A Twin Study of Erectile Dysfunction

Mary E. Fischer, PhD; Mary Ellen Vitek; Don Hedeker, PhD; William G. Henderson, PhD; Steven J. Jacobsen, MD, PhD; Jack Goldberg, PhD

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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gression modeling was performed using the MIXOR program. The software was SAS/ETS version 8 (SAS Institute Inc, Cary, NC). Mixed-effects regression models were used to consider genetic and environmental factors in the analysis of ED prevalence. The significance of the difference in the within-pair correlation of ED in MZ pairs (sharing 100% of their genes) was 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 age, 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 twins. The significance of the difference in the MZ and DZ within-pair correlations was determined through the likelihood ratio test. 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. 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. 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 1 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. The adjusted estimated heritabilities of liability are 29% for difficulty in having an erection and 36% for difficulty in maintaining an erection.

### 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).

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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. The adjusted estimated heritabilities of liability are 29% for difficulty in having an erection and 36% for difficulty in maintaining an erection.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>MZ Twins (n = 1438)</th>
<th>DZ Twins (n = 994)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in 1999, mean (SD), y</td>
<td>50.5 (3.1)</td>
<td>50.5 (2.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>78 (5.3)</td>
<td>51 (5.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>343 (23.9)</td>
<td>241 (24.3)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>74 (5.2)</td>
<td>46 (4.6)</td>
</tr>
<tr>
<td>Body shape, mean (SD)</td>
<td>5.0 (1.4)</td>
<td>4.9 (1.4)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>337 (23.4)</td>
<td>244 (24.6)</td>
</tr>
<tr>
<td>Alcohol use in past month</td>
<td>957 (66.6)</td>
<td>717 (72.1)</td>
</tr>
</tbody>
</table>

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.

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. 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, 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). 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.

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. 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

<table>
<thead>
<tr>
<th>Erectile Dysfunction</th>
<th>All Ages (N = 3018)</th>
<th>42-49 (n = 938)</th>
<th>50-51 (n = 890)</th>
<th>52-60 (n = 1190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in having an erection†</td>
<td>23.3 (21.8-24.8)</td>
<td>21.4 (18.8-24.2)</td>
<td>23.4 (20.6-26.3)</td>
<td>24.8 (22.4-27.3)</td>
</tr>
<tr>
<td>Difficulty in maintaining an erection‡</td>
<td>26.7 (25.1-28.3)</td>
<td>23.8 (21.1-26.6)</td>
<td>27.6 (24.7-30.7)</td>
<td>28.4 (25.6-31.1)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Erectile Dysfunction</th>
<th>MZ Twins</th>
<th>DZ Twins</th>
<th>P Value</th>
<th>Heritability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in having an erection</td>
<td>0.35 (0.28-0.41)</td>
<td>0.17 (0.09-0.27)</td>
<td>.002</td>
<td>35</td>
</tr>
<tr>
<td>Difficulty in maintaining an erection</td>
<td>0.39 (0.32-0.45)</td>
<td>0.18 (0.09-0.27)</td>
<td>&lt;.001</td>
<td>42</td>
</tr>
</tbody>
</table>

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

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

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.

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.

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 cohort 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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REFERENCES


