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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this analysis we chose the self-rated measures because it is not confounded by treatment-seeking behavior and is consistent with previous epidemiologic research.2,3,12,21 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 excellent. In the classical twin study analysis, the within-pair correlations was determined through tests. Heritability is defined as the percentage of the phenotypic variance in the liability to ED due to genetic factors.2,22 In this context, it is equivalent to 2(\rho_{MZ} - \rho_{DZ}). The significance of the differences in the MZ and DZ correlations (\rho) is estimated to be 35%. For difficulty in maintaining an erection, the correlations in the MZ and DZ pairs are 0.39 (95% CI, 0.28-0.41) and 0.18 (95% CI, 0.09-0.27), respectively. The differences in the MZ and DZ correlation 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.

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.1,16 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).25,26 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.28-30

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.31-33 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.
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. 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. 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. 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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### 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>

*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 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.
REFERENCES