

## Original Investigation

# Population-Based, Multigenerational Family Clustering Study of Obsessive-Compulsive Disorder

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**IMPORTANCE** Controlled family studies have consistently found that obsessive-compulsive disorder (OCD) aggregates in families but have typically relied on samples recruited from specialist clinics. Furthermore, previous studies could not disentangle genetic from environmental factors contributing to the observed familiarity.

**OBJECTIVE** To provide unbiased estimates of familial risk for and heritability of OCD at the population level.

**DESIGN AND SETTING** Population-based, multigenerational, case-control family and twin studies using the Swedish National Patient Register, Multi-Generation Register, and Twin Register.


**PARTICIPANTS** All individuals diagnosed as having OCD between January 1, 1969, and December 31, 2009 (n = 24 768) and all their available first-, second-, and third-degree relatives, as well as nonbiological relatives and matched general population control subjects. Twins (n = 16 383) were included from the population-based Twin Register.

**MAIN OUTCOME AND MEASURE** The risk for OCD among relatives of OCD probands.

**RESULTS** The risk for OCD among relatives of OCD probands increased proportionally to the degree of genetic relatedness. The risk for first-degree relatives was significantly higher than that for second- and third-degree and nonbiological relatives. Second-degree relatives had higher risk for OCD than third-degree relatives. Relatives at similar genetic distances had similar risks for OCD, despite different degrees of shared environment. Separate twin modeling analyses confirmed that familial risk for OCD was largely attributable to additive genetic factors (47%; 95% CI, 42%-52%), with no significant effect of shared environment. Nonbiological relatives (spouses or partners who have at least 1 child together) also had an elevated risk for OCD (odds ratio, 2.61; 95% CI, 1.99-3.42). Early-onset probands (3907 individuals; mean age, 13.7 years) had slightly (nonsignificantly) higher familial risk than the total sample, although this was substantially lower than previously reported. There were no significant sex differences in the familial pattern or heritability estimates.

**CONCLUSIONS AND RELEVANCE** Obsessive-compulsive disorder clusters in families primarily due to genetic factors. Nonshared environmental factors are at least as important. The finding of possible assortative mating in OCD is intriguing and should be investigated further.

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Obsessive-compulsive disorder (OCD) is widely acknowledged to run in families and possibly has a genetic or partly genetic cause. Consequently, the search for suitable candidate genes is well under way.<sup>1</sup> Although the observation that OCD may be a familial disorder was already made in the 1930s, the idea only really gained traction in the 1990s, when well-controlled family studies<sup>2-4</sup> began to emerge. These and subsequent investigations<sup>5,6</sup> indicate that OCD (and subthreshold obsessive-compulsive symptoms) is significantly more common in first-degree relatives of OCD probands than among first-degree relatives of healthy control subjects. Similar studies<sup>7,8</sup> conducted in juvenile cases of OCD reported even higher familial risks. A recent meta-analysis<sup>9</sup> of 6 adult and 5 pediatric OCD family studies reported odds ratios (ORs) for OCD of 4.7 (99% CI, 2.4-9.2) and 25.6 (99% CI, 9.3-70.6), respectively. Therefore, early-onset OCD may be a particularly familial form of the disorder, although the large CIs in that meta-analysis require cautious interpretation.

Although these studies were carefully conducted, they also had important limitations. First, with the exception of one study,<sup>6</sup> families were recruited from specialist clinics. Families with several affected members may have been more likely to participate in such studies, thus inflating the familial risk. Second, although controls were randomly selected using various procedures, families with greater (or fewer) concerns about emotional difficulties may have volunteered to participate more often, leading to inaccurate estimates.<sup>4</sup> These possible biases can be optimally addressed by examining the familial structure of OCD at the population level,<sup>10</sup> recruiting patients from nonspecialist clinics, and randomly selecting control families from the general population. Third, studies conducted to date were underpowered to calculate risks for relatives with different degrees of genetic relatedness to the proband and different degrees of shared environmental exposures. Consequently, these studies could not disentangle genetic from environmental factors contributing to the observed familiarity. While several twin investigations of diagnosed OCD cases exist, they were typically underpowered.<sup>11</sup> The results of more recent investigations of OC symptoms measured dimensionally in nonclinical populations suggest that both additive genetic effects (38%-40% of variance) and nonshared environment effects (50%-52% of variance) account for most of the variance in OC symptoms, with shared environment making a much smaller (5%-6% of variance) contribution.<sup>12</sup> However, twin investigations tend to underestimate the contribution of shared environment.<sup>13</sup> Most important, it is unclear how these results relate to clinically diagnosed OCD.

This population-based, multigenerational family clustering study aimed to address these limitations. In an attempt to provide unbiased estimates of family clustering and heritability of OCD, we analyzed data from the Swedish National Patient Register, including more than 24 000 individuals diagnosed as having OCD during 4 decades (January 1, 1969, to December 31, 2009). We also performed complementary data analyses from a nonclinical population-based sample of more than 16 000 twins who completed a questionnaire of OCD symptoms. We tested the following 4 hypotheses: (1) OCD will cluster in some families at the population level, (2) OCD risk

in relatives will increase proportionally to the degree of genetic relatedness to the proband (thus demonstrating genetic effects), (3) shared environment effects will be negligible, and (4) the familial risk for OCD will be greatest for early-onset probands (ie, first diagnosed before age 18 years). We also examined potential sex differences in observed patterns of familiarity and heritability.

## Methods

### National Registers and International Classification of Diseases Diagnostic Codes

This study was approved by the regional ethics committee at the Karolinska Institutet, Stockholm, Sweden. We linked 2 Swedish national registers using the individual national registration numbers assigned at birth.

The Multi-Generation Register contains information about the identity of biological and adoptive parents of each individual who was born in Sweden since 1932 (with the mother as informant) or who immigrated to Sweden together with one or both parents before age 18 years and lived in Sweden since 1961 for any period.<sup>14</sup> Unless the biological or adoptive parents have actually lived in Sweden since 1947, when the national personal identification number was introduced, it is impossible to identify them. The father was defined either as the mother's husband at the time of birth or the man acknowledged as father by unmarried mothers. With information about parents, it is possible to create family pedigrees for all individuals with relatives at increasing genetic and environmental distances from each index person. For instance, individuals sharing parents may be identified as siblings, and those sharing grandparents may be identified as cousins. It is also possible to include nonbiological relatives, such as adopted children and spouses and partners.

The National Patient Register contains diagnostic information about all psychiatric patients treated in Sweden since the 1960s, with each consultation as a unique record in the register. Initially, it contained information about all inpatient care. However, since 2001 it also includes individuals with outpatient visits to specialist physicians (other than general practitioners) that resulted in 1 or more psychiatric diagnoses according to the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*. This register has been heavily used for research, resulting in hundreds of publications.<sup>15</sup>

Probands with OCD were defined as individuals identified in the National Patient Register (1969-2009 for inpatients and 2001-2009 for outpatients) with at least 1 OCD diagnosis according to the following codes: *ICD-8* (1969-1986) code 300.3, *ICD-9* (1987-1996) code 300D, and *ICD-10* (1997 to the present) code F42. We did not exclude any participants based on comorbidities because we preferred not to make assumptions about the hierarchical structure of mental disorders.

### Twin Data

Twins were recruited from the population-based Screening Twin Adults: Genes and Environment (STAGE) study, which was based on all twins born between 1959 and 1985 from the

Swedish Twin Register.<sup>16</sup> The STAGE study was approved by the regional ethics committee at the Karolinska Institutet. Participants provided informed consent by responding to the online questionnaire or verbally over the phone before participation. The STAGE target population was approximately 43 000 eligible twin pairs among whom both twins lived at least to 1 year of age. In 2005-2006, twins were invited by mail to participate in the study and were given a personal log-in to the study Webpage. The questionnaire contained approximately 1300 questions about common complex diseases, including a section on obsessive-compulsive symptoms. Twins could also opt to complete a telephone interview with a trained interviewer using a computer-based data collection method. A total of 22 397 twins completed the questionnaire, representing a response rate of about 50%, but only 16 383 had answered all questions and were included in the twin analyses. The demographic characteristics of the included sample are given in Supplement eTable 1.

Obsessive-compulsive symptoms were measured on a 7-item instrument, with each item scored on a scale of 1 to 3 (where 1 indicates the symptom is not present; 2, a little; and 3, a lot). The total score ranged from 7 to 21. The scale was validated in a sample of 91 individuals with a confirmed diagnosis of OCD who participated in a clinical trial.<sup>17</sup> The scale showed acceptable reliability and good convergence with other measures of obsessive-compulsive symptoms (data are available from the corresponding author on request).

### Analyses of Family Data

The odds of OCD in relatives of a proband with OCD were compared with the odds in relatives of 10 randomly selected, unaffected control individuals matched by sex, birth year, migration status (living in Sweden or not), and county of residence at the time of the first recorded OCD diagnosis. Relatives were also matched by sex and birth year. Note that each proband may appear multiple times in different categories (eg, parent, sibling, and cousin) depending on family structure. For this reason, the matching was performed separately for each proband-relative pair to ensure adequate control of cohort and period effects and to allow for equal time at risk for proband relatives and control relatives. The matching procedure was used for all available first-, second-, and third-degree relatives, as well as nonbiological relatives of each proband. First-degree relatives included full siblings, parents, and children. Second-degree relatives included half siblings, grandparents and grandchildren, uncles and aunts, and nephews and nieces. Third-degree relatives consisted of first cousins. Nonbiological relatives were defined as persons who had at least 1 child together (eg, spouses or partners). Too few affected twins and adopted cases were available for inclusion.

Because the data were matched and the outcome was dichotomous, we used a conditional logistic regression model with the PROC PHREG procedure (SAS, version 9.3; SAS Institute, Inc).<sup>18</sup> Because several possibly correlated pairs of relatives from every family could be included in the analysis, we adjusted for the nonindependence of family members by computing corrected (less narrow) CIs with a robust sandwich estimator (covsandwich option in PHREG). This approach has

been previously validated and successfully applied to study other mental disorders and problematic behaviors, such as schizophrenia,<sup>19</sup> bipolar disorder,<sup>19</sup> violent offending,<sup>20</sup> and suicide.<sup>21</sup>

As a complementary measure of familial risk, tetrachoric correlations were calculated from the matched data. From this, we estimated additive genetic effects comparing full siblings and maternal half siblings (assuming that they have similar shared environments but 50.0% vs 25.0% genetic similarity on average). We used the following variation of the formula by Falconer<sup>22</sup>:  $V_A = 4(\rho \text{ for full siblings} - \rho \text{ for maternal half siblings})$ , where  $V_A$  indicates additive genetic effects, and  $\rho$  indicates tetrachoric correlation.

To test the hypothesis that the familial risk for OCD would be greatest for probands with onset in childhood or adolescence, we repeated all analyses in a subgroup of probands first diagnosed before age 18 years. We also examined potential sex effects by separately analyzing respective pairs of male-male, male-female, female-female, and female-male probands and relatives.

### Twin Analyses

Twin analyses were performed using available software (Mx; www.vcu.edu/mx/). Because scores on the STAGE Obsessive-compulsive Symptom Scale were positively skewed (skewness, 1.29), liability threshold modeling was applied to calculate polychoric correlations for monozygotic (MZ) and dizygotic (DZ) twins and to estimate genetic and environmental influences on obsessive-compulsive symptoms.<sup>23</sup> To retain variability in symptom severity, while ensuring sufficient numbers of individuals within each category, we used 2 thresholds, resulting in the following 3 groups of individuals: no symptoms (score, 7), mild symptoms (score, 8-12), and at least moderate symptoms (score,  $\geq 13$ ). The latter approximately correspond to at least mild OCD symptoms on the Yale-Brown Obsessive-compulsive Scale (data are available from the corresponding author on request). Note that these thresholds are arbitrary and were only intended for twin analyses; the use of different thresholds did not modify the results of the twin analyses.

We performed polychoric correlation analyses to test model assumptions and estimate the correlation in liability for obsessive-compulsive symptoms among MZ and DZ twins. We used maximum-likelihood univariate model-fitting analyses<sup>24</sup> to estimate the contribution of genetic and environmental factors to obsessive-compulsive symptoms, decomposing its variance into additive genetic (A), dominant genetic (D), shared environmental (C), and nonshared environmental (including measurement error) (E) components. This involved fitting the data to a full ACE or ADE model, in which genetic and environmental factors are allowed to vary across the sexes. Qualitative sex differences were assessed by allowing the genetic correlation across sexes to vary from 1.0 and testing whether this resulted in a significant improvement in model fit. Quantitative sex differences were examined by comparing the goodness of fit of the model in which the genetic and environmental parameters are constrained to be the same in both sexes to one allowing the effects of genetic and environmental para-

**Table 1. Risk for Obsessive-Compulsive Disorder in Relatives of 24 768 Probands Diagnosed as Having Obsessive-Compulsive Disorder in Sweden Over 4 Decades (1969-2009) Compared With Relatives of Matched Control Subjects, With Tetrachoric Correlations**

| Relation to Proband              | Mean Degree of Genetic Similarity, % | Dyads, No. | Concordant Pairs, No. | Matched Odds Ratio (95% CI) | Tetrachoric Correlation |
|----------------------------------|--------------------------------------|------------|-----------------------|-----------------------------|-------------------------|
| <b>First-degree Relatives</b>    |                                      |            |                       |                             |                         |
| Full siblings                    | 50.0                                 | 317 817    | 520                   | 5.03 (4.49-5.64)            | .25                     |
| Parents                          | 50.0                                 | 444 471    | 234                   | 4.70 (4.09-5.40)            | .17                     |
| Offspring                        | 50.0                                 | 217 903    | 237                   | 4.56 (3.97-5.24)            | .17                     |
| <b>Second-degree Relatives</b>   |                                      |            |                       |                             |                         |
| Maternal half siblings           | 25.0                                 | 47 672     | 49                    | 2.32 (1.50-3.58)            | .12                     |
| Paternal half siblings           | 25.0                                 | 59 456     | 44                    | 1.54 (1.04-2.31)            | .07                     |
| Uncles or aunts                  | 25.0                                 | 469 431    | 173                   | 2.04 (1.76-2.37)            | .06                     |
| Nephews or nieces                | 25.0                                 | 355 942    | 173                   | 2.12 (1.82-2.47)            | .06                     |
| Grandparents                     | 25.0                                 | 521 925    | 48                    | 1.68 (1.27-2.23)            | .03                     |
| Grandchildren                    | 25.0                                 | 130 142    | 48                    | 1.70 (1.28-2.25)            | .03                     |
| <b>Third-degree Relatives</b>    |                                      |            |                       |                             |                         |
| First cousins                    | 12.5                                 | 939 672    | 447                   | 1.41 (1.24-1.60)            | .06                     |
| <b>Nonbiological Relatives</b>   |                                      |            |                       |                             |                         |
| Spouses or partners <sup>a</sup> | 0.0                                  | 120 697    | 55                    | 2.61 (1.99-3.42)            | .13                     |

<sup>a</sup> Individuals who have at least 1 child together with the proband.

meters to vary across the sexes. Reduced submodels, where the genetic parameter, shared environmental parameter, and both these parameters are dropped (CE, AE, and E models), were tested to explain the observed data and pattern of variance using as few parameters as possible. Akaike information criterion and the difference in the  $\chi^2$  value relative to the change in *df* provided an indication of the models' goodness of fit and parsimony.<sup>24</sup>

## Results

### Sample Characteristics

From a total population of 13 614 587 unique individuals who were born in 1932 or later and who ever lived in Sweden from 1961 or later, we identified all 24 768 individuals diagnosed as having OCD between 1969 and 2009. Of these, 13 943 (56.3%) were women, and 10 825 (43.7%) were men. Regarding setting, 15 546 (62.8%) were outpatients, 6411 (25.9%) were inpatients, and 2811 (11.3%) had been both inpatients and outpatients.

The mean (SD) age at first diagnosis was 33.5 (16.6) years. In total, 20 861 received their first diagnosis of OCD at age 18 years or later (mean [SD] age, 37.2 [15.5] years) and another 3907 patients before age 18 years (mean [SD] age, 13.7 [2.9] years); the latter are defined herein as pediatric-onset cases.

### Familial Risk for OCD

Table 1 and Figure 1 summarize the ORs for OCD in biological and nonbiological relatives of probands having OCD compared with the risks in relatives of matched control individuals. The ORs for first-degree relatives (50.0% genetic similarity) were significantly higher than those for second-degree relatives (25.0% genetic similarity) and third-degree relatives (12.5% genetic similarity). Furthermore, second-degree rela-

tives had higher risk for OCD than third-degree relatives, although the CIs overlapped for some of the relations. Uncles and aunts and nephews and nieces (25.0% genetic similarity) were at significantly increased risk for OCD compared with first cousins of OCD probands (12.5% genetic similarity). Therefore, we found substantial evidence of genetic influences on the liability for OCD.

Shared environmental influences on OCD seemed to be considerably less important. Full siblings, parents, and children of OCD probands had comparable risk (all with 50.0% genetic similarity, but siblings were assumed to have more shared environment because they grew up together in the same family during approximately the same period). Moreover, maternal and paternal half siblings had comparable risks for OCD (both with 25.0% genetic similarity but with maternal half siblings sharing more environment because 90% of children in Sweden continue to live with their mother after parental divorce or separation<sup>25</sup>). Finally, first cousins (12.5% genetic similarity) had higher risk for OCD compared with controls (OR, 1.41; 95% CI, 1.24-1.60), despite no exposure or marginal shared environmental exposure with the OCD proband.

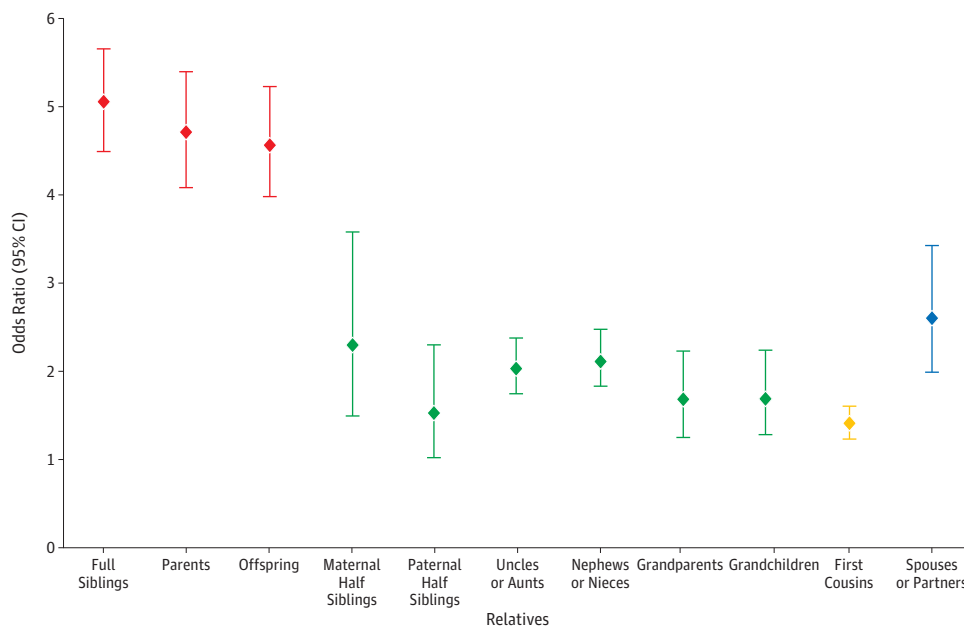
Unexpectedly, nonbiological relatives (eg, spouses or partners) who had at least 1 child together with a proband with OCD were more likely to have OCD themselves compared with nonbiological relatives of matched controls. The OR for nonbiological relatives was 2.61 (95% CI, 1.99-3.42).

These findings remained unchanged when probands diagnosed as having ICD-8 code 300.3 (before narrative descriptions of disorders were introduced) were excluded from the analyses. These results are summarized in Supplement eTable 2.

### Tetrachoric Correlations and Heritability Estimates

Tetrachoric correlations were substantially higher for first-degree relatives compared with second- and third-degree relatives (Table 1). Contrasting full siblings and maternal half sib-

**Figure 1. Risk for Obsessive-Compulsive Disorder Among Relatives With Differing Genetic and Environmental Distance to All Diagnosed Obsessive-Compulsive Disorder Cases in the Swedish National Patient Register (1969-2009) Compared With Matched Population Control Subjects**



Each individual in the study population may appear multiple times in different categories (eg, parent, sibling, and cousin) depending on family pedigree. Red indicates first-degree relatives; green, second-degree relatives; yellow,

third-degree relatives; and blue, nonbiological relatives. Nonbiological relatives are individuals who have at least 1 child together with the proband with obsessive-compulsive disorder.

**Table 2. Risk for Obsessive-Compulsive Disorder in Relatives of 3907 Proband First Diagnosed as Having Obsessive-Compulsive Disorder Before Age 18 Years Compared With Relatives of Matched Control Subjects**

| Relation to Proband            | Mean Degree of Genetic Similarity, % | Dyads, No. | Concordant Pairs, No. | Matched Odds Ratio (95% CI) |
|--------------------------------|--------------------------------------|------------|-----------------------|-----------------------------|
| <b>First-degree Relatives</b>  |                                      |            |                       |                             |
| Full siblings                  | 50.0                                 | 52 115     | 116                   | 6.32 (5.00-7.99)            |
| Parents                        | 50.0                                 | 83 526     | 73                    | 5.68 (4.41-7.32)            |
| Offspring                      | 50.0                                 | 4307       | 0                     | ...                         |
| <b>Second-degree Relatives</b> |                                      |            |                       |                             |
| Maternal half siblings         | 25.0                                 | 10 405     | 9                     | 1.92 (0.81-4.52)            |
| Paternal half siblings         | 25.0                                 | 13 209     | 4                     | 0.77 (0.23-2.66)            |
| Uncles or aunts                | 25.0                                 | 115 823    | 55                    | 2.32 (1.78-3.02)            |
| Nephews or nieces              | 25.0                                 | 14 105     | 2                     | 1.18 (0.29-4.75)            |
| Grandparents                   | 25.0                                 | 139 092    | 17                    | 1.61 (0.99-2.61)            |
| Grandchildren                  | 25.0                                 | 163        | 0                     | ...                         |
| <b>Third-degree Relatives</b>  |                                      |            |                       |                             |
| First cousins                  | 12.5                                 | 218 525    | 104                   | 1.50 (1.21-1.87)            |

Abbreviation: Ellipsis, not applicable.

lings (assuming similar shared environments but 50.0% vs 25.0% genetic similarity on average) allowed us to estimate that the genetic contribution to OCD liability is approximately 0.52 (or 52%).

**Familial Risk for Proband Diagnosed in Childhood or Adolescence**

Table 2 gives ORs for OCD in biological relatives of probands who first received an OCD diagnosis before age 18 years (mean age, 13.7 years) and thus can be confidently said to have had a pediatric or adolescent onset. Overall, ORs were slightly higher

than those for the full sample but not significantly so. Although the number of concordant pairs was modest for some relations, a similar familial pattern emerged; first-degree relatives had significantly higher risk for OCD than second- and third-degree relatives.

**Familial Effects by Sex of the Proband and Their Relatives**

Analyses by sex of the proband and sex of the relative showed comparable ORs for male-male, male-female, female-male, and female-female dyads. These results are summarized in Supplement eTable 3.

**Twin Modeling Findings**

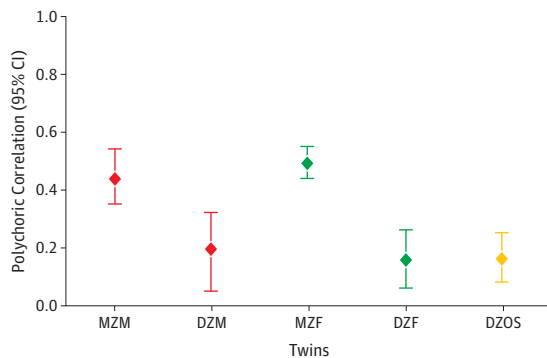
Polychoric correlations, stratified by zygosity and sex, are shown in **Figure 2**. The MZ correlations were significantly higher than the DZ correlations for both sexes, suggesting a meaningful genetic influence on obsessive-compulsive symptoms. Low to moderate MZ correlations are also indicative of nonshared environmental influences on obsessive-compulsive symptoms. The correlations for opposite-sex DZ twins were similar to the same-sex DZ twin correlations, sug-

gesting no significant qualitative differences in obsessive-compulsive symptom heritability across sexes. Note that the magnitude of DZ correlations was similar to that of the tetra-choric correlations for first-degree relatives in the family data (Table 1).

We first fitted full ACE and ADE models in which additive genetic (A), shared environmental (C) or dominant genetic (D), and nonshared environmental (E) influences were allowed to vary across sexes (Table 3, models 2 and 3). Because the full ACE and ADE models gave similar fits, with a nonsignificant Akaike information criterion difference of less than 3.0 between them,<sup>26</sup> the ACE model was chosen as the full model under which nested submodels were tested. A model to test for qualitative sex differences (model 4) was then fitted in which the genetic or shared environmental correlations across sexes were allowed to vary from 1.0. This model did not fit the data significantly better than the full ACE model, thus providing no evidence of qualitative sex differences in the liability for obsessive-compulsive symptoms ( $P = .21$ ). Next, we tested for quantitative sex differences by constraining the parameters A, C, and E to be equal across sexes (model 5). Again, this model did not fit significantly better, indicating that the proportions of genetic and environmental influences on obsessive-compulsive symptoms are comparable across sexes ( $P = .33$ ).

To explain the data using as few parameters as possible, submodels (ie, AE, CE, and E models) were tested and compared with the full ACE model without sex effects (ie, model 5). The best-fitting model was the AE model (Table 3, model 6). It was possible to drop the shared environmental (C) pa-

**Figure 2. Polychoric Correlations for Self-reported Obsessive-Compulsive Symptoms Among 16383 Twins Aged 20 to 47 Years in the Screening Twin Adults: Genes and Environment (STAGE) Study**



Stratified by zygosity and sex. DZF indicates dizygotic female; DZM, dizygotic male; DZOS, dizygotic opposite-sex; MZF, monozygotic female; and MZM, monozygotic male. Red indicates male twin pairs; green, female twin pairs; and yellow, opposite-sex twins.

**Table 3. Univariate Liability Threshold Model-Fitting Results for Self-reported Obsessive-Compulsive Symptoms Among 16383 Twins Aged 20 to 47 Years From the Screening Twin Adults: Genes and Environment (STAGE) Study**

| Model No. and Description           | Model-Fitting Results       |        |                            |         |                              | Parameter Estimates (95% CIs) |                  |                  |                  |
|-------------------------------------|-----------------------------|--------|----------------------------|---------|------------------------------|-------------------------------|------------------|------------------|------------------|
|                                     | -2 Log-Likelihood Statistic | df     | $\Delta\chi^2 (\Delta df)$ | P Value | Akaike Information Criterion | Model No. Compared With       | A                | C or D           | E                |
| 1 Saturated                         | 18 545.17                   | 14 132 | ...                        | ...     | ...                          | ...                           | ...              | ...              | ...              |
| 2 Full ADE, sex differences         | 18 551.98                   | 14 132 | 6.81 (0)                   | >.99    | 6.81                         | 1                             |                  |                  |                  |
| Men                                 | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.34 (0.31-0.39) | 0.12 (0.04-0.51) | 0.54 (0.53-0.64) |
| Women                               | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.16 (0.00-0.52) | 0.34 (0.26-0.55) | 0.50 (0.44-0.50) |
| 3 Full ACE, sex differences         | 18 554.62                   | 14 132 | 9.45 (0)                   | >.99    | 9.45                         | 1                             |                  |                  |                  |
| Men                                 | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.46 (0.17-0.54) | 0.00 (0.00-0.24) | 0.54 (0.46-0.64) |
| Women                               | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.49 (0.37-0.54) | 0.00 (0.00-0.09) | 0.51 (0.46-0.58) |
| 4 ACE, qualitative sex differences  | 18 556.15                   | 14 133 | 1.52 (1)                   | .21     | -0.47                        | 3                             |                  |                  |                  |
| Men                                 | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.35 (0.11-0.50) | 0.09 (0.04-0.29) | 0.56 (0.47-0.66) |
| Women                               | ...                         | ...    | ...                        | ...     | ...                          | ...                           | 0.47 (0.33-0.53) | 0.02 (0.00-0.13) | 0.52 (0.46-0.58) |
| 5 ACE, quantitative sex differences | 18 559.20                   | 14 136 | 4.58 (4)                   | .33     | -3.41                        | 3                             |                  |                  |                  |
| 6 AE <sup>a</sup>                   | 18 559.20                   | 14 137 | 0.00 (1)                   | >.99    | -2.00                        | 5                             | 0.47 (0.42-0.52) | ...              | 0.53 (0.48-0.58) |
| 7 CE                                | 18 617.00                   | 14 137 | 57.79 (1)                  | <.05    | 55.79                        | 5                             | ...              | 0.33 (0.29-0.37) | 0.67 (0.63-0.71) |
| 8 E                                 | 18 832.66                   | 14 138 | 273.45 (2)                 | <.05    | 269.45                       | 5                             | ...              | ...              | 1.00 (0.00-1.00) |

Abbreviations: A, additive genetic; C, shared environmental; D, dominant genetic; E, nonshared environmental;  $\Delta df$ , change between the submodel and the full model;  $\Delta\chi^2$ , difference in -2 log-likelihood statistic between the

submodel and the full model; ellipses, not applicable.

<sup>a</sup> Best-fitting model.

parameter without a significant reduction in fit, while dropping the additive genetic (A) parameter resulted in a significant decrease in fit. Dropping both the additive genetic and shared environmental parameters resulted in an increasingly worse fit. On the basis of the best-fitting model (model 6), additive genetic factors accounted for 47% (95% CI, 42%-52%) of the variation in liability for obsessive-compulsive symptoms, whereas nonshared environmental influences plus measurement error accounted for the rest of the variance (53%; 95% CI, 48%-58%). There was no evidence that shared environmental factors are of etiological importance for obsessive-compulsive symptoms.

## Discussion

This population-based, multigenerational family clustering study aimed to provide unbiased estimates of familial risk for and heritability of OCD using data from the Swedish National Patient Register, Multi-Generation Register, and Twin Register. Several conclusions can be drawn from the data.

### OCD Is a Familial and Heritable Disorder

Confirming previous, much smaller, controlled family studies<sup>3-6</sup> conducted in clinical settings, OCD was significantly more prevalent among biological relatives of OCD probands than in relatives of matched population controls. Furthermore, the risk for OCD in relatives increased proportionally with increasing genetic relatedness to the proband. Approximate ORs were 5, 2, and 1.5 for first-, second-, and third-degree relatives, respectively. This strongly indicates that at least some forms of OCD are under genetic influence. Based on family data, we estimated the genetic contribution to be approximately 50%, and twin modeling of data from a large non-clinical twin cohort further validated this estimate (47%; 95% CI, 42%-52%). A recent meta-analysis<sup>12</sup> of twin studies using dimensional obsessive-compulsive symptom measures (ie, not clinical OCD diagnoses) estimated the additive genetic contribution to be 35% to 46%. Therefore, our estimates are at the higher end of that range.

The familial risk for OCD tended to be (nonsignificantly) higher among probands first diagnosed before age 18 years. However, the ORs were considerably smaller than those reported in previous early-onset OCD family investigations, despite including probands of similar ages. This suggests that previous studies, which reported higher ORs but wide CIs (ranging from 9.3-70.6),<sup>9</sup> may have overestimated family risk, potentially due to power issues or selection biases, with "enriched" families being more likely to self-refer to specialist clinics and participate in family studies. Most adult OCD samples, including the present one, are likely to contain a substantial proportion of individuals who had a pediatric onset. Those experiencing early-onset OCD may wait many years before seeking help and receiving their first diagnosis.<sup>27</sup> Therefore, to confidently establish whether pediatric OCD is a particularly familial or genetic form of OCD, it may paradoxically be necessary to conduct family studies of adults who had a demonstrable adult symptom onset.

While men and women with OCD differ on several clinical variables, such as predominant symptom dimensions and comorbidities,<sup>28</sup> our results suggest that the familial risk for OCD is comparable in male and female probands regardless of the sex of the relative. Furthermore, our twin analyses showed no evidence of qualitative or quantitative sex differences in the heritability of obsessive-compulsive symptoms. The prediction for molecular genetic research would be that, when specific genes associated with OCD are identified, they will be associated with OCD in both sexes and that they will have similar effect sizes in male and female participants. However, the results do not preclude the role of sex-specific precipitating or maintaining factors, such as those linked to the reproductive cycle in female participants.<sup>29,30</sup>

### Unique, Rather Than Shared, Environment Is Important in OCD

Both our family and twin data consistently indicated that shared environmental factors have small or even negligible effects on the etiology of OCD. For example, various types of first-degree relatives had similar risks for OCD, despite different degrees of shared environment. Although the risk tended to be higher among maternal half siblings compared with paternal half siblings (assuming that the former have more shared environment), this did not reach statistical significance. Our twin analyses were also consistent with this observation. The possibility that shared environment has a small or negligible role in OCD had been suggested by the findings of previous twin investigations,<sup>12</sup> but family designs are better powered to detect such effects.<sup>13</sup> Therefore, our results confirm that unique or nonshared environmental influences, rather than those shared within families (eg, neighborhoods or family environment), confer increased risk for OCD and obsessive-compulsive symptoms. Even family factors traditionally considered as shared environment (eg, parenting factors) could technically be classified as nonshared (eg, parenting being experienced as different among siblings).<sup>31</sup> In the future, identification of environmental risk factors for OCD will be at least as important as, if not more important than, finding candidate genes for the disorder because these risk factors may potentially be amenable to prevention or intervention strategies. Longitudinal, population-based designs will be ideally suited to identify such risk factors.<sup>32</sup> The identification of genetic differences in susceptibility to particular environments (gene × environment interactions) in OCD will be an important challenge for the future.<sup>33</sup> Finally, the possibility of gene-environment correlations should also be investigated because it is plausible that genetic factors could influence the specific environmental experiences of children who are vulnerable to developing OCD.<sup>34</sup>

### Nonbiological Relatives of Patients With OCD Are Also at Elevated Risk for OCD

To our knowledge, an increased risk for clinically diagnosed OCD in spouses or partners sharing children with OCD probands has not been previously reported but is consistent with the results of a previous study<sup>35</sup> that found small (0.1-0.2) but significant correlations for obsessive-compulsive symptoms

in a community-based sample of Dutch twins and their spouses. The present study design did not enable delineating possible marital interaction effects from assortative mating, or social homogamy. Indeed, spouses could become more similar the longer they are married. Family accommodation is common, whereby family members of patients with OCD assist or participate in the patients' rituals to reduce their anxiety or anger.<sup>36,37</sup> With time, the originally unaffected spouse may eventually manifest as having "pseudo-OCD." These individuals may also be more likely to seek help and receive a diagnosis. However, given our finding that shared environmental effects are negligible in OCD, phenotypic assortment may be a more likely explanation. Individuals with OCD or subclinical obsessive-compulsive symptoms may seek partners with similar characteristics. For example, individuals preoccupied with contamination and cleanliness may be more likely to seek partners sharing this characteristic with them. This intriguing possibility should be studied further.

### Strengths and Limitations

A considerable strength of the present study is the large population-based sample consisting of all diagnosed OCD cases contained in the Swedish National Patient Register during 40 years, as well as carefully matched, randomly selected controls. This ensured minimal risk for selection bias in both OCD and control families. Furthermore, this is the first study to date to examine OCD familial risk across relatives at varying genetic and environmental distances from the probands. A complementary nonclinical twin study further validated the results.

Nevertheless, registers also have limitations. First, mothers might report someone other than the true biological father as the father of their child. Although paternal discrepancy is not known specifically for the Swedish Multi-Generation Register, a review article<sup>38</sup> suggested a median of 3.7% across prior international studies. Bearing in mind that the true paternity of a child is generally unknown, our estimates are meaningful, although they might underestimate genetically transmitted risk. Second, individuals diagnosed as having OCD in the register represent a fraction of all OCD cases

in the population. Most individuals with OCD and subsyndromal OCD may not seek help and thus never be diagnosed or treated.<sup>39,40</sup> Furthermore, the Swedish National Patient Register only includes patients seen by specialist physicians; those diagnosed and managed in primary care by general practitioners are not included. Finally, psychiatric outpatients were only included in the register since 2001. Therefore, the register may only include more severe forms of OCD, and our results may not generalize to milder OCD. Some of these limitations may apply to previous OCD family studies conducted in specialist centers. The influence of these factors on the current heritability estimates is unknown, but it may be reasonable to assume that there were no systematic biases in the patterns of missing data. In support of this idea, the results of the twin analyses (nonclinical sample) are entirely compatible with the family data. Furthermore, the only study to date that recruited a never-treated community sample of patients with OCD and their relatives<sup>6</sup> found similar relative risks for OCD in first-degree relatives as previous clinic-based studies and the present population-based study. Third, although we found evidence of marital concordance, we could not distinguish between marital interaction, social homogamy, and phenotypic assortment effects. Finally, we assumed in this study that OCD is an etiologically homogeneous condition, but it is plausible that some forms of OCD may be more strongly influenced by genetic or environmental factors than others. Preliminary evidence indicates that, while there is substantial etiological overlap across the different symptom dimensions of OCD, dimension-specific genetic, and particularly nonshared environmental, factors may be at least as important.<sup>41,42</sup>

In conclusion, the present study provided strong evidence that OCD is a familial disorder and that this familiarity is largely explained by genetic factors. Nonshared environmental factors are at least as important. The quest for candidate genes, specific (nonshared) environmental risk factors, and their potential interaction or correlation should continue. This research should factor in the likely etiological heterogeneity of the disorder. The finding of possible assortative mating in OCD is intriguing and should also be explored further.

### ARTICLE INFORMATION

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