

# A Twin Study of Erectile Dysfunction

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**Background:** The extent of genetic influence on erectile dysfunction (ED) is unknown. This study determines the contribution of heredity to ED in a sample of middle-aged men.

**Methods:** A classical twin study was conducted in the Vietnam Era Twin Registry, a national sample of male-male pairs (mean birth year, 1949) who served on active duty during the Vietnam era (1965-1975). A 1999 male health survey was completed by 890 monozygotic (MZ) and 619 dizygotic (DZ) pairs. The prevalence and heritability of 2 self-report indicators of ED, difficulty in having an erection and in maintaining an erection, are estimated.

**Results:** The prevalence of difficulty in having an erection is 23.3% and in maintaining an erection is 26.7%. Twin correlations for dysfunction in having an erection

are 0.35 (95% confidence interval [CI], 0.28-0.41) in MZ and 0.17 (95% CI, 0.09-0.27) in DZ pairs. For dysfunction in maintaining an erection, the twin correlations in MZ and DZ pairs are 0.39 (95% CI, 0.32-0.45) and 0.18 (95% CI, 0.09-0.27), respectively. The estimated heritability of liability for dysfunction in having an erection is 35% and in maintaining an erection is 42%. The heritable influence on ED remained significant after adjustment for ED risk factors.

**Conclusions:** The present study demonstrates an ED-specific genetic component that is independent of genetic influences from numerous ED risk factors. The results suggest that future molecular genetic studies to identify ED-related polymorphisms are warranted.

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**E**RECTILE DYSFUNCTION (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance,<sup>1</sup> is a highly prevalent condition that is increasing with the number of older men in the population. Several factors have been shown to be related to ED prevalence, including age, hypertension, diabetes, heart disease, cigarette smoking, alcohol use, obesity, and lipid disorders.<sup>2-16</sup> Inverse relationships of ED with higher education and physical activity have also been observed.<sup>2-4,7,11,17</sup> To our knowledge, the role of genetic factors for ED has never been investigated. The purpose of this study was to estimate the prevalence and genetic influence on ED in a sample of middle-aged twin pairs.

## METHODS

Study participants are members of the Vietnam Era Twin (VET) Registry. The VET Registry was established in the early 1980s and consists of 7368 male-male monozygotic (MZ) and dizygotic (DZ) twin pairs, born between the

years 1939 and 1957, with both members of the pair having served in the US military during the Vietnam era (1965-1975).<sup>18,19</sup> In 1987, a mail and telephone survey collected information to classify zygosity using an approach with an approximate 95% accuracy rate.<sup>20</sup> In total, 4774 pairs responded to the survey, of which 53.5% were MZ pairs, 43.8% were DZ pairs, and 2.7% could not be classified.

In 1999, a male health survey was sent to 10 762 VET Registry members (included 4636 pairs). With 2 mailed follow-ups, a response rate of 49.8% (5361 individuals; 1621 pairs) was achieved. The response rate was slightly higher among the MZ twins (51.2%) compared with the DZ twins (49.1%). Only pairs with ED information from both members are included in the present study, which leads to an analytic sample of 1509 twin pairs. All survey procedures were approved by the Hines VA Cooperative Studies Program Coordinating Center Human Subjects Committee.

The measurement of ED included 2 questions about the difficulty in the past month of (1) *having* an erection and (2) *maintaining* an erection. Twins rated their abilities along a 6-point scale ranging from very good to no erection. Responses to the ordinal questions were each significantly ( $P < .001$ ) correlated with the self-report of a physician diagnosis of ED; for

**Table 1. Prevalence of Erectile Dysfunction Risk Factors by Zygosity\***

Risk Factor	MZ Twins (n = 1438)	DZ Twins (n = 994)
Age in 1999, mean (SD), y	50.5 (3.1)	50.5 (2.7)
Diabetes	76 (5.3)	51 (5.1)
Hypertension	343 (23.9)	241 (24.3)
Coronary heart disease	74 (5.2)	46 (4.6)
Body shape, mean (SD)†	5.0 (1.4)	4.9 (1.4)
Current cigarette smoker	337 (23.4)	244 (24.6)
Alcohol use in past month‡	957 (66.6)	717 (72.1)

Abbreviations: DZ, dizygotic; MZ, monozygotic.

\*Data are number (percentage) unless otherwise specified. Includes only the 1216 pairs (2432 twins) with complete risk factor information.

†Body shape categories ranged from 1 (lean) to 9 (obese).

‡ $P < .01$  for difference between MZ and DZ twins.

this analysis we chose the self-rated measures because it is not confounded by treatment-seeking behavior and is consistent with previous epidemiologic research.<sup>2,3,5,12,21</sup> Risk factor data for ED were also collected in the survey and included diabetes, hypertension, coronary heart disease, body shape, cigarette smoking, and alcohol use.

The prevalence of ED is estimated (in percentage with 95% confidence interval [CI]) for all twins and for 3 age groupings (42-49, 50-51, and 52-60 years) corresponding to approximate tertiles. For the prevalence estimates, ED is dichotomized comparing those with responses of fair, poor, very poor, and no erection with those with responses of very good and good. In the classical twin study analysis, the within-pair correlation of ED in MZ pairs (sharing 100% of their genes) is compared with the within-pair correlation of ED in DZ pairs (sharing 50% of their genes); MZ correlations greater than DZ correlations imply genetic influence. The correlations are estimated using a multilevel, mixed-effects regression model specifying a probit link function with separate random effects for MZ and DZ twin pairs.<sup>22</sup> The significance of the difference in the MZ and DZ within-pair correlations was determined through the likelihood ratio  $\chi^2$  test statistic. Heritability, defined as the percentage of the phenotypic variance in the liability to ED due to genetic factors, was estimated from the within-pair correlations.<sup>23</sup> In this context, it is equivalent to  $2(r_{MZ} - r_{DZ})$ . Adjustment for age, diabetes, hypertension, coronary heart disease, body shape (surrogate for obesity), cigarette smoking, and alcohol consumption was made by including these factors as covariates in the regression model. A  $P$  value less than .05 was considered significant.

Prevalence was estimated using the SAS System for Windows version 8 (SAS Institute Inc, Cary, NC). Mixed-effects regression modeling was performed using the MIXOR program.<sup>24</sup>

## RESULTS

Complete ED data are available for 890 MZ and 619 DZ pairs. The mean age of the sample at the time of the 1999 survey is 50.5 years in both the MZ and DZ pairs (**Table 1**). In addition, the distributions of the remaining ED risk factors used for adjustment do not differ significantly by zygosity, with the exception of alcohol use in the month prior to survey completion ( $P < .01$ ). The prevalence of ED defined as difficulty in having an erection is 23.3% (**Table 2**). There is a significant trend in the age-specific prevalences, increasing from 21.4% in the youngest group to 24.8% in the oldest group ( $P = .07$ ).

The prevalence of ED defined as difficulty in maintaining an erection is 26.7% and also demonstrates a direct relationship with age ( $P = .02$ ).

**Table 3** presents the unadjusted twin correlations and heritability estimates for both ED measures. Overall, the correlations for difficulty in having an erection are 0.35 (95% CI, 0.28-0.41) for MZ and 0.17 (95% CI, 0.09-0.27) for DZ pairs. With respect to maintaining an erection, the correlations in the MZ and DZ pairs are 0.39 (95% CI, 0.32-0.45) and 0.18 (95% CI, 0.09-0.27), respectively. The differences in the MZ and DZ correlations for both measures of ED are highly significant. The heritability of liability for difficulty in having an erection is estimated to be 35%. For difficulty in maintaining an erection, the estimated heritability is 42%.

Adjustment for age, diabetes, hypertension, coronary heart disease, body shape, cigarette smoking, and alcohol consumption does not appreciably alter the magnitude of the correlations or the significance of the differences in the MZ and DZ correlations (**Table 4**). The adjusted estimated heritabilities of liability are 29% for difficulty in having an erection and 36% for difficulty in maintaining an erection.

## COMMENT

Our results indicate that there is a genetic component involved in the etiology of ED. This component has an effect that is independent of the genetic influences of the established ED risk factors. Many of the factors responsible for ED may exert their influence through genetic as well as environmental mechanisms. These influences include the effects of known risk factors in addition to the effects of factors yet to be discovered. What is known is that age, lower education, diabetes, hypertension, heart disease, cigarette smoking, alcohol use, obesity, lack of physical activity, and lipid disorders most likely contribute to ED development.<sup>1-16</sup> What is not known is the precise nature of the relationships between ED and these factors, their interaction with one another, and whether there are other physical health, psychological, and lifestyle/behavioral factors that contribute to ED risk. The mechanism underlying the inheritance of ED is also not known. Possible candidates are polymorphisms for endothelial nitric oxide synthase (an enzyme involved in the production of nitrous oxide, a neurotransmitter involved in cavernosal smooth muscle relaxation) and for angiotensin-converting enzyme (involved in regulation of the penile cavernous smooth muscle tone).<sup>25-27</sup> Also of particular interest are expression studies of phosphodiesterase genes in human cavernous tissue and the expression of the arginase II gene in the cavernous tissue of patients with diabetes.<sup>28-30</sup>

The present study has a number of potential limitations. The response rate was approximately 50%. While this is modest, it is similar to previous studies of this sensitive topic, including the Massachusetts Male Aging Study.<sup>4,31-33</sup> It is unlikely that nonresponse bias is producing the significant heritable effects—to do so would mean that the likelihood of response from ED-concordant MZ pairs relative to all MZ pairs was different than the likelihood of response from ED-concordant DZ pairs relative to all DZ pairs.

**Table 2. Prevalence of Erectile Dysfunction According to Age in 1999\***

Erectile Dysfunction	Age Group, y			
	All Ages (N = 3018)	42-49 (n = 938)	50-51 (n = 890)	52-60 (n = 1190)
Difficulty in having an erection†	23.3 (21.8-24.8)	21.4 (18.8-24.2)	23.4 (20.6-26.3)	24.8 (22.4-27.3)
Difficulty in maintaining an erection‡	26.7 (25.1-28.3)	23.8 (21.1-26.6)	27.6 (24.7-30.7)	28.4 (25.6-31.1)

\*Data are percentage (95% confidence interval). *P* values refer to the test for trend in age-specific prevalences.

†*P* = .07.

‡*P* = .02.

**Table 3. Unadjusted Twin Correlations and Heritability Estimates for Erectile Dysfunction\***

Erectile Dysfunction	MZ Twins	DZ Twins	<i>P</i> Value	Heritability, %
Difficulty in having an erection	0.35 (0.28-0.41)	0.17 (0.09-0.27)	.002	35
Difficulty in maintaining an erection	0.39 (0.32-0.45)	0.18 (0.09-0.27)	<.001	42

Abbreviations: DZ, dizygotic; MZ, monozygotic.

\*Data are correlation (95% confidence interval) unless otherwise specified. *P* values refer to the difference between MZ and DZ correlations. Results are based on the entire study population of 1509 twin pairs. Unadjusted results for the sample with complete risk factor information (1216 twin pairs) are, for difficulty in having an erection,  $r_{MZ} = 0.36$  (0.28-0.44) and  $r_{DZ} = 0.19$  (0.09-0.29) (*P* = .004), heritability = 35%, and, for difficulty in maintaining an erection,  $r_{MZ} = 0.42$  (0.34-0.48) and  $r_{DZ} = 0.20$  (0.10-0.30) (*P* < .001), heritability = 44%.

**Table 4. Adjusted Twin Correlations and Heritability Estimates for Erectile Dysfunction\***

Erectile Dysfunction	MZ Twins	DZ Twins	<i>P</i> Value	Heritability, %
Difficulty in having erection	0.32 (0.24-0.40)	0.18 (0.09-0.28)	.01	29
Difficulty in maintaining an erection	0.37 (0.29-0.45)	0.19 (0.10-0.29)	.002	36

Abbreviations: DZ, dizygotic; MZ, monozygotic.

\*Data are correlation (95% confidence interval) unless otherwise specified. *P* values refer to the difference between MZ and DZ correlations. The results are based on the sample of 1216 twin pairs with complete erectile dysfunction risk factor information, adjusted for age, history of diabetes, hypertension, and coronary heart disease, body shape, cigarette smoking, and alcohol consumption.

The use of self-reported ED is also of concern, yet studies have suggested that self-reported ED is the most appropriate method for assessing this condition.<sup>34,35</sup> In addition, it has been shown that a self-administered questionnaire such as the International Index of Erectile Function (IIEF) can provide a valid diagnosis of ED and its severity along with a valid assessment of treatment-related changes in ED severity.<sup>21,36,37</sup> As an indication of the validity of the ED items used in the present study, we demonstrated a highly significant association with the report of a physician diagnosis of ED.

Another possible limitation of our study is that information on the presence of a sexual partner was not collected, and the questions used in the measurement of ED are not restricted to those with partners. As a consequence, the self-report of ED could be affected by the absence of a sexual partner. However, using marital status as a surrogate for partner availability, a number of studies have suggested that marital status is not significantly related to the prevalence of ED after adjustment for age.<sup>6,7,11,38</sup> Lastly, our sample is relatively young and is composed solely of men who served in the military during the Vietnam era.

The independent, ED-specific genetic influence identified in the present study should be confirmed and further elucidated in longitudinal follow-up studies of our co-

hort into the years of highest ED prevalence. A better understanding of the etiology of ED can build on these results, concentrating on molecular genetic studies to identify polymorphisms contributing to ED development.

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