Circulation

RESEARCH LETTER

# Erectile Dysfunction as an Independent Predictor of Future Cardiovascular Events

## The Multi-Ethnic Study of Atherosclerosis

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Vascular erectile dysfunction (ED) and cardiovascular disease (CVD) share common risk factors including obesity, hypertension, metabolic syndrome, diabetes mellitus, and smoking. ED and CVD also have common underlying pathological mechanisms, including endothelial dysfunction, inflammation, and atherosclerosis.[1] Despite these close relationships, the evidence documenting ED as an independent predictor of future CVD events is limited.

We therefore leveraged the MESA study (Multi-Ethnic Study of Atherosclerosis), an ethnically diverse, community-based, multisite prospective cohort study, to examine the value of self-reported ED for predicting incident coronary heart disease (CHD) and CVD in those free of these CVD events at baseline. Details of MESA have been described previously.[2] Male MESA participants who attended visit 5 and answered the single Massachusetts Male Aging Study question[3] on ED symptoms were considered for our analysis (n=1914). A participant was considered to have ED if he responded "never able" or "sometimes able" to the Massachusetts Male Aging Study question. After excluding 155 participants with a CVD event before visit 5, 1757 participants were followed for 3.8 years (interquartile range, 3.5–4.2) and outcomes of hard CHD and CVD events were assessed. Hard CVD events included all hard CHD events (myocardial infarction, resuscitated cardiac arrest, and CHD death), plus stroke and stroke death. Participants provided informed consent, and each study site obtained approval from their institutional review board.

Cox proportional hazard models were developed to calculate hazard ratios for the outcomes by ED status (ED yes/no) after adjusting for age, race/ethnicity, and education (model 1); further adjusting for smoking status, diabetes mellitus, family history of CHD, total/high-density lipoprotein cholesterol ratio, systolic blood pressure, antihypertensive medication use, and lipid-lowering medication use (model 2); and further adjusting for β-blocker use and depression assessed by the Center for Epidemiological Studies Depression score (Center for Epidemiological Studies Depression score>16 versus ≤16) (model 3).

To further assess the potential bidirectional relationship of prior CVD with ED, an additional shifted-time cross-sectional analysis was conducted to see if an interim CVD event before MESA visit 5 was associated with self-reported ED at visit 5. For this analysis, all 1914 participants with an ED assessment were included in a multivariable-adjusted logistic regression adjusting for the above-mentioned covariates.

The mean age of the 1914 participants was 69±9.2 years and 42.3% were white, 24.2% were African American, 10.5% were Chinese American, and 22.9% were Hispanic. ED symptoms were reported by 877 (45.8%) participants. Participants with ED were more likely to have diabetes mellitus and a family history of CHD. They were also more likely to use β-blocker, antihypertensive, lipid-lowering, and antidepressant medications. Over the 3.8-year follow-up, there were a total of 40 CHD and 75 CVD hard

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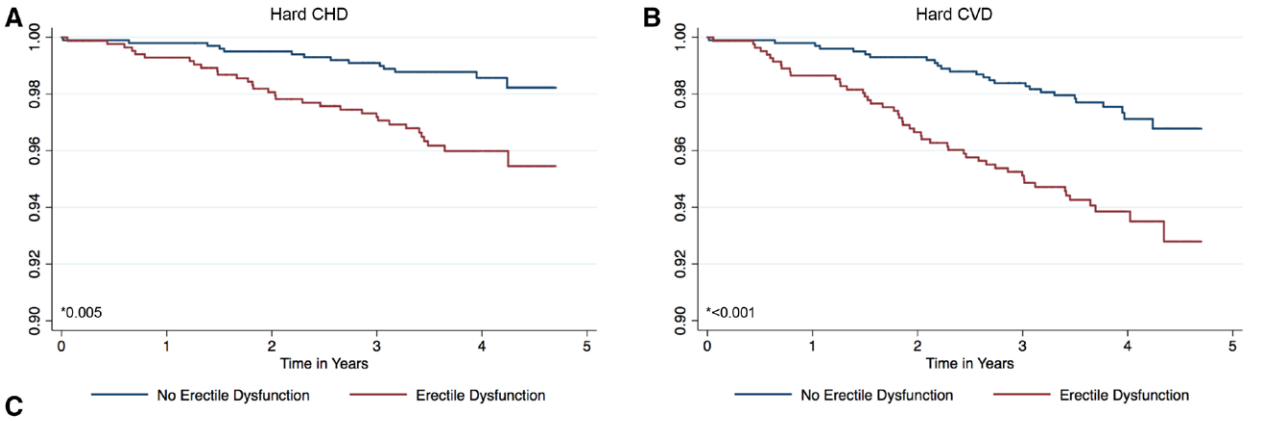


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| | Events, N (%) | Unadjusted HR (95% CI) | Model 1 HR (95% CI) † | Model 2 HR (95% CI) ‡ | Model 3 HR (95% CI) § |
|---|---|---|---|---|---|
| Hard CHD | 40 (2.3%) | 2.5 (1.3 – 4.8) | 1.7 (0.8 – 3.6) | 1.6 (0.8 – 3.4) | 1.8 (0.8 – 4.0) |
| Hard CVD | 75 (4.3%) | 2.6 (1.6 – 4.1) | 1.7 (1.0 – 2.9) | 1.8 (1.0 – 3.2) | 1.9 (1.1 – 3.4) |

**Figure. Association between ED and incident CHD and CVD hard events among 1757 male MESA participants.**
**A** and **B**, Kaplan-Meier cumulative survival function curves for hard CHD and CVD events by ED status. **C**, Cox proportional hazard ratios (95% CIs) of hard CHD and CVD events by ED status. **P* value by log-rank testing. †Model 1 adjusted for age, race/ethnicity and education. ‡Model 2 adjusted for model 1 + smoking status, diabetes mellitus, family history of CHD, total/HDL cholesterol ratio, systolic blood pressure, antihypertensive medication use, and lipid-lowering medication use. §Model 3 adjusted for model 2 + depression and β-blocker use. CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; ED, erectile dysfunction; HDL, high-density lipoprotein; and HR, hazard ratio.

events. A significantly greater proportion of participants with ED experienced hard events than those without ED (CHD hard events: 3.4% versus 1.4%, *P*<0.001; CVD hard events: 6.3% versus 2.6%, *P*<0.001).

In the unadjusted Cox models, ED was a significant predictor of both hard CHD (hazard ratio, 2.5; 95% confidence interval [CI], 1.3–4.8) and CVD (hazard ratio, 2.6; 95% CI,1.6–4.1) events. In the fully adjusted models (model 3), ED remained a significant predictor of hard CVD events (hazard ratio, 1.9; 95% CI, 1.1–3.4), whereas hard CHD events became nonsignificant, albeit with a similar point estimate of risk (Figure).

In the shifted-time cross-sectional analysis, a significant association was also seen between prior CVD event and ED at visit 5 (odds ratio, 2.1; 95% CI, 1.4–3.2), which remained significant but was attenuated by medication use and depression in the fully adjusted models (odds ratio, 1.7; 95% CI, 1.1–2.6).

In an ethnically diverse, community-based cohort, ED was found to be a significant predictor of hard CVD events after adjustment for traditional CVD risk factors, depression, and β-blocker use. To our knowledge, this is the first study of ED and subsequent CVD that adjusted for depression and β-blocker use. Our results suggest that these 2 factors may partially mediate the relationship between prior CVD and subsequent ED, but do not attenuate the prospective association of ED and incident CVD. Our findings strengthen the existing evidence for the independent association between ED and incident CVD, and could have important clinical implications for risk stratification in middle-aged men. We have previously documented increased subclinical atherosclerosis in those who subsequently report ED.[4] In 2017, the UK QRISK score was the first to incorporate ED as an independent risk factor for CVD,[5] yet ED remains absent from US risk prediction guidelines. Our results may justify more aggressive preventive therapy in such patients.

Our study had certain limitations. Although similar to the primary care assessment of ED, the single Massachusetts Male Aging Study question does not distinguish between vascular and nonvascular types of ED, which may have attenuated the association between ED and CVD. In addition, because our follow-up was just 3.8 years, additional 10-year data on the risk predictive value of ED are needed.

In conclusion, our study provides some of the strongest evidence to date for the independent predictive value of ED in a modern, multiethnic, well-phenotyped cohort.

## ARTICLE INFORMATION

MESA data are available by request at the study website at https://www.mesa-nhlbi.org/.

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## Disclosures

None.

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