Prediction of Cardiovascular Events and All-Cause Mortality With Erectile Dysfunction
A Systematic Review and Meta-Analysis of Cohort Studies
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Background—Erectile dysfunction (ED) carries an independent risk for cardiovascular (CV) events. We conducted a meta-analysis of all longitudinal studies for determining the ability of ED to predict risk of clinical events and to dissect factors influencing this ability.

Methods and Results—We conducted a comprehensive search of electronic databases through July 2012. Longitudinal studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) were included. Of the 14 studies included (92,757 participants; mean follow-up, 6.1 years; 16 articles), 13 (14 articles) reported results on total CV events (91,831 individuals), 4 on CV mortality (34,761 individuals), 4 on myocardial infarction (35,523 individuals), 6 on cerebrovascular events (27,689 individuals), and 5 on all-cause mortality (17,869 individuals). The pooled RRs for the above-mentioned end points were 1.44 (95% CI, 1.27–1.63), 1.19 (95% CI, 0.97–1.46), 1.62 (95% CI, 1.34–1.96), 1.39 (95% CI, 1.23–1.57), and 1.25 (95% CI, 1.12–1.39), respectively, for men with versus without ED. The RR was higher in intermediate- compared with high- or low-CV-risk populations and with younger age. The RR for studies that diagnosed ED with the use of a questionnaire compared with a single question was higher (RR, 1.61; 95% CI, 1.38–1.86 versus RR, 1.27; 95% CI, 1.18–1.37, respectively; P=0.006).

Conclusions—ED is associated with increased risk of CV events and all-cause mortality. RR is higher at younger ages, in intermediate-risk groups, and when a questionnaire is used instead of a single question. (Circ Cardiovasc Qual Outcomes. 2013;6:99-109.)

Key Words: cardiovascular diseases ■ erectile dysfunction ■ meta-analysis ■ mortality ■ stroke

Erectile dysfunction (ED) is a common clinical problem worldwide with thousands of new cases each year.1,2 In the Massachusetts Male Aging Study, the prevalence of ED was 52% in men 40 to 70 years of age and 70% in men >70 years of age.3 Cardiovascular (CV) disease (CVD) and ED share common risk factors,4 whereas evidence-based studies have identified pathophysiological links between ED and other vascular diseases, such as endothelial dysfunction and inflammation.5,6 thus identifying ED as an appealing candidate marker for future CV events. Screening and diagnosing ED could be of great importance for primary prevention because ED assessment offers an easy, low-cost alternative to several investigational CV biomarkers and could describe the risk over and beyond traditional risk factors, particularly for those patients belonging to the intermediate-CV-risk category. ED may precede clinically overt CVD by 2 to 5 years,6 providing a valuable time window for earlier modification of risk factors and potential improvement in outcomes. Importantly, studies have implicated that improvement of ED and ED-associated comorbidities by either pharmacological or lifestyle interventions might be beneficial in terms of prognosis.8

A number of studies examined the ability of ED to predict the risk of future fatal and nonfatal CV events and all-cause mortality.7-20 Although there is a general impression that ED has an important predictive role based on the results of individual studies,7-20 the overall quantitative estimate of this role has not been fully clarified,21,22 and implementation in clinical practice is suboptimal. In addition, because most studies yielded positive results, publication bias may have been involved. Finally, an important issue is whether the predictive ability of ED extends beyond CV events. Accordingly, we conducted the present study to calculate robust quantitative estimates of the predictive value of ED for different outcomes. Second, we investigated whether publication bias could have affected the true predictive ability of ED. Third, we evaluated clinically meaningful issues such as the effect of different baseline CV risk factors and of different diagnostic methods for ED (eg, questionnaire versus single question) on the predictive ability of ED. Toward this end, we included new landmark studies20,27 that have advanced our knowledge of the predictive value of ED for CVD. The robustness of our findings is ensured by the overall population size of the present meta-analysis (92,757 subjects) and by the lengthy follow-up.

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99
WHAT IS KNOWN

• Cardiovascular disease and erectile dysfunction share common risk factors, whereas evidence-based studies have identified pathophysiological links such as endothelial dysfunction and inflammation, thus identifying erectile dysfunction as an appealing candidate marker for future events.

• Although there is a general impression that erectile dysfunction has an important predictive role based on the results of individual studies, the overall quantitative estimate of this role has not been fully clarified.

WHAT THE STUDY ADDS

• The presence of erectile dysfunction increases the risk for future cardiovascular events, myocardial infarction, cerebrovascular events, and all-cause mortality, whereas it shows a trend to increase risk for cardiovascular mortality.

• Relative risk is higher at younger ages, in intermediate-risk groups, and when a questionnaire is used instead of a single question.

Methods

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology.31 Outcomes of interest were (1) total CV events, (2) CV mortality, (3) myocardial infarction (MI), (4) cerebrovascular events (stroke, transient ischemic attacks, intracranial hemorrhage), and (5) all-cause mortality. Total CV events were defined as CV death, MI, revascularization, cerebrovascular events, peripheral vascular disease, angina, heart failure, and arrhythmia.

Data Sources and Searches

Studies were drawn from a systematic review of the literature in the PubMed, Cochrane, and Embase databases until July 2012. The search terms are cited in the online-only Data Supplement. Data sources were also identified through a manual search of the references of articles.

Study Selection

Studies were deemed eligible on the following conditions: (1) if they were full-length publications in peer-reviewed journals; (2) if they evaluated ED (for details, see Table 1 in the online-only Data Supplement); (3) if they reported a combined CV outcome or a separate outcome such as CV mortality, MI, cerebrovascular event and all-cause mortality; (4) if the follow-up period was at least 1 year; and (5) if they were longitudinal cohort studies, either retrospective or prospective. Studies with cancer patients were excluded from our meta-analysis. Otherwise, no restriction criteria were imposed with regard to the type of the population studied (general population or populations with risk factors or disease) or to the size of the population. All but 3 longitudinal studies (4 articles)3,9,11,20 included in the meta-analysis were prospective studies. Retrospective studies were intentionally included (see Discussion for rationale).

Data Extraction and Quality Assessment

The literature search, selection of studies, quality assessment (for details, see the online-only Data Supplement), and extraction of data were done independently by 2 reviewers (C.V.V., D.G.T-P). Disagreements were resolved by consensus. For each study, we recorded a risk estimate for ED. Numeric data appearing in the articles were used.

Data Synthesis and Analysis

The risk estimates of each study were reported as hazard ratio, relative risk (RR), odds ratio, or dichotomous frequency data. We treated hazard ratios as RRs. When available, we used the adjusted-risk estimates from multivariate models. Details of all available multivariate models, we chose the one that had adjusted for the largest number of possible clinically relevant confounding factors. We performed meta-analyses of studies investigating ED to obtain the pooled RRs separately for the following: (1) total CV events, (2) CV mortality, (3) MI, (4) cerebrovascular events, and (5) all-cause mortality. The proportion of inconsistency across studies not explained by chance was quantified with the I² statistic. Heterogeneity between subgroups was calculated with the Cochran Q test.35 When significant heterogeneity existed among studies (P<0.05), the random-effects model was used to obtain the pooled RRs. We also calculated adjusted RRs of ED versus no ED groups in each study. We performed a sensitivity analysis to evaluate whether the strength of risk estimates differs between intermediate-risk groups (subjects with a 10-year risk of CVD between 10% and 20% based on Framingham Risk Score) and high-risk groups (subjects with CVD or diabetes mellitus and a 10-year risk of CVD >20% based on the Framingham Risk Score) or low-risk groups (subjects with a 10-year risk of CVD <10% based on the Framingham Risk Score) and between different methods of ED diagnosis (single question versus questionnaire). Risk estimates in subgroups were compared by use of a test of interaction.34 The RRs and confidence intervals (CIs) of individual studies were illustrated with forest plots. To estimate the contribution of continuous study moderators to the overall heterogeneity, we ran a meta-regression analysis with fixed-effects estimates. When pooled RRs were statistically significant, the presence of publication bias was investigated graphically by funnel plots of precision, and its implications for our results were assessed by the Duval and Tweedie trim-and-fill method37 and the classic fail-safe N method as introduced by Rosenthal.38 All analyses were performed with comprehensive meta-analysis version 2 (Biostat, Englewood, NJ).

Results

Literature Search

Literature search results are shown in Figure 1. We retrieved 8335 articles from our preliminary search. Of these, 23 were identified for full review. For details on the exclusion of studies20,22–25,28,29 after full review, see the online-only Data Supplement.

Study Characteristics

Our meta-analysis included 16 original articles. In total, the included studies analyzed 92757 subjects. Several populations such as patients with hypertension, diabetes mellitus, or coronary artery disease and subjects from the general population were included. Details of the individual studies are shown in Table 1. Of the 14 studies included (92757 participants; mean follow-up, 6.1 years; 16 full-text articles),7,9,11,21–26,27 13 (14 full-text articles)2,3,10–12,14–17,19,21,26,27 reported results on total CV events (91831 individuals; 5005 incident cases during 471636 person-years of follow-up), 4 reported on CV mortality (34761 individuals),14,16,20,27 4 reported on MI (35523 individuals),9,14,20 6 reported on cerebrovascular events (27689 individuals),9,14,18,20,21,26 and 5 reported on all-cause mortality (17869 individuals).3,16,17,20,21 All studies were published since 2003, and the mean/median follow-up ranged from 1 year7,8 to 15.2 years.16 The sample sizes ranged from...
291^4 to 31 296^7 individuals. Age and other risk factors for CVD were controlled for in most of the studies.

**Meta-analysis**

**ED and Total CV Events**

The magnitude of risk in individuals who had ED was significantly higher compared with the risk of individuals without ED. The pooled RRs for ED were 1.44 (95% CI, 1.27–1.63) for total CV events (Figure 2A). By applying a sensitivity analysis, we excluded the 3 retrospective studies without significant changes in our final results for total CV events (RR, 1.42; 95% CI, 1.22–1.65; *P* <0.001).

Because we observed significant heterogeneity (*I*^2^ =66.4%, *P* <0.001) among the included studies, we conducted between-study subgroup analyses to investigate its sources. The RR was significantly different across studies with different baseline CV risk populations. (*P* =0.003; Figure 3). Specifically, the RR for ED was significantly higher in intermediate-risk^9^,^12^,^15^,^19^ populations compared with high-risk^13^,^14^,^20^,^21^ and low-risk^18^,^27^ populations (RR, 1.51; 95% CI, 1.35–1.70 versus RR, 1.30; 95% CI, 1.20–1.42; *P* =0.048; and RR, 0.93; 95% CI, 0.72–1.19; *P* =0.001, respectively). Moreover, the RR for ED was significantly higher in high-risk populations compared with low-risk populations (*P* =0.011).

In terms of the method of ED diagnosis, the RR for ED was higher in studies in which ED was diagnosed with a questionnaire^14^,^15^,^18^–^20^ compared with a single question^9^,^12^,^13^,^21^,^27^ (RR, 1.61; 95% CI, 1.38–1.86 versus RR, 1.27; 95% CI, 1.18–1.37; *P* =0.006).

To further investigate the incremental predictive role of ED above and beyond conventional risk factors, we performed a sensitivity analysis in which we included studies^9^,^12^,^13^,^19^–^21^,^27^ that had adjusted for age, smoking, diabetes mellitus, cholesterol, and hypertension/blood pressure (as opposed to the remainder of the studies that had adjusted for only some of those parameters). The RR in these studies (RR, 1.41; 95% CI, 1.16–1.71; *P* <0.001) was similar to the overall combined estimated risk. Moreover, we applied a sensitivity analysis in which we included only high-quality studies as assessed by our quality analysis^9^,^12^,^13^,^19^–^21^,^27^ with similar results (RR, 1.34; 95% CI, 1.17–1.54; *P* <0.001).

**ED and CV Mortality, MI, and Cerebrovascular Events**

The magnitude of risk for most clinical end points in individuals who had ED was significantly higher compared with the risk of individuals without ED, except for CV mortality, which showed a trend toward significance (*P* =0.089). The pooled RRs for ED were 1.19 (95% CI, 0.97–1.46), 1.62 (95% CI, 1.34–1.96), and 1.39 (95% CI, 1.23–1.57) for CV mortality, MI, and cerebrovascular events, respectively (Figure 2B–2D).

**ED and All-Cause Mortality**

The magnitude of risk in individuals who had ED was significantly higher compared with the risk in individuals without ED. The pooled RR for ED was 1.25 (95% CI, 1.12–1.39) for all-cause mortality (Figure 2E).

Because we observed heterogeneity (*F* =31.9%; *P* =0.204) among the included studies, we conducted between-study subgroup analyses. The RR of ED patients for all-cause mortality was significantly higher in patients with known CVD^17^,^20^ compared with patients without (predominantly) known CVD^16^,^21^ (RR, 1.90; 95% CI, 1.31–2.77 versus RR, 1.20; 95% CI, 1.07–1.34; *P* =0.021).

**Publication Bias**

The funnel plots were asymmetrical at the bottom (Figure I in the online-only Data Supplement) for all end points, suggesting an absence of small studies with small or negative
<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Population (Sample Size), n</th>
<th>Mean Age (SD) or Age Range, y</th>
<th>Follow-up Duration, y</th>
<th>ED Population, n</th>
<th>Events</th>
<th>Diagnosis of ED</th>
<th>Adjusted for</th>
<th>Quality Analysis*</th>
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<tbody>
<tr>
<td>Blumentals et al, 2003†‡</td>
<td>25 650 men</td>
<td>40.1</td>
<td>1</td>
<td>12 825 men (50%)</td>
<td>76 cases of PVD</td>
<td>ED was diagnosed with ICD-9 codes</td>
<td>Age at ED diagnosis, smoking, obesity and use of ACE inhibitors, β-blockers, and statins</td>
<td>Y Y N</td>
</tr>
<tr>
<td>Blumentals et al, 2004†‡</td>
<td>25 650 men</td>
<td>40.1</td>
<td>1</td>
<td>12 825 men (50%)</td>
<td>72 cases of MI</td>
<td>ED was diagnosed with ICD-9 codes</td>
<td>Age at ED diagnosis, smoking, obesity, and use of ACE inhibitors, β-blockers, and statins</td>
<td>Y Y N</td>
</tr>
<tr>
<td>Thompson et al, 2005</td>
<td>8063 men with no CVD</td>
<td>62±6</td>
<td>7 y ±90 d</td>
<td>3816 men (47.3%)</td>
<td>CVD as any of the following events: MI or surgical treatment of CAD, including CABG or angioplasty, angina, cerebrovascular accident, TIA, HF graded at a minimum of mild, fatal cardiac arrest, or nonfatal cardiac arrhythmia (955: first CV event, 382: death by any cause)</td>
<td>ED was graded as follows: grade 0, absent; grade 1, decrease in normal function but ability to achieve vaginal penetration with difficulty; or grade 3, no erections. ED was defined as the first report of ED of any grade</td>
<td>Age, BMI, SBP, DBP, total cholesterol, HDL, history of diabetes mellitus, parent or sibling with a history of MI, race (white vs other), current smoking, current use of antihypertensive medication, physical activity (moderate or very active vs sedentary or light), and global, self-reported health status (excellent or very good vs fair or poor)</td>
<td>N N N</td>
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<td>Frantzen et al, 2006‡</td>
<td>1183 men before the introduction of sildenafil</td>
<td>35–74</td>
<td>Up to 2</td>
<td>278 men</td>
<td>38 incident CVD cases</td>
<td>ED reported by general practitioners</td>
<td></td>
<td>Y Y N</td>
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<tr>
<td>Schouten et al, 2008</td>
<td>1248 men in a community-based study</td>
<td>60.67</td>
<td>6.33</td>
<td>392 men (31.4%, 284 with reduced rigidity and 108 with severely reduced rigidity)</td>
<td>58 cardiovascular events (39 MIs, 5 sudden deaths, or 14 strokes)</td>
<td>A single question on erectile rigidity included in the International Continence Society male sex questionnaire</td>
<td>Age, total cholesterol, HDL, SBP, diabetes mellitus, and smoking</td>
<td>N N N</td>
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<tr>
<td>Ma et al, 2008</td>
<td>2306 diabetic men</td>
<td>54.2±12.7</td>
<td>4.0</td>
<td>616 men (26.7%)</td>
<td>123 CHD events (MI or death resulting from coronary cause; or other nonfatal CHD)</td>
<td>A single question on the inability to attain and maintain penile erection sufficient for satisfactory sexual performance</td>
<td>Age, duration of diabetes mellitus, SBP, DBP, albuminuria, retinopathy at baseline, eGFR, use of lipid-lowering agents, use of antihypertensive medications, use of ACE inhibitors/ARBs</td>
<td>N N N</td>
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<tr>
<td>Gazzaruso et al, 2008</td>
<td>291 type 2 diabetic men with silent CAD documented with angiography</td>
<td>54.8±7.3</td>
<td>3.9±1.8</td>
<td>118 men (40.5%)</td>
<td>49 MACE: CAD death (3), sudden death (2), nonfatal MI (14), death resulting from HF (1), unstable angina (8), need for repeat revascularization (3, aside from restenosis), stroke or TIA (16), and symptomatic PVD (2) documented by angiography</td>
<td>IIEF-5 questionnaire</td>
<td>Age, diabetes mellitus duration, hypertension, family history of CAD, smoking, microalbuminuria, glycohemoglobin, BMI, cholesterol, triglycerides, LDL, HDL, and autonomic dysfunction</td>
<td>N N Y</td>
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<tr>
<td>Inman et al, 2009</td>
<td>1402 community-dwelling men</td>
<td>55.4</td>
<td>10</td>
<td>158 men (11.3%)</td>
<td>156 (23 MI, 123 angiographic anomalies, and 10 sudden cardiac death)</td>
<td>Brief male sexual function inventory</td>
<td>Diabetes mellitus, hypertension, history of smoking, and BMI</td>
<td>Y N N</td>
</tr>
<tr>
<td>Araujo et al, 2009§</td>
<td>1655 men in population-based study</td>
<td>55.2</td>
<td>15.2</td>
<td>338 men (20.4%)</td>
<td>CVD death (140), includes CHD, HF, PVD, cerebrovascular disease, and other vascular diseases, death resulting from malignant neoplasms (124), and death resulting from other causes (107)</td>
<td>23-item questionnaire on sexual activity</td>
<td>Age, BMI as continuous variables, and the following as categorical variables: alcohol consumption (&lt;1, 1, and ≥2 drinks/d), calories expended in physical activity (none, &lt;200 kcal/d, and ≥200 kcal/d), current smoking, self-assessed health (excellent, very good, good, fair/poor), and self-reported chronic disease (heart disease, hypertension, and diabetes mellitus)</td>
<td>N N N</td>
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<tr>
<td>Hebert et al, 2009</td>
<td>328 male HF patients</td>
<td>55.4</td>
<td>8.4</td>
<td>293 men (89.3%)</td>
<td>All-cause mortality (96 deaths)</td>
<td>SHIM</td>
<td>...</td>
<td>Y N N</td>
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<tr>
<td>Ponholzer et al, 2010</td>
<td>2506 men without a history of CHD or cerebral vascular disease</td>
<td>45±12</td>
<td>6.5</td>
<td>870 men (34.7%, 634 with mild ED, 236 with moderate to severe ED)</td>
<td>58 CVD events</td>
<td>IIEF-5 questionnaire</td>
<td>Age</td>
<td>Y N N</td>
</tr>
<tr>
<td>Araujo et al, 2010§</td>
<td>1057 men free of CVD and diabetes mellitus</td>
<td>54</td>
<td>11.7</td>
<td>178 men (16.8%)</td>
<td>261 new cases of CVD</td>
<td>23-item questionnaire on sexual activity</td>
<td>BMI (continuous) and the variables that are part of the Framingham risk score: age, HDL, and total cholesterol (all as continuous variables), as well as current smoking (yes/no), and hypertension categorized according to BP readings (optimal, normal, high normal, stage I, and stage II to IV)</td>
<td>N N N</td>
</tr>
<tr>
<td>Böhm et al, 2010</td>
<td>1519 high-risk CVD patients</td>
<td>64.8</td>
<td>4.4 (ONTARGET) and 4.5 (TRANSCEND)</td>
<td>842 men (55.4%)</td>
<td>A composite (primary outcome) of death resulting from CV causes, MI, stroke, or hospitalization for HF (206). Other outcomes were death resulting from any cause (133)</td>
<td>The IIEF-5 and the Kölner (Cologne) evaluation of ED scores</td>
<td>Age, SBP, DBP, smoking, history of hypertension, diabetes mellitus, MI, stroke/TIA, PVD, alcohol consumption, use of β-blockers and calcium channel blockers, ankle-brachial index, and lower urinary tract surgery</td>
<td>N N N</td>
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Table 1. Continued

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<tr>
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<tr>
<td>Batty et al, 2010</td>
<td>6304 type 2 diabetic men</td>
<td>65.9 ± 3158 men (50.1%)</td>
<td>5</td>
<td>3158 men</td>
<td>Deaths resulting from any cause (695), CV events (1549), CHD events (773), cerebrovascular events (411), dementia events (58), cognitive decline events (1013)</td>
<td>Nurses asked subjects whether they had ED (categorized as yes or no)</td>
<td></td>
<td>N N N</td>
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<tr>
<td>Chung et al, 2011 ‡</td>
<td>9006 men in a nationwide population-based study</td>
<td>58.5 ± 1501 men (16.7%)</td>
<td>5</td>
<td>1501 men</td>
<td>Strokes (918)</td>
<td>ICD-9 codes for ED</td>
<td>Patient’s monthly income, geographical location, hypertension, PVD, diabetes mellitus, CHD, atrial fibrillation, and hyperlipidemia</td>
<td>Y Y N</td>
</tr>
<tr>
<td>Hotaling et al, 2012</td>
<td>31 296 men in western Washington</td>
<td>62 ± 7762 men (24.8%)</td>
<td>7.8</td>
<td>486 CV deaths</td>
<td>&quot;Have you experienced impotence in the last year?&quot;</td>
<td></td>
<td></td>
<td>N N N</td>
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ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; ED, erectile dysfunction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; ICD, International Classification of Diseases; IIEF, international index erectile function; LDL, low-density lipoprotein; MACE, major adverse cardiac events; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; SHIM, sexual health inventory for men; and TIA, transient ischemic attack.

†Studies have the same population but different clinical end points. The Blumentals et al 2003 study was used for estimation of total CV events and myocardial infarction, and the Blumentals et al 2004 study was used for estimation of total CV events.

‡Retrospective studies.

§Studies have a part of their population in common. The Araujo et al 2009 study (which is larger) was used for estimation of CV and all-cause mortality, and the Araujo et al 2010 study was used for estimation of total CV events.
The trim-and-fill method imputed missing studies and recalculated our pooled risk estimate (Figure IA–ID in the online-only Data Supplement). The imputed RR was 1.32 (95% CI, 1.16–1.51), 1.52 (95% CI, 1.28–1.80), 1.37 (95% CI, 1.21–1.54), and 1.20 (95% CI, 1.08–1.33) for total CV events, MI, cerebrovascular events, and all-cause mortality, respectively, which are lower than our original risk estimates but are still significant. Importantly, the results of the fail-safe N test of our pooled analysis are 300, 21, 34, and 22 respectively, which for all end points are reassuring. The fail-safe N test computes the number of missing studies (with a mean effect of zero) that would need to be added to the analysis to yield a statistically nonsignificant overall effect, and it is unlikely that there are >23 (300/13=23.1), >5 (21/4=5.3), >5 (34/6=5.7), and >4 (22/5=4.4) unpublished or undiscovered studies for every 1 study that we found for total CV events, MI, cerebrovascular events, and all-cause mortality, respectively. These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way.

**Meta-regression Analysis**

Age at enrollment was the strongest predictor of the magnitude of the log RR in ED patients and inversely related to the predictive role of ED for total CV events (P<0.001; Figure 4A). Duration of follow-up was not a predictor (P=0.52). The percentage of smokers and total cholesterol in each study showed positive associations with the predictive role of ED (P=0.003 and P=0.001, respectively), and pulse pressure, HDL, and BMI showed inverse associations with the predictive role of ED (P=0.03, P=0.01, and P=0.02, respectively), whereas inverse associations of percentage of diabetics and systolic blood pressure with the predictive role of ED were not statistically significant or showed a trend (P=0.29 and P=0.07, respectively; Figure 4A–4H). Exclusion of outliers had minimal effects on the above-mentioned results.

**Discussion**

In this systematic review and meta-analysis, we pooled the data for 92,757 subjects investigated for ED from 16 available published articles who were followed up for a mean of 6.1 years. Our study is the first to investigate in a thorough manner whether the presence of ED increases the risk for future events and to assess factors influencing such a predictive ability. Our principal finding is that patients with ED compared with subjects without ED have a significantly increased risk by 44% for total CV events, 62% for MI, 39% for cerebrovascular events,
and 25% for all-cause mortality. The risk for CV mortality was also increased by 19%, but this increase only showed a trend toward significance. Importantly, the RR is higher in younger patients and in patients with intermediate CV risk. Furthermore, diagnosis of ED by a questionnaire is associated with a higher RR compared with diagnosis of ED with a single question. Finally, the RR increases with increased percentage of smokers, decreased pulse pressure, and deteriorated dyslipidemic profile.

Clinical Implications

Our findings are potentially applicable to clinical practice. First, they support inclusion of ED by the European guidelines for CVD prevention.37 Our analysis showed that the risk conferred by ED on events is of a magnitude similar to that of the risk conferred on events by established risk predictors such as hypertension and dyslipidemia commonly encountered in clinical practice. Thus, our results stress the importance of early diagnosis of ED and the meticulous CV investigation that is required in specific groups of ED patients.38 Furthermore, an important finding of our analysis is that ED is a significant predictor of all-cause mortality in addition to CV outcomes. Interestingly, ED is a stronger predictor of all-cause mortality in patients with known CVD compared with patients without CVD. Although pathophysiological explanations are not readily identifiable, this predictive ability for all-cause mortality could reflect the existence of common pathogenetic mechanisms such as aging, inflammation, and oxidative stress over a wide range of conditions. Moreover, rates of depression are increased in patients with CVD and ED. Depression worsens the outcome of comorbid physical conditions, and depressed patients show decreased adherence to treatment.

Improvement of ED by lifestyle interventions per se might be beneficial in terms of prognosis,14,39,40 and our results highlight the role of ED as a potential low-cost biomarker that would call for more aggressive CV risk factor modification.41 Of special interest is the effect of pharmacological treatment of ED, because it seems that this may also have a beneficial impact on risk. Indeed, Frantzen et al11 showed that 2 years after the introduction of sildenafil, the RR of the incidence of CVD among men with ED compared with healthy men significantly decreased from 1.7 to 1.1. Furthermore, Gazzaruso et al12 showed that type 5 phosphodiesterase inhibitors offer marginal protection against the development of major adverse cardiac events in diabetic patients with coronary artery disease and ED. Undoubtedly, more data are needed, and future follow-up studies should ideally collect information on ED treatment and investigate such an effect.

Further dissection of our principal finding provided interesting information. The RR was higher in patients with intermediate baseline CV risk compared with ED patients with high or low CV risk. This is particularly important because this intermediate-risk group is in need of further risk reclassification with a predictor such as ED. Furthermore, the RR was higher in younger ED patients despite the fact that the probability of ED increases with age. In fact, ED as a predictor may be particularly useful in these young patients in whom the Framingham Risk Score may underestimate risk by examining forward only 10 years.42 In addition to younger age, the RR was higher in the presence of smoking and dyslipidemic profile. Although risk factors become more frequent with advancing age, we interpret these findings as being complementary rather than contradictory. Overall, this combination of younger age and multiple risk factors may imply an aggressive pathophysiological background that is exacerbated by environmental factors such as smoking and unhealthy diet and stresses the necessity for their identification and treatment in patients with ED.

Our study provides interesting caveats for the heterogeneity of methods used across studies to diagnose ED. Although the medical and sexual history is essential and frequently the most revealing aspect of the ED assessment process, the diagnostic potential of assessment questionnaires has certain limits. The use of a validated questionnaire such as the International Index of Erectile Function questionnaire, which has been widely used for assessment of presence and severity ED and has been shown to correlate with Gensini score in patients undergoing coronary angiography,43 improves the diagnosis of ED and is the preferred strategy; however, this is not universally adopted. The importance of the use of a validated questionnaire is supported by our findings that in patients in whom ED was diagnosed with a questionnaire, the RR for total CV events was higher compared with that in patients in whom ED was diagnosed with a single question. Thus, it seems reasonable that ED when better substantiated and carefully investigated could provide more useful information about the future CV risk of the ED patient.

Of the studies included in the analysis, 5 used a validated questionnaire,14,15,18–20 and of these, only 3 reported data according to the severity of ED.18–20 Two more studies,12,23 despite using a single question to assess ED, categorized the answers according to ED severity on a 3-point scale. Taken as a whole, this evidence points toward a grading effect of the severity of ED in the predictive ability of this condition for CV events.12,20,23 However, more studies are needed to substantiate this notion.

Methodological Considerations

An important strength of our study is the exhaustive search strategy that likely enabled us to capture most, if not all,
relevant studies. Moreover, our study for the first time uses data from the published studies for meta-regression analyses, thus enhancing the identification of the predictive role of ED in CVD. Furthermore, as a meta-analysis, the present study overcomes the potentially biased inclusion and weighing of results that may appear in reviews when interpreting the available evidence. Finally, although we would ideally want to have a larger number of high-quality studies, we dealt effectively with potential publication bias.

We intentionally included both prospective and retrospective longitudinal studies to allow a multifaceted approach to the estimation of risk. However, we took under consideration the more confounding and biased nature of retrospective studies. By applying a sensitivity analysis, we excluded these 3 retrospective studies without significant changes in our final results for total CV events.

In the majority of studies, ED patients were in most cases older, had higher blood pressure, and were more often diabetic or dyslipidemic. Thus, it is reasonable to assume that ED patients were a priori at higher baseline risk than non-ED patients. However, this inherent limitation of most prospective studies was dealt with in most of them by adjustment for the potential confounders between ED and non-ED patients. Furthermore, as it was shown in our sensitivity analysis for

![Figure 4. Relative risk (RR) of total cardiovascular events in patients with erectile dysfunction as a function of (A) age (data from 13 studies7–9,11–15,18–21,27), (B) smoking percentage in study population (data from 10 studies7–9,12–14,16–21), (C) systolic blood pressure (data from 7 studies9,12,13,18,19,21), (D) pulse pressure (data from 6 studies7,13,18,20,21), (E) cholesterol (data from 8 studies9,12–15,18–21), (F) high-density lipoprotein (data from 7 studies9,12–14,18,19,21), (G) body mass index (data from 7 studies9,12–14,18,19,21), and (H) diabetes mellitus percentage in study population (data from 10 studies9,12–15,18–21). Each study is represented by a circle that shows the actual coordinates (observed effect size by each of the above-mentioned variables) for that study. The size of each circle is proportional to the weight of the respective study in the analysis, that is, the inverse of the within-study variance for each study. The center line shows the predicted values by fixed-effects meta-regression. The vertical axis is on a log scale.]
adjustment of risk factors, the RR in studies that adjusted for all conventional risk factors was lower but not substantially different from the overall combined risk. Thus, it seems that the increased risk for ED patients is unlikely to be a consequence of the higher baseline CV risk of ED patients.

Our results are in accordance with the results of 2 previous meta-analyses that estimated the RR for CVD at 47% and 48%, respectively. However, these meta-analyses did not include landmark studies such as the VITAL (Vitamins and Lifestyle), ONTARGET/TRANSCEND (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease), and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) studies. Furthermore, in 1 study results may have been influenced by a duplicate study inclusion (similar populations in the 2 studies) for the same end point, as well as by inclusion of a study with a population made up exclusively of ED patients.

Links Between ED and Events
Because CVD and ED overlap in risk factors, prevalence, and manifestation, they are thought to share both pathophysiological basis of pathogenesis and progression. The artery-size hypothesis proposes that the differential timing of the onset of signs (2–5 years) and symptoms of ED and CVD is caused by the difference between larger vessels and smaller ones (eg, pudendal or cavernous arteries) with regard to their ability to tolerate encroachment on the lumen. Moreover, we have shown that ED is associated with an incremental inflammatory and endothelial-prothrombotic activation on top of that found in patients with coronary artery disease. Accelerated arterial aging may be the background responsible for adverse outcome in ED, as pointed by the independent predictive ability of aortic stiffness (Vlachopoulos et al, unpublished observations) and pulse pressure (a crude index of aortic stiffness) for events in ED patients. Moreover, low testosterone may be implicated in the common pathogenetic pathways of ED and CVD; however, this warrants further substantiation.

Study Limitations
We used aggregate data as reported in published articles (or calculated from other data provided in these) rather than individual data, and thus we could not deal with potential methodological problems of the original studies. Only 1 included study provided robust estimates of the discriminatory and reclassification power of ED beyond classic risk factor or the Framingham Risk Score. The ability of ED to discriminate, calibrate, and reclassify risk can be assessed only on a patient-level data analysis, which seems to be the next desirable step. Finally, although CV mortality and all-cause mortality were uniformly defined, the definition of total CV events differed among the studies included in the analysis.

Conclusions
The presence of ED increases the risk for future CV events, MI, cerebrovascular events, and all-cause mortality, whereas it shows a trend to increase risk for CV mortality. The RR is higher in young subjects, in subjects with intermediate baseline CV risk, and when ED is diagnosed by a questionnaire rather than a single question. These findings support implementation of ED into clinical practice and stress the need to establish standardized methods to diagnose ED and to investigate the potential effect of treatment of ED on CV events and all-cause mortality.

Disclosures
None.

References
Erectile Dysfunction and Clinical Events


Prediction of Cardiovascular Events and All-Cause Mortality With Erectile Dysfunction: A Systematic Review and Meta-Analysis of Cohort Studies
Charalambos V. Vlachopoulos, Dimitrios G. Terentes-Printzios, Nikolaos K. Ioakeimidis, Konstantinos A. Aznaouridis and Christodoulos I. Stefanadis

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After full review, 2 studies on CVD were excluded because of the short follow-up period (6 and 10 months, respectively),1,2 2 studies on all-cause mortality were excluded because patients were diagnosed with prostate cancer,3,4 1 study was excluded because study population comprised only ED patients,5 1 study on CVD was excluded because study population was similar to an included study6 and 1 study was excluded because it did not report precise data on hazard ratio or clinical events.7

Quality analysis

We evaluated the quality of the included studies by assessing selection, detection, and attrition bias (Table S1). For control of selection bias, we assessed whether each study’s risk estimates from multivariate analysis included age, most CV risk factors, and previous CV disease when necessary in analysis. For control of detection bias, we recorded whether the investigators who were assessing outcomes were aware of the patient’s erectile function. Finally, for control of attrition bias, we evaluated the extent of loss to follow-up by calculating the ratio of the number of individuals lost to follow-up to the number of clinical events in the study. This ratio comprises a measure of how loss to follow-up influenced the
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Subjects with CVD or diabetes were considered as high risk. A FRS was derived for each study using the prediction formulae for men proposed by Wilson et al. \(^13\) for 10-year risk of coronary heart disease based on baseline mean values of conventional cardiovascular risk factors of the study population (age, total and HDL cholesterol categories, blood pressure categories, diabetes and smoking status), as previously shown. \(^14\) Instead of the dichotomous categories for smoking, the proportion of smokers was used. When data on few of the variables necessary to calculate the FRS were incomplete,\(^15\,^16\) an approximate estimation of the risk category based on the available data was made.

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An important issue is whether ED has a causal effect on the clinical end-points.\(^17\) To assess such possible causality, Hill's criteria of causation\(^18\) may be used. Interestingly, most of these
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Supplemental Tables

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Araujo et al.,\textsuperscript{11} 2009 and Araujo et al.,\textsuperscript{12} 2010

The subject was given a 23-item questionnaire on sexual activity to be completed in private and returned in a sealed envelope. The questionnaire included 13 items related to ED, such as, “During the last 6 months have you ever had trouble getting an erection before intercourse begins?” The 13 items were combined in a discriminant-analytic formula to assign a degree of erectile function to each subject. Calibration data for the discriminant formula were taken from an additional single-question, subjective self-assessment of ED, included in the follow-up questionnaire in response to recommendations of the National Institutes of Health Consensus Panel. Impotence was defined as “being unable to get and keep an erection that is rigid enough for satisfactory sexual activity.” The subject rated himself as completely impotent (“never able to get and keep an erection . . .”), moderately impotent (“sometimes able. . .”), minimally impotent (“usually able . . .”), or not impotent (“always able . . .”).

No evidence of bias

Hebert et al.,\textsuperscript{25} 2009

All participants were administrated the SHIM survey to measure ED at the baseline of the study. The SHIM consists of five questions designed to cover the major constituents of ED. Respondents were asked about their experience related to ED during the past 6 months. Responses were recorded on a 5-point Likert scale ranging from rarely (1) to almost always (5). A score of 21 or lower on the SHIM scale has been used to identify ED. Based on the SHIM, the patients were placed into two categories: No ED $\geq 22$ and ED $\leq 21$.

The investigators did not adjust for any CV risk factors

Ponholzer et al.,\textsuperscript{26} 2010

The IIEF-5 questionnaire was used to assess the prevalence and severity of ED. The classification system developed by was slightly modified by combining the ‘mild-to-moderate’ and ‘moderate’ groups into one group to facilitate statistical evaluation into three categories, such as no ED (IIEF-5 score=22–25), mild ED (IIEF-5 score=17–21) and moderate-to-
severe ED (IIEF-5 score=5–16).

Böhm et al.,19 2010 The authors used the 5-item short form of the IIEF and the Kölner (Cologne) Evaluation of Erectile Dysfunction scores. These evaluating tools were incorporated into 1 questionnaire as internal controls for each other. The Kölner Evaluation of ED score consists of 6 questions on a 5-point Likert scale. An ascending score indicates worsening of ED, with a cutoff at >17 points for the diagnosis of ED. The IIEF score ranges from 5 to 25 points, in which a descending score indicates worsening of erectile function in patients, with a cutoff below 22 points for a diagnosis of ED. Individuals scoring 5 to 7 points on the IIEF score were diagnosed as having severe ED, whereas 8 to 11 points indicated moderate ED, 12 to 16 points was mild to moderate ED, 17 to 21 points indicated mild ED, and 22 to 25 points signified no ED. No evidence of bias

Batty et al.,27 2010 Nurses asked subjects whether they had ED (categorized as “yes” or “no”). No evidence of bias

Chung et al.,28 2011 Patients who had visited ambulatory care centers for the treatment of ED (with a principal diagnosis of Impotence, organic [ICD-9 code 607.84] or Impotence, psychogenic [ICD-9 code 302.72]) The investigators who were assessing outcomes were aware of the patient’s erectile function due to the retrospective design of the study and did not adjust for CV risk factors (adjustment for patient’s monthly income, geographical location, hypertension, PVD, diabetes, CHD, atrial fibrillation, and hyperlipidemia)

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ED: Erectile dysfunction; ICD: International Classification of Diseases; IIEF: International Index Erectile Function; SHIM: Sexual Health Inventory for Men; PVD: Peripheral vascular disease; ICD: International classification of diseases; CHD: Coronary heart disease; BMI: Body-mass index.
Supplemental Figure Legends

Figure S1. Publication bias for total CV outcomes and all-cause mortality and its potential impact. (A) Total CV events; (B) myocardial infarction; (C) cerebrovascular events and (D) all-cause mortality. The open circles in the left and right plots represent individual studies relating ED with events, and the open diamonds are the RR and 95% CI for the meta-analysis. The solid circles in the right plots represent imputed studies, and the solid diamonds are the RR and 95% CI for the meta-analysis after adjusting for publication bias.
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**Supplemental Discussion**

An important issue is whether ED has a causal effect on the clinical end-points. To assess such possible causality, Hill's criteria of causation may be used. Interestingly, most of these
criteria were met in our study. Firstly, the strength of association between ED and clinical endpoints is significant thus it is less likely that the relationship is due to an extraneous variable. Secondly, the criterion of temporality was met since ED preceded clinical endpoints in all studies. Thirdly, the criterion of consistency is met since multiple observations, of this association, with different populations under different circumstances and with different measurement instruments increase the credibility of our finding. Fourthly, there is a dose-response effect between ED severity and clinical outcome. Fifth, there are experimental data that support the association between ED and clinical endpoints. Finally, the criterion of theoretical plausibility is also met since ED and CVD share common pathophysiological pathways.
Supplemental References


high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. Circulation. 2010;121:1439-46.


Supplemental Tables

**Table S1.** Definition of erectile dysfunction diagnosis and quality analysis of studies.

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>Diagnosis of ED</th>
<th>Quality analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumentals et al., 8 2003</td>
<td>ED was diagnosed with ICD-9 codes (302.72 and 607.84)</td>
<td>The investigators who were assessing outcomes were aware of the patient’s erectile function due to the retrospective design of the study and did not adjust for all major CV risk factors (adjustment for age at ED diagnosis, smoking, obesity and use of ACE inhibitors, beta blockers and statins)</td>
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<tr>
<td>Blumentals et al., 9 2004</td>
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<tr>
<td>Thompson et al., 21 2005</td>
<td>ED was graded as follows: grade 0, absent; grade 1, decrease in normal function but ability to achieve vaginal penetration with difficulty; or grade 3, no erections. ED was defined as the first report of ED of any grade over the previous 4 weeks</td>
<td>No evidence of bias</td>
</tr>
<tr>
<td>Frantzen et al., 22 2006</td>
<td>Men consulting their general practitioner for ED were defined as incident cases if they had not consulted a physician for this disorder for at least 1 year before the consult</td>
<td>The investigators who were assessing outcomes were aware of the patient’s erectile function due to the retrospective design of the study and did not adjust for any CV risk factors</td>
</tr>
<tr>
<td>Schouten et al., 10 2008</td>
<td>ED was assessed by the International Continence Society male sex questionnaire. The answers on the question: ‘Do you get erections?’ were categorized into: (a) no erectile dysfunction: a self-reported normal erection; (b) moderate erectile dysfunction: a report of erections with ‘reduced rigidity’; and (c) severe erectile dysfunction: a report of erections with ‘severely reduced rigidity’ or ‘no erections’</td>
<td>No evidence of bias</td>
</tr>
<tr>
<td>Ma et al., 23 2008</td>
<td>Patients were asked directly whether they suffered from ED according to the definition of the National Institutes of Health Consensus Conference 1992. ED was defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance. The response to the question was either “Yes” or “No.”</td>
<td>No evidence of bias</td>
</tr>
<tr>
<td>Gazzaruso et al., 24 2008</td>
<td>ED was considered present when the IIEF-5 score was ≤21</td>
<td>The lost in follow-up to events ratio is 15/49=31% which is more than 15% that we use as a cut-off point</td>
</tr>
<tr>
<td>Inman et al., 15 2009</td>
<td>The Brief Male Sexual Function Inventory was used to evaluate the sexual function. This self-report questionnaire is composed of 11 items</td>
<td>The investigators did not adjust for all major CV risk factors (adjustment for diabetes, hypertension, history of smoking,</td>
</tr>
</tbody>
</table>
that are rated on a scale of 0 to 4, with higher scores representing better sexual function. The items are grouped into 4 functional domains: sexual drive (2 items), erectile function (3 items), ejaculatory function (2 items), and problem assessment (3 items). A final item addressing overall sexual satisfaction is also included. Patients reporting a cumulative score of 3 or lower for the 3 questions in the erectile function domain were considered to have ED.

Araujo et al., 2009 and Araujo et al., 2010

The subject was given a 23-item questionnaire on sexual activity to be completed in private and returned in a sealed envelope. The questionnaire included 13 items related to ED, such as, “During the last 6 months have you ever had trouble getting an erection before intercourse begins?” The 13 items were combined in a discriminant-analytic formula to assign a degree of erectile function to each subject. Calibration data for the discriminant formula were taken from an additional single-question, subjective self-assessment of ED, included in the follow-up questionnaire in response to recommendations of the National Institutes of Health Consensus Panel. Impotence was defined as “being unable to get and keep an erection that is rigid enough for satisfactory sexual activity.” The subject rated himself as completely impotent (“never able to get and keep an erection . . .”), moderately impotent (“sometimes able . . .”), minimally impotent (“usually able . . .”), or not impotent (“always able . . .”).

Hebert et al., 2009

All participants were administrated the SHIM survey to measure ED at the baseline of the study. The SHIM consists of five questions designed to cover the major constituents of ED. Respondents were asked about their experience related to ED during the past 6 months. Responses were recorded on a 5-point Likert scale ranging from rarely (1) to almost always (5). A score of 21 or lower on the SHIM scale has been used to identify ED. Based on the SHIM, the patients were placed into two categories: No ED $\geq 22$ and ED $\leq 21$.

Ponholzer et al., 2010

The IIEF-5 questionnaire was used to assess the prevalence and severity of ED. The classification system developed by was slightly modified by combining the ‘mild-to-moderate’ and ‘moderate’ groups into one group to facilitate statistical evaluation into three categories, such as no ED (IIEF-5 score=22–25), mild ED (IIEF-5 score=17–21) and moderate-to-

No evidence of bias

The investigators did not adjust for any CV risk factors

The investigators did not adjust for all major CV risk factors (adjustment for age)
severe ED (IIEF-5 score=5–16).

Böhm et al., 2010

The authors used the 5-item short form of the IIEF and the Kölner (Cologne) Evaluation of Erectile Dysfunction scores. These evaluating tools were incorporated into 1 questionnaire as internal controls for each other. The Kölner Evaluation of ED score consists of 6 questions on a 5-point Likert scale. An ascending score indicates worsening of ED, with a cutoff at >17 points for the diagnosis of ED. The IIEF score ranges from 5 to 25 points, in which a descending score indicates worsening of erectile function in patients, with a cutoff below 22 points for a diagnosis of ED. Individuals scoring 5 to 7 points on the IIEF score were diagnosed as having severe ED, whereas 8 to 11 points indicated moderate ED, 12 to 16 points was mild to moderate ED, 17 to 21 points indicated mild ED, and 22 to 25 points signified no ED.

Batty et al., 2010

Nurses asked subjects whether they had ED (categorized as “yes” or “no”).

Chung et al., 2011

Patients who had visited ambulatory care centers for the treatment of ED (with a principal diagnosis of Impotence, organic [ICD-9 code 607.84] or Impotence, psychogenic [ICD-9 code 302.72])

Hotaling et al., 2012

Answering yes to the question “Have you experienced impotence in the last year?”

ED: Erectile dysfunction; ICD: International Classification of Diseases; IIEF: International Index Erectile Function; SHIM: Sexual Health Inventory for Men; PVD: Peripheral vascular disease; ICD: International classification of diseases; CHD: Coronary heart disease; BMI: Body-mass index.
Supplemental Figure Legends

**Figure S1.** Publication bias for total CV outcomes and all-cause mortality and its potential impact. (A) Total CV events; (B) myocardial infarction; (C) cerebrovascular events and (D) all-cause mortality. The open circles in the left and right plots represent individual studies relating ED with events, and the open diamonds are the RR and 95% CI for the meta-analysis. The solid circles in the right plots represent imputed studies, and the solid diamonds are the RR and 95% CI for the meta-analysis after adjusting for publication bias.
Supplemental Figures

Figure S1