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HERITABILITY OF AUTISTIC TRAITS IN THE GENERAL POPULATION

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HERITABILITY OF AUTISTIC TRAITS IN THE GENERAL POPULATION

Abstract

Objective: 1) To explore genetic and environmental influences on individual differences in autistic traits in late adolescence. 2) To test if there is assortative mating (non-random partner choice) for autistic traits in the general population.

Design: Twin family study using structural equation modeling.

Setting: Population based twin family sample from the Netherlands.

Participants: Twins aged 18 years (n=370) and their siblings (n=94); parents of twins (128 couples).

Main Outcome Measure: Self-reported Autism-Spectrum Quotient (AQ) scores, a quantitative measure of autistic traits.

Results: Autistic traits were continuously distributed in the population. Twins and siblings did not significantly differ in AQ scores; men obtained significantly higher AQ scores than women (in twin-sibling sample, $P < .001$; twin-parent sample, $P = .02$).

Individual differences in endorsement on autistic traits show substantial heritability (57%). No significant shared environmental influences were detected. The genes affecting autistic traits appear to be the same across the sexes. The correlation in AQ score between spouses was low and not significant (Pearson $r = .05$; $P = .59$).

Conclusion: Previous general population twin studies reported high heritability for autistic traits in childhood and early adolescence. This study extends these findings to late adolescence and yields no evidence for sex-specific genetic influences on autistic traits in later stages of development. As autistic traits show substantial variation in the general

population, future genetic studies may be facilitated by measuring autistic traits on a continuous scale like the AQ. No evidence for assortative mating for autistic traits was found, suggesting that, in the general population, there is no passive or active partner selection for autistic traits.

Introduction

Autism spectrum disorders (ASD) are characterized by a triad of features: (1) difficulties in social interaction, (2) difficulties with communication, and (3) the presence of restricted repetitive and stereotyped patterns of behavior, interests, and activities.¹ Twin and family studies have shown that ASD are highly heritable.² While the concordance of autism in monozygotic twins is 60-90%, concordance in dizygotic twins is only 0-5%,^{3,4} which results in a heritability estimate above 90%.² Moreover, relatives of autistic individuals show increased rates of social deficits, impairments in communication and language, a preference for routines and difficulty with change⁴⁻⁸.

Rather than treating autism as a distinct disorder, recent studies have used a dimensional approach to study autistic traits.^{9,10} These studies suggest that ASD represent the upper extreme of a constellation of traits that may be continuously distributed in the population.^{7,9-11} Studies quantifying autistic traits have found elevated scores in relatives of people with ASD^{12,13} and in children whose parents showed high (but sub-diagnosis) endorsement on autistic traits.¹⁴

The dimensional approach has also been incorporated in twin studies. A study in 7-15 year old twins using the Social Responsiveness Scale yielded mixed results.^{9,15} A first report in male twins only suggested strong heritability (76%), no shared environmental influences, and moderate non-shared environmental influences (24%).¹⁵ In a subsequent report also including female and opposite sex twin pairs, heritability decreased to 48%, and both significant shared (32%) and non-shared (20%) environmental influences were found.⁹ In more than 3000 7-year old male, female, and opposite sex twin pairs, both social and non-social autistic behaviors were found to be

highly heritable.¹⁶ A study in the same sample one year later reported high heritability of autistic traits and no shared environmental influences.¹⁷ The latter study also used a categorical approach (extreme vs typical endorsement on autistic traits) and found results similar to the dimensional approach, yielding no indication that etiology is different at the extreme end of the spectrum. These studies were all conducted in children and young adolescents. No studies into the heritability of autistic traits at later ages have been reported yet, and none have included siblings of twins. Furthermore, the studies mentioned above were all based on parent or teacher ratings. Previous studies of behavioral problems have shown that external and self-rated reports may yield other results as different raters can provide different perspectives on behavior.^{16,18,19} The present study aims to examine genetic and environmental influences on self-reported autistic traits in a sample of 18-year old twins and their siblings, using the Autism-Spectrum Quotient (AQ)¹⁰ a well-validated instrument used to quantify autistic traits.²⁰

Additionally, assortative mating (non-random partner choice) for autistic traits will be examined. Assortative mating for traits related to autism has been proposed as a risk factor for having a child with autism.²¹ Moreover, if present in the general population, assortative mating could influence the frequency of the genotypes related to autistic traits, bias correlations in first-degree relatives and consequently the heritability estimates. One previous study¹⁴ of assortative mating for autistic traits reported a spouse correlation of .38. However, in this study spouses rated each other and not themselves on the endorsement of autistic traits. Shared beliefs or perceptions about the couple's relationship may have inflated the results. Various studies explored partner resemblance for personality traits and reported modest to moderate similarity for introversion²²⁻²⁴ and

modest similarity in preference for consistency and routine.²⁴ We examined assortative mating for autistic traits in a general population sample using self-reported AQ scores.

Methods

Participants

The twin families participating in the heritability study were recruited via the Netherlands Twin Register kept by the Department of Biological Psychology at the VU University in Amsterdam.^{25,26} The current study sample is part of an ongoing longitudinal project examining development of cognition and behavioral problems and comprised 194 families. Participation rate for this data collection was 54%. Participating families did not significantly differ from non-participating families in socioeconomic status (Mann-Whitney's $U=10382.00$, $P=.23$, $r=0.07$) but parental education level was slightly higher in participating families (education mother: $U=9538.00$, $P=.05$, $r=.012$; father: $U=7773.00$, $P=.01$, $r=0.16$). No information about ASD diagnoses was available. Mean age of the twins was 18.18 years ($SD=.22$; range 17.61 – 18.99); mean sibling age was 18.77 years ($SD=4.71$; range 10.52 – 35.39). Most twin families ($n=184$) completed the AQ in the university laboratory as part of an extensive test protocol. The other families ($n=10$) filled out the questionnaire at home. The sample consisted of 36 monozygotic male twins, 35 dizygotic male twins, 45 monozygotic female twins, 39 dizygotic female twins, and 39 dizygotic twins of opposite sex. Zygosity of the same-sex twins ($n=155$) was determined by DNA analyses ($n=101$), blood group polymorphisms ($n=45$), or discriminant analyses of longitudinally collected questionnaire items ($n=9$). This method has proven to be of sufficient reliability.²⁷ This study was approved by the Central

Committee on Research Involving Human Subjects and the institutional review board of the VU University Amsterdam. Written informed consent was obtained from all participating subjects.

To study assortative mating for autistic traits, parents of twins (unrelated to the twin families mentioned above) were asked to fill out the AQ during an information day for parents of multiples. They either completed the AQ during the day or returned it to our research group by mail. The response rate was 62%, no information was available about non-responders. Mean age of the participants was 35.68 years (SD=6.33). Only data of male-female couples were included, complete partner data on the AQ were available for 128 pairs. All couples were either living together or married.

The Dutch Autism-Spectrum Quotient

The AQ consists of 50 items, assessing personal preferences and habits. Subjects rate to what extent they agree or disagree with the statements on a 4-point Likert scale, with the following answer categories: 1 representing definitely agree; 2, slightly agree; 3, slightly disagree; and 4, definitely disagree. Total AQ scores were calculated as the sum of the Likert scale scores. For items in which an agree response was characteristic for autism, the scoring was reversed (definitely agree scored 4 points; slightly agree 3 points; slightly disagree, 2 points; and definitely disagree, 1 point). The minimum AQ score (50) indicates no autistic traits, the maximum score (200) suggests full endorsement on all autistic items.

The original English version of the AQ¹⁰ was translated into Dutch using a backward translation procedure. After comparing the outcome of the retranslated version

to the original text a final version was established. The Dutch translation of the AQ has good internal consistency (Cronbach's $\alpha=.79$) and test-retest reliability (Pearson $r=.78$ in a group of 75 subjects with a 1-6 month time interval).²⁰

If more than 5 items were left blank, the AQ was considered incomplete and the data were discarded in subsequent analyses ($n=7$ in the twin-sibling sample). Complete AQ's were available for 370 twins and 94 siblings. If 5 or fewer answers were missing, the AQ score was corrected for the number of missing items by making the following calculation: total AQ score + (mean item score x number of missing items). Twenty-one individuals were missing 1 answer, and 3 individuals were missing 2 answers.

Data analyses

Descriptive statistics were calculated using SPSS 13.0 for Windows (SPSS Inc, Chicago, Ill). Twin-sibling differences in AQ score and effects of birth order, zygosity, age, and sex were examined using a saturated model in the structural equation modeling program Mx.²⁸ Twin and twin-sibling correlations for AQ score were estimated for each zygosity group. Sex differences in mean AQ score in the twin-parent sample were examined using analysis of variance. Assortative mating was studied by calculating the Pearson correlation between AQ scores of spouses.

Figure 1 about here

Because monozygotic twins are genetically identical, while dizygotic twins and siblings share on average 50% of their segregating genes, genetic modeling of twin-

sibling data allows decomposing of the observed phenotypic variance into genetic and environmental components (see Figure 1). Additive genetic influences (A) result from the additive effects of alleles at all contributing genetic loci. Shared environmental influences (C) result from environmental effects common to all members of the family. Non-shared environmental influences (E) represent environmental factors unique to each family member and also include measurement error. These variance components were estimated by using Mx.²⁸ The fit of various models was compared using a likelihood ratio test, which is the difference between minus twice the log likelihoods (-2 LL) under two nested models and is distributed as a χ^2 . The df are given as the difference in the number of parameters estimated in the two models. A high increase in χ^2 against a low gain of df denotes a worse fit of a sub model compared to the full model. The most parsimonious model was chosen as the best model. Analyses were performed on the raw data. The significance of sex differences in the variance components was tested by examining the deterioration in model fit after constraining the magnitude of additive genetic influences, shared environmental influences, and nonshared environmental influences to be equal across the sexes. The significance of the contribution of additive genetic influences and shared environmental influences was tested by assessing the deterioration in model fit after each component was dropped from the full model.

Table 1 and Figure 2 about here.

Results

Table 1 presents the descriptive statistics for AQ scores in the twins and their

siblings, and in spouses drawn from the sample of parents of twins. Autism-Spectrum Quotient scores were continuously distributed (Figure 2). No differences in mean AQ scores between twins and siblings were found (102.1 vs 102.9, respectively; $\chi_1^2=1.18$, $P=.28$). Moreover, no effects of birth order ($\chi_2^2=1.66$, $P=.44$), zygosity ($\chi_1^2=1.44$, $P=.23$), or age ($\chi_1^2=.59$, $P=.44$) could be detected. A significant sex effect on the mean was found; mean AQ scores were significantly higher in men than in women (104.0 vs 100.8, respectively; $\chi_1^2=12.97$; $P < .001$, effect size $d=0.30$). Similarly, in the twin-parent sample, men obtained significantly higher AQ scores than women (mean 106.0 vs 102.8, respectively; $F_{1,254}=5.32$; $P=.02$; $d=0.28$). No evidence for assortative mating for autistic traits was found. The partner correlation for AQ score was $r=0.05$ ($P=.59$).

Table 2 about here

Twin and twin-sibling correlations are presented in Table 2. Inspection of the monozygotic, dizygotic, and twin-sibling correlations gives a first impression of what factors influence individual differences in AQ scores. Although the confidence intervals overlap, the estimates for monozygotic correlations are higher than dizygotic and twin-sibling correlations, indicating that genetic factors may play a role. As the twin correlations in opposite sex twins are not attenuated, compared with the correlations in same sex dizygotic twins, there is no indication for sex specific genes influencing variance in AQ scores. The monozygotic correlations are not twice as high as the dizygotic correlations and twin-sibling correlations, suggesting that shared environmental factors could also be of importance.

Model-fitting statistics for the full model, including both additive genetic, shared environmental, and non-shared environmental influences (referred to as the ACE model), and various submodels are presented in Table 3. Constraining the parameters that represent the effect of additive genetic, shared environmental, and nonshared environmental influences as equal across the sexes did not significantly worsen the fit ($\chi^2_3=2.88$; $P=.41$), confirming that the relative effects of these components were the same in men and women. Dropping the shared environmental component from the model did not result in a worse model fit ($\chi^2_1=0.78$; $P=.37$). The genetic effects, however, were of significant importance ($\chi^2_1=4.35$; $P=.04$). In the best-fitting parsimonious model, individual differences in autistic traits were explained by additive genetic influences (accounting for 57% of the variance) and non-shared environmental effects (accounting for 43% of the variance).

Table 3 about here

Comment

The present study shows that autistic traits, as measured by the AQ in the general population, are continuously distributed; show a significant sex difference in mean scores, with men scoring higher than women; and are unrelated to age or to being born a twin or singleton. Moreover, individual differences in autistic traits show substantial heritability, and are influenced by the same additive genetic factors in men and women. No evidence for assortative mating for autistic traits was found.

The finding of a significant sex difference in mean AQ scores in both the twin-

sibling and the twin-parent sample is in concordance with findings using other measures of autistic traits, such as the Social Responsiveness Scale⁹ and the Childhood Asperger Syndrome Test,¹⁷ and with earlier studies using the AQ from the United Kingdom and Japan,^{10,29} suggesting cross-cultural similarities. All studies report higher endorsement on autistic traits in men than in women, which is in line with the observation that ASDs are more common in men than in women.³⁰

We did not find a difference in mean AQ scores between twins and singletons. Some studies have suggested the process of twinning as a risk factor for the development of autism.^{31,32} Large population-based studies did not support these findings.³³⁻³⁵ Our results indicate that in the general population, endorsement of autistic traits is unrelated to being born a twin or singleton.

In 18-year-old twins and their siblings, variance in autistic traits is largely explained by additive genetic effects (57%). Shared environmental effects were not of significant importance; nonshared environmental effects accounted for 43% of the variance. Twin correlations in same-sex dizygotic twins were of similar magnitude as the correlation in opposite-sex twins, yielding no evidence for sex-specific genes for autistic traits. Comparable dizygotic same-sex and opposite-sex correlations were found in twin studies in childhood and early adolescence.^{9,16,17} Our results indicate that even in more advanced stages of development, the set of genes influencing autistic traits is the same across the sexes.

The correlations in first-degree relatives in this study ($r=0.32$) are similar to the dizygotic twin correlations reported in other studies assessing autistic traits on a continuum^{9,16,17} but are considerably larger than dizygotic twin concordance rates and

sibling prevalence rates for clinical diagnosis of autism (0-5%)^{2-4,36}. It is found that dizygotic twin concordance rates and sibling prevalence increase when diagnostic criteria are relaxed and include a broader phenotype of autistic traits.⁴⁻⁸ It may be that first-degree relative correlations in clinical samples increase even more when autistic traits are measured on a continuous scale such as the AQ. Although tentative, these findings may have implications for genetic studies, as the strong disparity between monozygotic and dizygotic twin concordance rates for diagnosed autism have led to the hypothesis that gene-gene interactions play an important role in the risk for autism.

Our results suggest that shared environmental effects are not of major importance in explaining the variance of autistic traits, but the power to detect such effects was limited with our sample size.³⁷ In previous studies including larger sample sizes,^{9,16,17} one study found no shared environmental effects,¹⁷ one reported a small but significant contribution of shared environment in girls but not in boys,¹⁶ and one reported moderate shared environmental influences in both sexes.⁹ The studies reporting significant shared environmental effects were both based on parental reports. As the parent rates the behavior of both members of the twin pair, rater bias may have inflated the shared environmental effects in these studies.

Our study relied on self-report measurement of autistic traits. As subjects with autism may underestimate their social impairment, the AQ asks about preferences rather than behavioral judgments. Previous studies have indicated that the AQ is a valid instrument to assess autistic traits.^{10,20} However, the agreement between self-ratings and other ratings of autistic traits is as yet unexplored. Future studies should include multiple raters of autistic behavior to account for rater bias and rater-specific views, as previous

studies have shown that different raters can provide substantial additional information.^{16,38} No information about ASD diagnoses were available in this study, and the sample included few extreme scorers on the AQ. Previous studies yielded no evidence that the etiology of autistic traits is different in the general population vs the extreme. However, the real test for this should come from genetic studies.

No evidence for assortative mating for autistic traits was found. The correlation of AQ scores between partners was close to zero. This is in contrast to a previous study¹⁴ that reported a spouse correlation of $r=0.38$. However, as their assessment of autistic traits was based on spouse-report, shared perceptions about the relationship may have inflated the correlation.¹⁴ All participants in our assortative mating study were recruited on an informational day for parents of multiples. Individuals who dislike being confronted with large crowds may be unlikely to attend this event. Our sample may therefore not be completely representative for the general population. The results suggest that in the general population, people do not actively or passively select their partner for autistic characteristics. One theory has proposed assortative mating for extreme autistic traits as a risk factor for having a child with ASD.²¹ Our sample included insufficient numbers of extreme AQ scorers to test this hypothesis.

From these data, we conclude that variance in autistic traits, as measured with the AQ, show substantial heritability. There is no indication that the heritability estimate reported here is confounded by assortative mating. This study shows that the strong heritability is not limited to the clinical autism spectrum, but also accounts for variance in autistic traits in the general population. Singletons do not differ from twins in endorsement of autistic traits. Genetic studies may be facilitated by measuring autistic

traits on a continuous scale like the AQ. Such studies can elucidate whether the genes associated with the clinical spectrum are also associated with normal variation in autistic traits.

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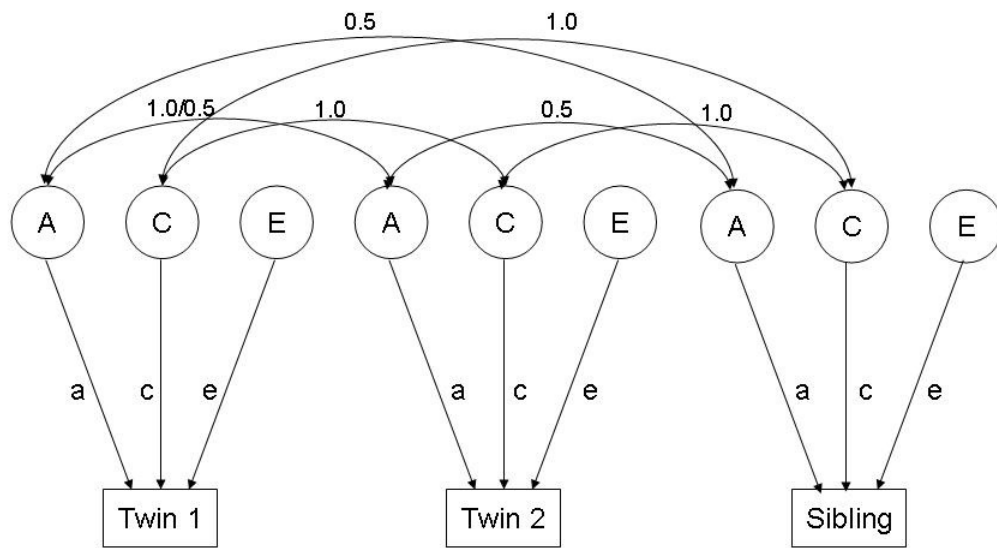
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Legend Figure 1: Univariate path diagram representing the contribution of additive genetic (A), shared environmental (C), and non-shared environmental (E) influences to the trait under investigation (Autism-Spectrum Quotient scores). The factor loadings of these influences are represented by a, c, and e. The correlation of the additive genetic factors is 1.0 in monozygotic twins and, on average, 0.5 in dizygotic twins and between twins and siblings. The correlation of the shared environmental effects is 1.0 between twins and between twins and siblings. E represents effects unique to a family member and are thus uncorrelated.

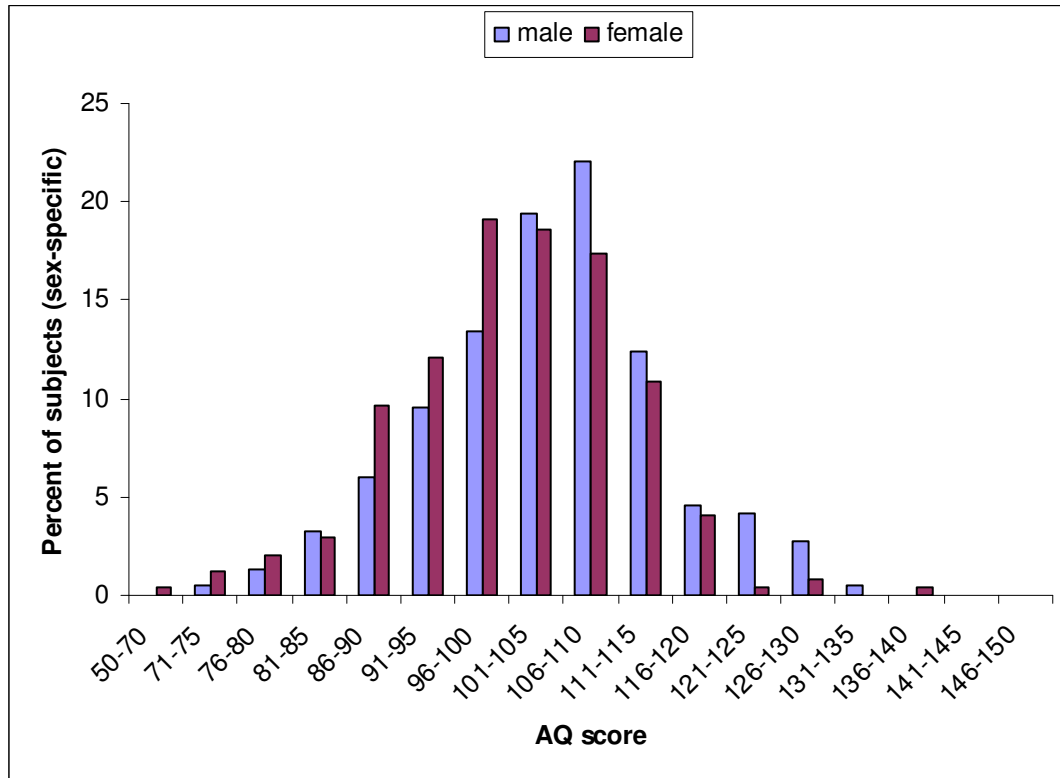


Figure 2. Distribution of Autism-Spectrum Quotient (AQ) scores in twins and their siblings..

Note under Table 1: Abbreviation: AQ, Autism-Spectrum Quotient.

*Parents of twins not in the twin sample

Table 1. Sample Sizes and AQ Score in Twins, Their Siblings, and in Spouses

<i>Subject</i>	<i>Sample Size</i>	<i>AQ Score, Mean \pm SD</i>
Twin sample		
Twin	370	102.1 \pm 10.5
Sibling	94	102.9 \pm 11.0
M	217	104.0 \pm 10.5
F	247	100.8 \pm 10.5
All	464	102.3 \pm 10.6
Spouse sample*		
M	128	106.0 \pm 10.9
F	128	102.8 \pm 11.5
All spouses	256	104.4 \pm 11.3

Table 2. Twin and Twin-Sibling Correlations

<i>Subject Pair</i>	<i>Complete Pair, No.</i>	<i>Incomplete Pair, No.</i>	<i>Correlation (95% Confidence Interval)</i>
Monozygotic male twin pair	33	3	.59 (.32 - .74)
Dizygotic male twin pair	31	4	.36 (.01 - .60)
Monozygotic female twin pair	43	2	.51 (.23 - .68)
Dizygotic female twin pair	35	4	.43 (.07 - .65)
Dizygotic twin pair of opposite sex	36	3	.35 (.11 - .55)
All monozygotic twin pairs	76	5	.55 (.37 - .67)
All dizygotic twin pairs	102	11	.37 (.20 - .52)
Male twin-sibling pairs	48	1	.04 (-.23 - .29)
Female twin-sibling pairs	58	2	.47 (.24 - .62)
Twin-sibling pairs of opposite sex	74	5	.33 (.12 - .50)
All twin-sibling pairs	180	8	.28 (.12 - .41)
All first-degree relative pairs	282	19	.32 (.19 - .43)

Table 3. Model Fit Statistics and Parameter Estimates for the Best-Fitting Model (shown bold faced)

<i>Model</i>	<i>-2LL</i>	<i>df</i>	<i>Comp ared With Model</i>	χ^2	<i>P Value</i>	<i>A (95% CI)</i>	<i>E (95% CI)</i>
1. ACE, sex differences	3444.32	454					
2. ACE, no sex differences	3447.19	457	1	2.88	.41		
3. AE, no sex differences	3447.98	458	2	0.78	.38	.57 (.43 - .68)	.43 (.32 - .57)
4. CE, no sex differences	3451.54	458	2	4.35	.04		
5. E, no sex differences	3496.69	459	3	48.71	<.001		

Abbreviations: A, additive genetic influences; C, shared environmental influences; CI, confidence interval; E, nonshared environmental influences; -2LL = -2 log likelihood.