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Erectile Dysfunction, Vascular Risk, and Cognitive Performance in Late Middle Age

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Caitlin S. Moore developed the study concept. All authors contributed to the study design. Caitlin S. Moore, Michael D. Grant., and Matthew S. Panizzon performed the data analysis and interpretation under the supervision of Mark W. Logue, Michael J. Lyons, and William S. Kremen. Caitlin S. Moore drafted the article, and all other authors provided critical revisions. All authors approved the final version of the article for submission.

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Abstract

Vascular disease is the most common etiology of erectile dysfunction (ED). Men with ED are at a 65% increased relative risk of developing coronary heart disease and a 43% increased risk of stroke within 10 years. Vascular disease is associated with cognitive impairment; ED—an overt manifestation of vascular dysfunction—could also signal early compromised cognition. We sought to determine whether cognitive differences existed between men with ED and healthy peers. Our sample consisted of 651 men (ages 51–60 years) from the Vietnam Era Twin Study of Aging. ED was associated with poorer cognitive performance, particularly on attention–executive–psychomotor speed tasks. ED remained significantly associated with cognition after inclusion of other cardiovascular risk factors (including hypertension, high cholesterol, body mass index, and smoking). These findings underscore the importance of further study of ED as a predictor of cognitive and cardiovascular health.

Keywords

erectile dysfunction; cognitive dysfunction; cardiovascular disease

Cardiovascular disease (CVD) is detrimental for cognitive function, quality of life, morbidity, and mortality. A vast literature exists on the negative impact that CVD has on cognition. It is well established that CVD can cause mild to severe cognitive dysfunction (Hachinski, 2008), and that it plays a significant role in cognitive decline. Early identification of those at risk for CVD is critical to attenuate the atherosclerotic process and prevent or delay cognitive impairment.

In the past two decades, erectile dysfunction (ED) has become recognized as an early indicator of microvascular disease. ED is extremely common, and it is estimated that by the year 2025, more than 320 million men worldwide will suffer from it (Aytaç, McKinlay, & Krane, 1999). There have long been stigmatizing misconceptions about ED, but it is now known that up to 80% of ED cases are due to physiological causes, with vascular disease the most common etiology (Jackson, Rosen, Kloner, & Kostis, 2006; Kendirci, Nowfar, & Hellstrom, 2005; Solomon, Man, & Jackson, 2003). Not only is ED frequently due to vasculopathic processes, it has been well established that ED is a strong predictor of future cardiovascular diagnoses. For example, ED frequently precedes the onset of angina by 2–3 years and adverse cardiovascular events by 3–5 years (Hodges, Kirby, Solanki, O'Donnell, & Brodie, 2007; Montorsi et al., 2006). Over the course of 10 years, men with moderate-to-severe ED are at a 65% increased relative risk of developing coronary heart disease and a 43% increased risk of stroke compared with those without ED (Ponholzer, Temml, Obermayr, Wehrberger, & Madersbacher, 2005). Moreover, ED severity is related to the number and severity of CVD risk factors (Feldman, Goldstein, Hatzichristou, Krane, & McKinlay, 1994) and they tend to co-occur, with up to 75% of coronary artery disease patients experiencing some degree of erectile difficulties. (Feldman et al., 1994). ED has proven to be a very valuable warning sign of vasculopathic processes.

Accordingly, the Princeton II Consensus guidelines suggest that “a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise” (Jackson et al.,

2006, p. 34). Although not all cases of ED are due to vascular factors, given the implications of progressive atherosclerosis, it is important for medical professionals to assume a vascular origin (and later rule it out, if necessary) so that cardiovascular assessments and interventions can be introduced as soon as possible. There is, of course, a literature on psychogenic ED. However, in men over 50 years old, only 10% of ED cases have a psychogenic etiology (Finelli, Hirshberg, & Radomski, 1998; Slag et al., 1983). Thus, assuming that a man with ED is a cardiovascular patient makes sense statistically, and is the most conservative approach to ensure that a cardiac work-up is conducted.

The established link between ED and CVD lies in the endothelium and smooth muscle. ED and vascular diseases share a similar pathogenic process that leads to endothelial dysfunction and structural vascular changes, impairing the arteries' and arterioles' ability to dilate appropriately (for review, see Montorsi et al., 2005). Currently, the prevailing theory connecting ED and CVD is the "artery size" hypothesis (Montorsi et al., 2005), although it should be noted that it has not received uniform support (Ponholzer et al., 2012). This theory posits that because artery size varies markedly according to location (e.g., cerebral small vessels are less than 0.1 mm, penile arteries are 1–2 mm, carotid arteries are 5–7 mm, and femoral arteries are 6–8 mm), the same level of endothelial and smooth muscle dysfunction—and subsequent atherosclerotic progression—will have a greater effect on the smallest arteries first. Thus, the effects of penile atherosclerosis (ED) should become apparent long before the effects of coronary or carotid atherosclerosis. In addition, because penile arteries are more similar in size to cerebral small vessels, ED may be an early warning sign of accruing cerebrovascular damage.

Studying endothelial dysfunction is particularly helpful given that CVD has widely heterogeneous manifestations. Patients present with myriad risk factors of differing severities, which makes it challenging to quantify the overall burden of their illness. A commonality among all of the cardiovascular risk factors is that they each have been shown to damage the endothelium (Hadi, Carr, & Al Suwaidi, 2005). Accordingly, the more risk factors one has, the more impaired the endothelium will be. In this regard, the endothelium has been viewed as an integrated measure of vascular burden. Given that ED is an overt sign of endothelial dysfunction, as severity of CVD risk increases, so does the severity of ED. Thus, ED may serve as a behavioral measure of overall vascular burden.

Vascular dysfunction has been studied directly by others (Hoth et al., 2007; Moser et al., 2008) who have found that degree of endothelial and smooth muscle dysfunction in CVD is associated with poorer cognition. It is possible that ED—an overt manifestation of vascular dysfunction—could signal that cognition may already be subtly compromised even prior to more serious cardiovascular events (e.g., myocardial infarction, stroke) or procedures (e.g., stent placement).

It now is widely established that individuals with CVD exhibit subtle cognitive deficits long before the onset of vascular dementia and even prior to major cardiac events such as myocardial infarction or stroke (Gorelick et al., 2011). Assessment of cognitive function in this population is important because it has been hypothesized that even mild cognitive difficulties may account for some of the self-care decision-making problems frequently

found in patients with CVD (Cameron et al., 2010). For example, cognitive impairments can make it difficult to identify and interpret symptoms, adhere to medication regimens, and remember medical appointments. Elucidating early warning signs of vascular cognitive impairment is thus important for preventive medicine (Bowler, 2000). Relatedly, because ED is predictive of future cardiovascular events, the onset of ED may spur men to seek neuropsychological evaluations to establish a baseline. Through this, neuropsychologists and physicians can better monitor cognitive functioning over time in case a cardiovascular event occurs in the future.

The exact cognitive profile associated with CVD may vary as a function of the underlying etiology (O'Brien, 2006). Deficits are most prominent in attention–executive–psychomotor speed domains (Haley et al., 2007) because frontosubcortical networks subserving these cognitive abilities appear to be particularly vulnerable to ischemic damage (Pantoni & Garcia, 1997). However, significant findings have been reported in every major cognitive domain, including deficits in retrieval (Garrett et al., 2004), organization and learning efficiency (Waldstein & Wendell, 2010), and verbal and nonverbal memory (Muller, Grobbee, Aleman, Bots, & van der Schouw, 2007).

A small previous study has suggested that treating ED with phosphodiesterase Type 5 inhibitors may improve cognitive function in men with ED (Shim et al., 2011). The results of this study suggest that men with ED may not be performing to their optimal level. However, the study did not include a comparison group to rule out practice effects. Practice effects on cognitive tests have been well documented after 5 years (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005), so they could easily have a strong impact on their 1-month follow-up.

In this study, we assessed whether ED is associated with poorer cognitive function in middle-aged men without CVD. The literature suggests that men with ED are at increased risk of developing CVD within 3–5 years (Hodges et al., 2007; Jackson et al., 2006). Accordingly, we reasoned that systemic subclinical vascular processes could already be influencing cognitive function in this at-risk population compared with men without ED. We hypothesized that poorer erectile function would be associated with poorer cognitive performance, particularly with regard to attention–executive–psychomotor functions.

Method

Participants

The present study used data from the Vietnam Era Twin Study of Aging (VETSA), a longitudinal study of cognition and aging beginning in midlife (Kremen et al., 2006). VETSA participants are from the Vietnam Era Twin Registry (VETR), a nationally representative sample of male–male twin pairs who served in the U.S. military sometime between 1965 and 1975. Most did not serve in combat. Detailed descriptions of the VETR and ascertainment methods have been previously reported (Kremen, Franz, & Lyons, 2012; Kremen et al., 2006). VETSA participants are similar to the general population of middle-aged American men in terms of socioeconomic status and health characteristics (Kremen et al., 2012). Participants traveled to laboratories at Boston University or the University of

California, San Diego. The study was approved by local institutional review boards. Of 1,237 participants, the final sample for the analyses reported here comprised 651 men with an average age of 55.3 years ($SD = 3.1$, range: 51–60 years).

Given our interest in examining the relationship between cognition and ED as a subclinical harbinger of vascular disease, individuals were excluded if they were already diagnosed with heart disease (angina, peripheral vascular disease, myocardial infarction, heart failure, stent placement, or heart surgery) or if they ever had diabetes, a history of substance abuse or dependence, multiple sclerosis, stroke, or seizure disorder. All of these conditions can affect cognition and/or erectile function, irrespective of underlying vascular burden. History of any of these conditions was based on participants' endorsement when asked whether a doctor had ever told them that they had the condition.

Perhaps counterintuitively, because we were interested in the relationship between cognition and the presence of ED, all participants who were already taking ED drugs (e.g., sildenafil, tadalafil) were excluded from analyses. This was a relatively small number of men (under 2% of our sample); however, these drugs would alter their self-reported erectile function scores without altering their underlying vascular burden and thus could misrepresent that relationship. Moreover, many drugs used to treat ED are also regularly used to treat other disorders (e.g., pulmonary hypertension, benign prostatic hyperplasia). Thus, we cannot unequivocally claim that men taking these medications would qualify for an ED diagnosis. There was a range of erectile function scores in this group, with many scoring in the normal range.

Participants were also excluded if they had not attempted sex in the past month, in part because that is the timeframe on which the erectile function measure is validated. Moreover, men who had not been sexually active in this timeframe may have suffered recall bias when making judgments about the last time they had attempted intercourse, which for many was several years prior.

Materials

Erectile function was assessed with the International Index of Erectile Function–6 (IIEF-6; Rosen et al., 1997), a well-validated self-report questionnaire. The score represents the sum of six questions that address ED symptoms over the past 4 weeks. This measure has been published in continuous, categorical, and binary formats. When scored categorically, ED is classified as severe (6–10), moderate (11–16), minimal (17–25), or none (26–30). The prevalence of our ED severity was highly skewed (the overwhelming majority of positive ED cases were mild), so we opted to use a binary erectile function variable indicating the presence (≤ 25) or absence (>25) of ED. In addition, we felt that a binary format may provide the most clinical utility and more readily transfers across ED measures, whereas the definition of severity groups may vary. Importantly, all analyses were run using ED as a continuous, categorical, and binary measure and produced consistent results.

We assessed 11 neuropsychological abilities. When a cognitive ability score incorporated more than one measure, individual measures were standardized (z -scored) and a composite score equal to the mean of the standardized scores was calculated (Franz et al., 2011). *Verbal*

ability was assessed with the Vocabulary subtest from the Wechsler Abbreviated Scale of Intelligence. *Visual-spatial ability* was based on the Hidden Figures Test and the Card Rotation Test (Ekstrom, French, & Harman, 1976; Wechsler, 1997a).

Verbal memory was assessed with the California Verbal Learning Test—Version 2 and the Logical Memory subtest from the Wechsler Memory Scale—3 (WMS-3; Wechsler, 1997b). California Verbal Learning Test scores were the immediate free recall, delayed free recall, and delayed free recall adjusted for immediate free recall. Logical memory scores were the immediate recall, delayed recall, and delayed recall adjusted for immediate recall.

Visual-spatial memory was measured using the WMS-3 Visual Reproductions subtest. *Short-term memory* (STM) was based on scores from WMS-3 digit span forward and spatial span forward. *Working memory* included three WMS-3 tests: digit span backward adjusted for digits forward, spatial span backward adjusted for spatial span forward, and letter–number sequencing adjusted for digits. Thus, STM involves only maintenance of information, whereas working memory only involves manipulation of information controlling for STM ability.

Processing speed was derived from the Stroop word reading condition and Delis–Kaplan Executive Function System (Delis, 2001) Trail Making Test (Trails), both number sequencing trial and letter sequencing trial. *Abstract reasoning* ability was measured with scores from the Wechsler Abbreviated Scale of Intelligence Matrix Reasoning subtest.

Three aspects of executive function were addressed in our study. An *inhibitory control* measure was based on the Stroop Color–Word Test interference condition score (Golden, 1978) adjusted for Stroop word reading. *Set-shifting* was based on Trails number–letter switching condition adjusted for number sequencing and adjusted for letter sequencing, and the category-switching condition from Delis–Kaplan Executive Function System Verbal Fluency (alternating between saying fruit words and furniture words) adjusted for Category (animal) Fluency scores. These adjustments were performed to isolate the contribution of cognitive inhibition or set-shifting abilities from processing speed. *Verbal fluency* was based on the total correct on the Delis–Kaplan Executive Function System Letter (F,A,S) and Category (animals, boys’ names) Fluency tests.

Participants were also assessed for a variety of measures that could be related to cognitive function, including age, body mass index (BMI), smoking, high cholesterol, hypertension, depressive symptoms, testosterone, and cognitive ability from early adulthood. Hypertension was ascribed to participants if they were taking antihypertensive medications, endorsed that a physician had given them this diagnosis, or had blood pressure above 140 systolic or 90 diastolic on the day of testing. High cholesterol was ascribed to participants taking lipid-lowering medication or endorsing that a physician had diagnosed them as having hypercholesterolemia. Depressive symptoms were measured by the Center for Epidemiologic Studies—Depression Scale (Radloff, 1977). Lifetime smoking was indexed by pack years (cigarettes smoked per day $\times$ years the participant smoked/20). Race/ethnicity was ascribed based on self-report. Salivary (free) testosterone levels were based on the average testosterone level for five times across 3 collection days (Panizzon et al., 2012).

Testosterone was only available on a subset of participants ($n = 410$), as testosterone assessment was an add-on study that began 3 years after VETSA had begun.

Groups were compared on early adulthood cognitive ability as measured by the Armed Forces Qualification Test (AFQT; Bayroff & Anderson, 1963), a 100-item multiple-choice test that is highly correlated with Wechsler IQ and other general cognitive ability measures (Lyons et al., 2009; McGrevy, Knouse, & Thompson, 1974). VETSA affords a unique opportunity to use premorbid cognitive ability scores because all participants were administered the AFQT at around age 20. Mean AFQT percentile score during the VETSA was 64, corresponding to a WAIS score of approximately 105. The AFQT has high reliability, demonstrating a test–retest correlation of .74 over the 35-year interval between average age 20 and the VETSA study (Lyons et al., 2009).

Statistical Analysis

The analyses were nontwin analyses, that is, individuals, not twin pairs, were the unit of analysis. All analyses adjusted for the clustering of twins within pairs with mixed modeling in SPSS 19. We began by testing for mean differences in demographic and health variables between ED and non-ED (N-ED) groups.

For our first mixed models, we compared ED and N-ED groups on 11 cognitive domains; each cognitive domain was run separately. In the series of second models, age, health factors, and premorbid cognitive ability were included as covariates. Testosterone level was not included as a covariate because data were available for only a subset of participants; however, testosterone was unrelated to ED. Presented estimates and significance levels represent each parameter's influence after all other terms have been entered into the equation (Type III fixed effects).

We used a standardized mean difference effect-size measure that is the difference between group means divided by the estimate of the total standard deviation from the mixed model (both random and fixed effects), which equals the square root of the sum of estimated twin and error variances. This is analogous to Cohen's d (Cohen, 1992) and is conservative compared with standardized mean differences based on within-group variance alone.

To correct for multiple analyses being run, we employed the false discovery rate (FDR) control in each of our models (Benjamini & Hochberg, 1995). The FDR is determined by computing a_i by ranking the p value of each of the n tests from smallest (p_1) to largest (p_n) and multiplying each p value by n divided by the rank (i) of that p value ($a_i = p_i * n/i$). Tests in which $a < .05$ remain significant, and those with $a > .05$ are deemed false discoveries.

Results

After applying exclusionary criteria, 651 participants remained. In total, 586 men were excluded for the following reasons: taking ED medications ($n = 22$), no sexual activity over the past month ($n = 315$), cardiovascular disease ($n = 211$), neurologic disease ($n = 8$), substance use disorder ($n = 16$), or did not complete the IIEF-6 ($n = 14$). Demographic and health comparisons are shown in Table 1.

Included participants did not differ from excluded participants on age, ethnicity, education, or premorbid cognitive ability, but they were less depressed ($F[1, 1182.4] = 41.3, p < .001$), smoked less ($F[1, 1117.2] = 10.4, p = .001$), had lower BMI ($F[1, 1032.2] = 10.0, p = .002$), had less hypertension ($F[1, 1188.0] = 26.8, p < .001$), and had less hypercholesterolemia ($F[1, 1211.5] = 38.0, p < .001$). Of the included sample, 25.3% ($n = 165$) endorsed some degree of ED (74% mild [$n = 122$]), 18% moderate [$n = 30$], and 8% severe [$n = 13$]). All ED subgroups were collapsed to form the final ED group. Comparisons between the ED and N-ED groups can be found in Table 2.

Men with ED had significantly more lifetime smoking ($F[1, 504] = 6.8, p = .009$) and more depressive symptoms [$F(1, 624.6) = 5.0, p = .03$]. There were trend-level findings of lower education, lower premorbid cognitive ability, and higher BMI. No significant differences were found between groups on total testosterone ($p = .39$) and proportion of participants with hypercholesterolemia ($p = .16$) or hypertension ($p = .56$).

In the first series of mixed models, the ED group performed significantly worse on 10 of the 11 cognitive abilities (see Table 3). No differences were found on tasks of visual-spatial ability. Overall, small-to-medium effects (analogous to Cohen's convention) between the ED group and N-ED group were observed (standardized mean differences = .17–.39). Based on the FDR adjustment, findings with processing speed, verbal fluency, STM, visual-spatial memory, working memory, inhibition, verbal ability, and abstract reasoning remained significant.

After accounting for covariates, ED remained significantly associated with cognitive function in seven domains (see Table 4). Moreover, in these seven domains, ED was more strongly associated with current cognition than any other health variables analyzed. All of our significant findings survived the FDR adjustment. ED showed strongest associations with processing speed, STM, and verbal fluency. Hypertension and BMI had no significant independent association with any of the cognitive domains. Pack years, cholesterol, and depression had limited associations with cognition, with each exhibiting significant associations with only a few domains. As mentioned above, when ED was analyzed as a continuous rather than binary variable, similar results were obtained (these results are available in the Appendix).

Discussion

The importance of ED has evolved from its beginnings as a presumed psychogenic disorder to a serious health outcome widely recognized as a putative harbinger of cardiovascular health outcomes. Our results suggest that underlying vascular dysfunction is already influencing cognitive performance even after excluding men with cardiovascular illness and adjusting for demographic and medical conditions associated with ED that are known to influence cognitive performance.

Poorer erectile function was significantly associated with poorer cognitive performance, with particularly strong relationships found in the domains of STM (also commonly referred to as an aspect of attention), verbal fluency (an aspect of executive functioning), and

processing speed. These results are consistent with the hallmark impairment of the attention–executive–psychomotor functions found in the vascular cognitive profile.

The importance of these findings is threefold. First, this is the first study to demonstrate a significant relationship between ED and decreased cognitive performance, relative to healthy controls. In otherwise healthy men, ED was more strongly associated with cognitive performance than more conventional vascular risk factors such as smoking, high cholesterol, hypertension, and obesity. As every CVD risk factor is known to impair the endothelium, overt signs of endothelial dysfunction (e.g., ED) may serve as an integrated measure of overall vascular burden and thus would likely show stronger relationships to cognition. This point is critical because many CVD risk factors are relatively silent, whereas ED is an overt and recognizable condition.

Second, our findings are notable because we demonstrated a relationship between ED and cognitive performance in a relatively young, nonpatient cohort of middle-aged men who have not yet experienced substantial cognitive decline. Third, with nearly 75% of the ED group classified as having only mild ED, our results suggest that even mild ED is associated with poorer cognitive performance. If our ongoing longitudinal investigation reveals that ED is not only cross-sectionally related to but also predictive of cognitive change over time, it would suggest that ED assessment will be useful in the early identification of men at greatest risk for vascular-related cognitive decline.

Our findings are consistent with the artery size hypothesis, but some aspects of this hypothesis have been called into question. A small postmortem study showed that atherosclerosis can be present in the vasculature in the absence of penile atherosclerosis (Ponholzer et al., 2012). However, the ED status of participants in that study was unknown and the histological analysis did not include brain tissue. Further work is needed to better elucidate the artery size hypothesis and evaluate alternative theories.

One important factor that was not included in our analyses was low testosterone levels. Given testosterone's association with ED (Traish, Guay, Feeley, & Saad, 2009), cardiovascular risk factors (Maggio & Basaria, 2009), and cognition (Yeap et al., 2008) in previous research, it is plausible that it too could play a role. However, testosterone was unrelated to ED or cognition in the subset of our participants for whom testosterone data were available. Testosterone has received extensive attention in the sexual dysfunction literature because testosterone—like sexual functioning—tends to decline with age. Although low testosterone has been implicated in low sexual desire (Morley, 2003), its relationship with erectile functioning seems to be mediated, in some cases, by vascular health. It has been shown that high androgen levels have an anti-inflammatory effect (Malkin, Pugh, Jones, Jones, & Channer, 2003), and thus reductions in testosterone may be coupled with increased cardiovascular risk (Kupelian et al., 2010). In this sense, if testosterone had been shown to account for the relationship between ED and cognition, it would still be unclear whether that association was direct (e.g., low testosterone causes impaired cognition and ED) versus indirect (e.g., low testosterone causes high inflammation, which results in vasculogenic ED and cognitive impairments). Future studies including testosterone and direct vascular assessment could help tease apart these relationships.

Strengths and limitations of the study should be noted. It is likely that some ED cases had nonvascular etiologies (e.g., trauma, medication side effects, performance anxiety, stress); however, the likelihood of this representing a substantial proportion of our cases is quite low. Up to 80% of ED can be attributed to organic causes, with vascular dysfunction most prominent (Virag, Bouilly, & Frydman, 1985). Moreover, the Princeton III Consensus guidelines suggest that a man with ED and no cardiac symptoms should be considered as having vascular disease until vascular disease is ruled out (Nehra et al., 2012). It is also possible that correlates of ED (e.g., low socioeconomic status, physical inactivity, psychological stress) account for its relationship with cognition, independent of vascular health. Unfortunately, direct assessment of vascular function was beyond the scope of the present study, but future research is warranted to better elucidate these findings.

We assessed ED with a self-report measure rather than physiological assessment. However, the IIEF-6 is considered one of the gold-standard self-report assessments of ED and it has been well validated. The IIEF-6 does ask about only the past 4 weeks of sexual activity. It is possible that a more expansive window of time could be useful because it would allow for inclusion of more participants, although that could be offset by greater reliance on more distant recall.

Relatedly, some men who are not attempting sex are doing so because they have erectile difficulties. Including them in the analyses may have increased generalizability of the sample. However, there are several valid reasons why men may not attempt sex, many of which have nothing to do with erectile function (e.g., no partner availability/no partner interest, physical disability of self or partner, etc.). For some of our men, their last sexual attempts ranged from months to years prior. If we included these men in our analyses, we would be comparing their past erectile function with their current cognition, thereby changing the nature of the findings. Future studies could evade this issue by using direct physiological assessment to diagnose ED rather than relying on self-report measures.

Another limitation concerns our reliance on self-report for medication regimen and history of medical conditions. It is possible that some of our participants had been previously diagnosed with one of our exclusionary criteria (e.g., angina) and failed to recall this during the medical interview. Although this could result in the improper inclusion of some participants in the present analyses, the likelihood of this representing a meaningful portion of our sample is quite low. Indeed, Baumeister and colleagues (2010) have shown that self-report for medical history is highly reliable and valid.

We cannot unequivocally determine the temporal relationship between cognitive performance and ED symptoms. Nevertheless, there is a large literature suggesting that impaired vascular function results in both ED and cognitive changes (Ponholzer et al., 2005; Schneider, Arvanitakis, Bang, & Bennett, 2007). By following this sample longitudinally, we can determine the temporal nature of this relationship.

It might be considered a limitation that 47% of our sample was excluded. Despite our exclusionary criteria, we were still left with a relatively large sample, and it was necessary to exclude many conditions to confidently conclude that it was ED—rather than other factors—

that was associated with poorer cognition. In one study of men ages 50–80 years, ED was associated with increased cardiovascular risk, but it was not an age-independent predictor (Ponholzer, Gutjahr, Temml, & Madersbacher, 2010). With a 30-year age range, the effects of age may have been substantial enough to overshadow ED effects. In contrast, our age-homogeneous sample enhanced the ability to detect individual differences unrelated to age differences. Therefore, the importance of ED is supported and strengthened by the fact that it remained a significant factor even with stringent exclusion criteria in a relatively young, age-homogeneous sample. However, given these exclusions, our findings are only relevant in men without CVD. It will be important to determine whether ED is indicative of compromised cognition in clinical populations, but that was beyond the scope of this initial study.

Relatedly, it is possible that the observed relationships between cognition and conventional cardiovascular or other risk factors would be more prominent had we not excluded individuals with CVD (as these individuals would be most likely to exhibit hypertension, high cholesterol, increased smoking, etc.). However, these effects still appear to be small in middle-aged adults. For example, in the full VETSA sample when these conditions were not excluded, blood pressure was uncorrelated with cognition (Vasilopoulos et al., 2012) and depressive symptoms still had very small correlations with cognition (Franz et al., 2011). That said, it is also plausible that individuals with CVD would also exhibit more cases of ED, and thus our findings may be strengthened. Future studies are warranted to extend these findings to clinical populations. Nevertheless, the findings presented in this study are clinically relevant because they inform clinicians that ED can negatively impact cognitive function even in men free of CVD.

In sum, results from this study demonstrate a significant relationship between ED and cognition in a community-dwelling midlife sample of men with no diagnosed CVD. Our results suggest that individuals at greater risk of developing CVD are already demonstrating significant cognitive differences from those at lesser risk. CVD can lead to vascular cognitive impairment and dementia, and early identification of impaired individuals is critical to preserve cardiovascular health and cognitive capacity. Although extensive research demonstrates that ED is primarily a microvascular rather than psychogenic disorder, the medical significance of ED has not been effectively conveyed to the public. As the prevalence of ED continues to rise—with over 320 million predicted to have ED in 2025 (Aytaç et al., 1999)—it is important to better characterize the disorder in terms of cognitive correlates and medical comorbidities. The morbidity, mortality, and economic impact of CVD and cognitive impairment make this an important public health issue.

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Appendix

Mixed Model Analyses for Cognitive Performance Using a Continuous ED Measure, Including Demographic and Health Variables

Parameter	Age		ED		AFQT		Cholesterol		Pack Years		Depression	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
Processing Speed ^{ab}	-.12 (.03)	<.001	.09 (.03)	.001	.16 (.03)	<.001	<i>ns</i>	<i>ns</i>	-.07 (.03)	.01	<i>ns</i>	<i>ns</i>
ST Memory ^b	-.08 (.03)	.01	.09 (.03)	.004	.18 (.03)	<.001	-.16 (.07)	.03	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Verbal Ability	<i>ns</i>	<i>ns</i>	.07 (.03)	.05	.48 (.04)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Verbal Memory	-.06 (.03)	.047	<i>ns</i>	<i>ns</i>	.19 (.03)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
VSP Memory ^b	-.1 (.03)	.005	.09 (.03)	.004	.23 (.03)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Abstract Reasoning	-.14 (.04)	<.001	<i>ns</i>	<i>ns</i>	.47 (.04)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Working Memory ^b	<i>ns</i>	<i>ns</i>	.07 (.06)	.005	.18 (.03)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Verbal Fluency ^b	-.16 (.04)	<.001	.09 (.04)	.01	.18 (.04)	<.001	-.22 (.09)	.01	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Set-Shifting ^a	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	.26 (.04)	<.001	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>
Inhibition	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	<i>ns</i>	.12 (.05)	.008

Note. Presented estimates and significance levels represent each parameter's influence after all other terms have been entered into the equation. Results are Type III Fixed Effects and are controlled for correlated variance of twin data. Hypertension and BMI were also included in the model, but because they produced no significant Type III Fixed Effects, they have been excluded from the table. AFQT is an index of premorbid cognitive ability at military induction. ST memory = short term memory; VSP Memory = visual-spatial memory; BMI = body mass index; Ns = non-significant Type III Fixed Effects.

^aTime scores were reverse-coded so that higher scores indicate better performance on all measures.

^bRemained significant after FDR.

Table 1

Group Differences Between Included Participants and Excluded Participants in the Present Analyses

Variable	Included (<i>n</i> = 651)	Excluded (<i>n</i> = 586)	<i>F</i>	<i>p</i>
Mean (<i>SE</i>) age (years)	55.4 (0.1)	55.5 (0.1)	0.99	.32
Mean (<i>SE</i>) education (years)	13.9 (0.09)	13.8 (0.1)	0.29	.59
White, <i>n</i> (%) ^a	598/642 (93.1)	512/559 (91.6)	0.02	.89
Mean (<i>SE</i>) AFQT score	61.8 (0.95)	60.9 (1.0)	0.64	.43
Mean (<i>SE</i>) depression score	6.9 (0.34)	9.8 (0.36)	41.3	<.001
Mean (<i>SE</i>) smoking (pack years)	17.7 (1.0)	22.0 (1.06)	10.4	.001
Mean (<i>SE</i>) BMI	29.0 (0.21)	29.8 (0.22)	10.0	.002
Hypertension, <i>n</i> (%)	342 (52.5)	398 (67.9)	26.8	<.001
High cholesterol, <i>n</i> (%)	145 (22.2)	228 (38.9)	38.0	<.001
Myocardial infarction, <i>n</i> (%) ^b	0	80 (13.7)	102.3	N/A
Stroke, <i>n</i> (%) ^b	0	24 (4.1)	6.3	N/A
Diabetes, <i>n</i> (%) ^b	0	136 (23.2)	185.9	N/A
Peripheral vascular disease, <i>n</i> (%) ^b	0	16 (2.7)	17.1	N/A
Heart surgery, <i>n</i> (%) ^b	0	90 (15.4)	21.0	N/A
Heart failure, <i>n</i> (%) ^b	0	11 (1.9)	12.3	N/A
Stent placement, <i>n</i> (%) ^b	0	47 (8.0)	110.4	N/A

Note. AFQT = Armed Forces Qualification Test; BMI = body mass index. All analyses control for the clustering of twins within pairs. AFQT serves as index of premorbid cognitive ability from age 20.

^aSome participants preferred not to disclose their race, and thus different sample denominators are presented for this category.

^bExclusionary criterion.

Table 2

Group Differences on Demographics and Cardiovascular Risk Factors Between Erectile Dysfunction (ED) and Non-Erectile Dysfunction (N-ED) Groups

Variable	N-ED (<i>n</i> = 486)	ED (<i>n</i> = 165)	<i>F</i>	<i>p</i>
Mean (<i>SE</i>) age (years)	55.4 (0.12)	55.3 (0.12)	2.8	.1
Mean (<i>SE</i>) education (years)	14.0 (0.11)	13.6 (0.16)	3.4	.07
Mean (<i>SE</i>) AFQT score	62.5 (1.1)	59.2 (1.7)	3.3	.07
Mean (<i>SE</i>) BMI	28.6 (0.22)	29.3 (0.33)	3.7	.06
Mean (<i>SE</i>) depression score	6.5 (0.32)	7.8 (0.52)	5.0	.03
Mean (<i>SE</i>) smoking (pack years)	16.4 (1.1)	21.4 (1.7)	6.8	.009
Mean (<i>SE</i>) testosterone (pg/ml)	104.4 (2.0)	107.3 (3.1)	0.7	.39
High cholesterol, <i>n</i> (%)	102 (21.0)	43 (26.1)	2.0	.16
Hypertension, <i>n</i> (%)	254 (52.2)	88 (53.3)	0.3	.56

Note. AFQT = Armed Forces Qualification Test; BMI = body mass index. Results are Type III fixed effects and are controlled for correlated variance of twin data. AFQT serves as index of premorbid cognitive ability from age 20.

Table 3
Cognitive Performance in Erectile Dysfunction (ED) and Non-Erectile Dysfunction (N-ED) Participants

Cognitive ability	df = 1	N-ED M (SE)	ED M (SE)	F	p	SMD
Processing speed ^{a,b}	583.5	.13 (.03)	-.14 (.05)	20.5	<.001	.39
Visual-spatial ability		.05 (.04)	-.07 (.06)	2.7	.1	—
Verbal ability ^b	579.8	.06 (.05)	-.13 (.08)	5.4	.02	.20
Verbal memory	602.4	.06 (.03)	-.06 (.05)	3.9	.048	.17
Verbal fluency ^b	581.2	.10 (.05)	-.20 (.08)	13.6	<.001	.32
Visual-spatial memory ^b	622.9	.09 (.04)	-.14 (.06)	9.9	.002	.28
Short-term memory ^b	623.9	.09 (.04)	-.16 (.06)	14.3	<.001	.33
Working memory ^b	614.9	.06 (.03)	-.12 (.05)	8.7	.003	.26
Set-shifting ^a	601	.03 (.04)	-.10 (.06)	4.0	.05	.17
Abstract reasoning ^b	594.1	.16 (.05)	-.12 (.08)	10.8	.001	.28
Inhibition ^b	632	.05 (.05)	-.16 (.08)	5.5	.02	.21

Note. SMD = standardized mean difference effect size. Results are Type III fixed effects and are controlled for correlated variance of twin data. All cognitive scores were centered with a mean = 0 and standard deviation = 1.

^aTime scores were reverse-coded so that higher scores indicate better performance on all measures.

^bRemained significant after false discovery rate adjustment to *p* value.

Table 4

Mixed Model Analyses for Cognitive Performance in Erectile Dysfunction (ED) Versus Non-Erectile Dysfunction (N-ED) Including Demographic and Health Variables

Parameter	Age		ED		AFQT		Cholesterol		Pack years		Depression	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Processing speed ^a	-.13 (.03)	<.001	.19 (.06)	.001	.24 (.04)	<.001	ns	ns	-.07 (.03)	.02	ns	ns
Short-term memory	-.09 (.03)	.01	.22 (.07)	.002	.27 (.05)	<.001	-.17 (.07)	.02	ns	ns	ns	ns
Verbal ability	ns	ns	ns	ns	.70 (.05)	<.001	ns	ns	ns	ns	ns	ns
Verbal memory	-.06 (.03)	.045	ns	ns	.27 (.04)	<.001	ns	ns	ns	ns	ns	ns
Visual-spatial memory	-.10 (.03)	.004	.18 (.07)	.02	.34 (.05)	<.001	ns	ns	ns	ns	ns	ns
Abstract reasoning	-.14 (.04)	<.001	.17 (.08)	.03	.7 (.05)	<.001	ns	ns	ns	ns	ns	ns
Working memory	-.06 (.03)	.03	.14 (.06)	.02	.27 (.04)	<.001	ns	ns	ns	ns	ns	ns
Verbal fluency	-.15 (.04)	<.001	.25 (.09)	.004	.27 (.06)	<.001	-.22 (.09)	.01	ns	ns	ns	ns
Set-shifting ^a	ns	ns	ns	ns	.29 (.05)	.001	ns	ns	ns	ns	ns	ns
Inhibition	ns	ns	.25 (.09)	.01	ns	ns	ns	ns	ns	ns	.15 (.06)	.007

Note. AFQT = Armed Forces Qualification Test; BMI = body mass index; ns = nonsignificant Type III fixed effects. Presented estimates and significance levels represent each parameter's influence after all other terms have been entered into the equation. Results are Type III fixed effects and are controlled for correlated variance of twin data. Hypertension and BMI were also included in the model, but because they produced no significant Type III fixed effects, they have been excluded from the table. AFQT is an index of premorbid cognitive ability at military induction.

^aTime scores were reverse-coded so that higher scores indicate better performance on all measures.