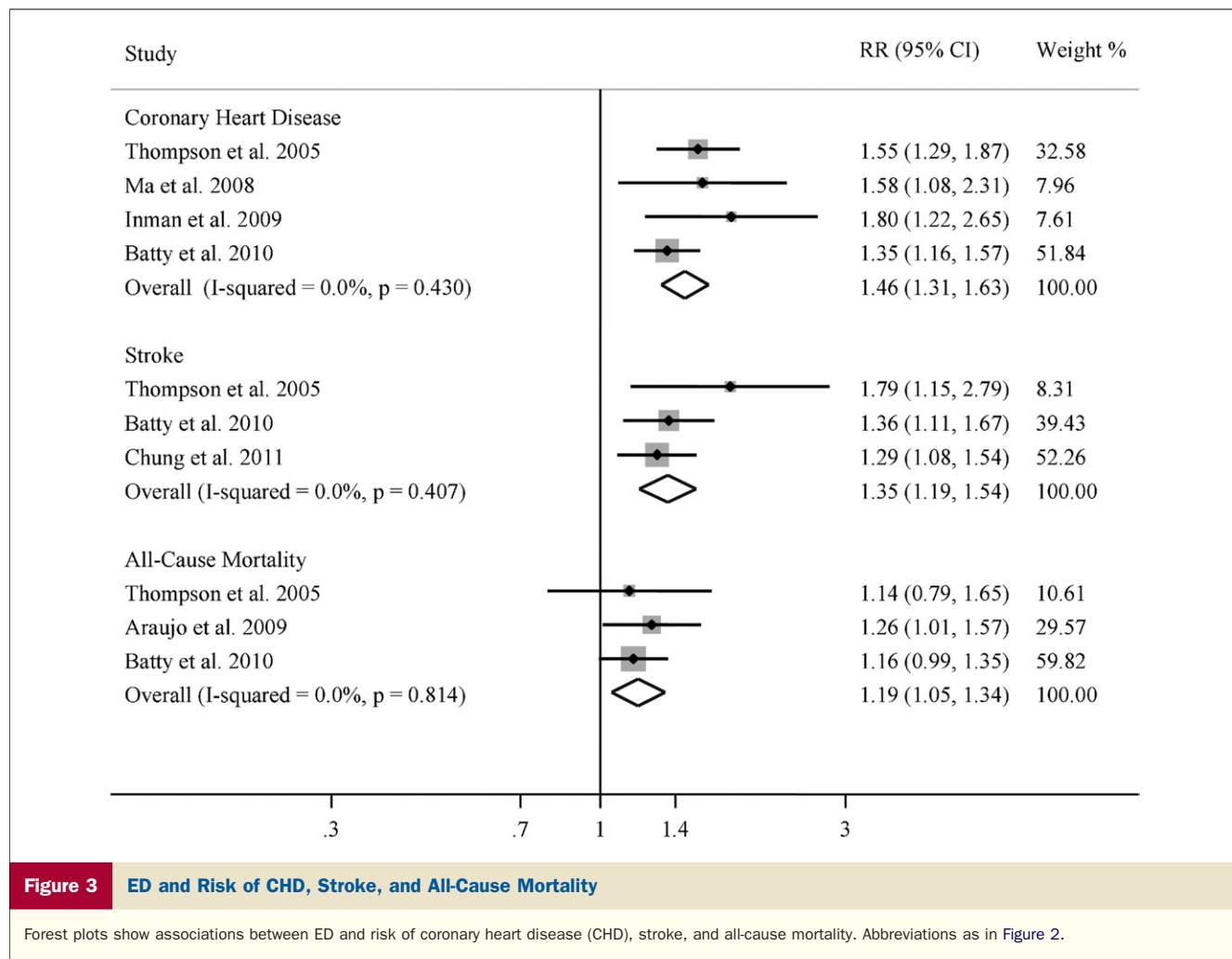


The underlying mechanisms involved in the association between ED and CVD are uncertain. One possible explanation is the “artery size hypothesis” (33). According to this hypothesis, because atherosclerosis affects all major vascular beds to the same extent, penile arteries, which are smaller in diameter than coronary arteries, are affected earlier by the same size of atherosclerotic plaque and hence ED manifests before cardiovascular events. Another explanation is endothelial dysfunction, a shared etiologic factor of both diseases (34). Endothelial dysfunction without atherosclerotic plaque narrowing the penile arteries is more likely to lead to ED than the case in the coronary arteries leading to angina (35). In addition, there may be a smooth muscle dysfunction beyond the endothelial dysfunction in patients with ED, which can occur before onset of systemic vascular diseases (36). However, these theories cannot explain an independent role of ED in the development of CVD. Depression, an important risk factor of CHD (37), may lie on the pathway between ED and CVD. ED and depression are known to be strongly correlated (38). A population-based, prospective cohort study has provided evidence that ED may independently increase depression risk (39). As a result, men with ED experience a higher risk of depression and hence an increased risk of subsequent cardiovascular events than those free of it. It should be noted that observational studies cannot prove causality. However, our study meets several of the Hill criteria (40) for causation. First, there was a clear temporal relationship: ED preceded the onset of CVD in all primary studies. Second, the strength of the

association with ED is not negligible and somewhat comparable to that of conventional cardiovascular risk factors, including diabetes, hypertension, smoking, and obesity (13). Third, the positive association was broadly consistent across different studies and among various populations. Fourth, there is a dose-response effect. Several studies (11,14,18) have observed the risk of CVD increasing when ED symptoms are severe. Finally, plausible biological explanations exist, as noted previously.

Sources of heterogeneity. Substantial heterogeneity was observed among studies of ED and CVD risk, which was not surprising given the differences in characteristics of populations, ascertainment of ED, and adjustment for confounding factors. Our sensitivity analyses suggest that 2 studies (9,16) conducted in patients with diabetes probably contributed to the heterogeneity. In addition to differences in features of study populations, these 2 studies also differed from others in some aspects. For one study (9), the small number of cases and participants increased the possibility that chance accounted for their results. For another study (16), participants were categorized as ED or non-ED patients through a simple question asked by nurses, which may lead to misclassification bias and hence underestimated results. In fact, the RR reported by that study (16) was evidently smaller than others.

Study strengths and limitations. A major strength of our study is that all the included original studies used a prospective cohort design, which eliminates the possibility of reverse causation (i.e., the presence of CVD might have



caused ED) and minimizes selection bias. Moreover, the association of ED with risk of CVD persists and remains statistically significant in sensitivity analyses based on various exclusion criteria. In addition, with the accumulating evidence and enlarged sample size, we have enhanced statistical power to provide more precise and reliable risk estimates.

One potential limitation of the present meta-analysis was the various assessments of ED used between studies. The International Index of Erectile Function questionnaire, which was developed and validated in 1996 to 1997 (41), has been adopted as the gold standard measure for efficacy assessment of ED (42). However, this questionnaire was not used in most included studies because they were initiated before its introduction. One advantage of this questionnaire is that it captures information on the severity of ED, which provides the opportunity to examine dose-response effects. Conversely, the absence of such a validated questionnaire increases the likelihood of misclassification bias, thereby underestimating the strength of the association. For instance, interview may result in underdiagnosis of ED because of embarrassment by patients and their reluctance to discuss the topic.

A second limitation is the substantial heterogeneity among studies for the association between ED and risk of CVD. Nevertheless, we were able to detect the major source of heterogeneity through the sensitivity analyses. In addition, residual confounding is of concern. Uncontrolled or unmeasured risk factors potentially produce biases. Although restricting analysis to studies (7,9,11,15,16,18) that adjusted for a group of conventional cardiovascular risk factors did not materially alter the combined risk estimate, we still cannot rule out the possibility that residual confounding could affect the results because these factors do not explain all of the risk for cardiovascular events (43). Furthermore, because current data in relation to ED and outcomes for CHD, stroke, and all-cause mortality are sparse, we were unable to investigate stroke subtypes and CVD mortality. Nevertheless, results for these outcomes were consistent. Finally, although little evidence of publication bias was observed, the statistical power for these tests was limited due to a relatively small number of included studies.

Suggestions for further studies. On the basis of our findings, several questions arise. First, is the association of ED with CVD causal? To answer this question, several

issues should be considered, including use of a validated ED questionnaire (41), the interval between the incidence of the 2 diseases, and adequate control for confounding factors. Second, by what exact mechanisms does ED independently increase the risk of CVD? Psychological factors, such as anxiety and depression, may offer insights. Third, could treating ED through drug intervention, lifestyle modification, and/or dietary therapy protect against cardiovascular events? A similar question was posed by the landmark report (7) in 2005, but it remains unanswered to date. Further studies, including well-designed clinical trials, are warranted to address these questions for a better understanding of the association and to provide convincing evidence for clinical practice in CVD prevention.

Conclusions

This meta-analysis of prospective cohort studies suggests that ED significantly increases the risk of CVD, CHD, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors.

Reprint requests and correspondence: Dr. Li-Qiang Qin, Department of Nutrition and Food Hygiene, School of Radiation Medicine and Public Health, Soochow University, 199 Renai Road, Dushu Lake Higher Education Town, 215123 Suzhou, China. E-mail: dongqj@mail3.sysu.edu.cn.

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Key Words: cardiovascular disease ■ cohort studies ■ erectile dysfunction ■ meta-analysis ■ risk factors.