Published in final edited form as:
Arch Gen Psychiatry. 2010 June ; 67(6): 624–630. doi:10.1001/archgenpsychiatry.2010.51.

Genetic and Environmental Influences on Disordered Gambling in Men and Women

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Abstract

Context—Women now represent nearly half of all individuals in treatment for pathological gambling (PG), but relatively little is known about the causes of PG among women or potential sex differences in the causes of PG.

Objectives—To (1) investigate the role of genetic and environmental risk factors in the development of disordered gambling (DG) among women and (2) determine the extent to which the genetic and environmental risk of DG among women differs quantitatively or qualitatively from the risk of DG among men. (*Disordered gambling* refers to the full continuum of gambling-related problems that includes PG disorder.)

Design—Twin study.

Setting—The national community-based Australian Twin Registry.

Participants—Four thousand seven hundred sixty-four individuals from 2889 twin pairs; twins were aged 32 to 43 years and 57% were women.

Main Outcome Measure—Disordered gambling was defined based on lifetime *DSM-IV* PG symptom counts.

Results—The estimate of the proportion of variation in liability forDGdue to genetic influences was 49.2% (95% confidence interval, 26.7–60.9). There was no evidence for shared environmental influences contributing to variation in DG liability. There was no evidence for quantitative or qualitative sex differences in the causes of variation in DG liability.

Conclusions—This study establishes for the first time that genes are as important in the etiology of DG in women as they are in men and that the susceptibility genes contributing to variation in liability for DG are likely to overlap considerably in men and women.

Pathological gambling (PG) runs in families.[1] In a recent family study,8%of the first-degree relatives of PG-affected probands, compared with 2% of the first-degree relatives of unaffected controls, had a lifetime history of PG.[1] The results of such family studies raise the question of the extent to which the familial transmission of PG can be explained by shared genes or shared environments. To date, only a single study has addressed this question. In the Vietnam Era Twin Registry, 23% of the monozygotic (MZ) and 10% of the

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Financial Disclosure: None reported.

Additional Contributions: Dixie Statham, MPsychClin, Bronwyn Morris, BSc, and Megan Fergusson, BSc, coordinated the data collection for the twins, and David Smyth, BSc, Olivia Zheng, BSc, and Harry Beeby, BSc, provided data management of the Australian Twin Registry. We thank the Australian Twin Registry twins for their continued participation.

dizygotic (DZ) co-twins of men with PG, compared with 1.4% of the full sample, had a lifetime history of PG.[2] Biometric modeling revealed that the familial aggregation of PG was mainly attributable to shared genetic rather than shared environmental factors.[2,3] Whether the results from the all-male Vietnam Era Twin Registry study can be generalized to women has still not been established.

Although women are outnumbered by men approximately 2-fold in their probability of being affected with PG,[4–6] they now represent nearly half of all individuals in treatment for the disorder.[7–10] Despite this, women are still underrepresented in most etiologic research,[11,12] and the familial transmission of PG among women and potential sex differences in the familial transmission of PG are largely uncharted territory. Given how poorly represented women have been in gambling research, there are only a few modest pieces of evidence to point to: (1) a review of 17 family studies suggested that the familial transmission of PG was weaker for women than for men (although the more recent study cited earlier[1] did not detect such a sex difference) and that having a mother affected with PG did not increase the risk of PG in the offspring[13]; (2) a small twin study of 155 twin pairs (63 female pairs) that concluded that gambling involvement was significantly heritable among men but not among women[14]; and (3) a genetic association study of 68 individuals with PG (21 women) reported 3 associations that were significant in men but not in women[15] (appropriate tests of sex differences[16–18] were not always conducted in these early studies). Some have speculated that PG among women may not have genetic underpinnings.[13,14]

In the present study, we investigated the role of genetic and environmental risk factors in the development of disordered gambling (*disordered gambling* [DG] refers to the full continuum of gambling-related problems that includes PG as well as subclinical problems[19]) in a large community-based sample of male, female, and opposite-sex twin pairs. Based on previous twin research on related disorders, we did not expect there to be significant sex differences in the role of genetic and environmental influences in the risk of DG. Metaanalyses of population-based twin studies of alcohol dependence[20,21] and major depression[22] have yielded very similar estimates of the contribution of genetic and environmental factors for men vs women. Based on these more developed literatures, we hypothesized that the same would also be observed for DG, and the main goal was to establish for the first time that DG has genetic underpinnings in women as well as men. The extent to which the genetic and environmental risk factors differ in men vs women was also explored by comparing twins from same- and opposite-sex twin pairs.

METHODS

PARTICIPANTS

Participants for this study were 4764 members of the Australian Twin Registry Cohort II (details about the study participants and the zygosity determination have been published previously[23]). In 2004–2007, a telephone interview containing a thorough assessment of gambling behaviors was conducted in the Australian Twin Registry Cohort II members (individual response rate of 80.4%).[23] The mean age was 37.7 years (range, 32–43 years), and 57.2% of the sample was female. There were 1875 complete twin pairs (867 MZ pairs [520 female and 347 male] and 1008 DZ pairs [367 female/female, 227 male/male, and 414 female/male]), and 1014 individual twins from incomplete pairs (304 MZ individuals [151 female and 153 male] and 710 DZ individuals [181 women from female/female pairs, 216 men from male/male pairs, and 207 women and 106 men from female/male pairs]).

PROCEDURE

Twins were assessed through a structured telephone interview. Interviews were administered by trained lay interviewers who were blind to the status of the co-twin. Interviewers were supervised by a project coordinator, a clinical psychologist with more than 10 years of experience. All interview protocols were reviewed either by the project coordinator or by research editors (veteran, skilled interviewers from previous studies who had maintained consistently low error rates in coding). All interviews were tape-recorded and a random sample of 5% of the interview tapes was reviewed for quality control and coding inconsistencies. A small subsample of the participants (n=166) were reinterviewed several months after their initial interview (mean interval, 3.4 months [SD, 1.4 months]; range, 1.2–9.5 months) to establish the test-retest reliability of the interview measures. Individuals with a history of PG symptoms were oversampled for the test-retest reliability study. The institutional review boards at the University of Missouri–Columbia and the Queensland Institute of Medical Research approved this study. All of the participants provided informed consent.

MEASURES

Disordered Gambling—The National Opinion Research Center *DSM-IV* Screen for Gambling Problems (NODS)[24] was used to assess DG. The NODS *DSM-IV* diagnostic criteria were assessed for all participants who reported that they had ever gambled at least 5 times within a single 12-month period; most participants (77.5%) surpassed this gambling threshold.

The NODS is a structured interview that was developed for a national United States gambling prevalence survey conducted in 1999.[24] The NODS assesses the 10 *DSM-IV* diagnostic criteria for PG. The test-retest reliability of the lifetime diagnosis of PG from the NODS was high (κ=0.67; Yule Y=0.79). Exploratory factor analyses provided strong and convincing evidence consistent with a single-factor model of PG for the *DSM-IV* symptom set: there was only a single large eigenvalue greater than 1, and the root mean square error of approximation and root mean square residual were 0.021 and 0.03, respectively. Typically, a single eigenvalue greater than 1, a root mean square error of approximation of less than 0.06, a root mean square residual of less than 0.05, and all of the indicators having high loadings on a single factor support the hypothesis that a single factor is sufficient for explaining the interitem correlations. The exploratory factor analyses support the proposition that all of the *DSM-IV* symptoms are measuring the same underlying dimension and that endorsing even a single item is informative about an individual's DG liability.

Because the *DSM-IV* diagnostic criteria for PG also include an exclusion criterion that the "gambling behavior is not better accounted for by amanic episode," amania screen was also included in the interview. Participants who endorsed having a period of unusually elevated mood accompanied by behaviors noticeable to others (rapid speech and impulsive behaviors) and treatment (hospitalization or medication) were considered to have probable mania; 1.2% of the sample met these criteria. This included 6 individuals with *DSM-IV* PG. Only 2 of the 6 individuals with *DSM-IV* PG who were classified with probable mania reported that there was an increase in the frequency and quantity of gambling expenditures during the manic episode. Because there were so few individuals who met this criterion for exclusion, and to maintain consistency with previous research (this exclusion was a new addition to the *DSM-IV*), we retained these individuals in the sample.

Environmental Similarity—Data obtained from a previous structured telephone interview[23] conducted in 1996–2000 (on average 7.8 years prior to the present study when the participants were aged 24–36 years) were used to evaluate the validity of the equal

environmental similarity assumption of twin studies for DG. Childhood environmental similarity was assessed with 4 questions. Each twin was asked how often they (1) shared the same friends when they were aged 6 to 13 years, (2) dressed alike when they were aged 6 to 13 years, and were in the same classes in (3) primary school or (4) high school. The responses from twins within pairs were combined for each item, and the 4 items were combined into a composite indicator of childhood similarity. Adult environmental similarity was assessed with 2 questions. Each twin was asked how often they (1) saw each other or (2) contacted each other by letter, e-mail, fax, or telephone. The responses from twins within pairs were combined for each item, and the 2 items were combined into a composite indicator of adult environmental similarity.

STATISTICAL ANALYSIS

Prior to conducting biometric modeling, we tested for cross-sex measurement invariance of DG as measured by the 10 *DSM-IV* PG symptoms. This was done to ensure that any sex differences that emerged in the biometric analyses could be interpreted as actual sex differences in DG, rather than sex differences in our chosen measurement of DG. The analyses were conducted using *Mplus* software[25] with a mean- and variance-adjusted weighted least-squares estimator. Measurement invariance analyses were conducted using the methods detailed by Neale et al.[26]

Biometric models were fit by themethod of maximum likelihood directly to the raw twin data using the Mx program,[27] using data from incomplete as well as complete twin pairs. Liability-threshold models were fit to the twin data.[28,29] This model assumes that there are latent liability continua underlying the categorical diagnoses. The decision to use this model was based on the following 2 considerations: (1) maintaining consistency with the previous twin study of DG,[2,3,30] and (2) the use of a continuous symptom count measure was intractable because the distribution was highly skewed even after a data transformation.

In fitting a liability-threshold model, a decision must be made about the appropriate threshold to use. Typically, this will correspond to whether or not an individual is affected vs unaffected with a disorder. However, with dimensional diagnoses such as PG, this diagnostic cutoff also represents a count on a continuous symptom scale (ie, 5 of 10 symptoms for *DSM-IV* PG). When the symptoms making up the scale are all indicators of the same unidimensional construct, as indicated by the exploratory factor analyses and previous research,[31] the cutoff used for the threshold in the liability-threshold model does not necessarily have to correspond to the cutoff used for a clinical diagnosis. The liability-threshold model assumes that the causes of variation in risk will be the same at any point along the liability distribution and for any threshold imposed.[32] Therefore, to maximize the statistical power, we dichotomized the *DSM-IV* symptom counts at 1 or more symptoms. Although this threshold conforms most closely to the idea of problem gambling, the assumption of the underlying model that we are imposing suggests that the results will apply equally to all levels of disordered gambling behavior, including PG.

Biometric model fitting was conducted to partition the variation in DG liability into additive genetic, shared environmental or nonadditive genetic, and nonshared environmental influences (estimates of nonshared environmental variation will also include measurement error). The evidence for 2 different types of sex difference was evaluated. Quantitative (also known as scalar) sex differences refer to differences in the magnitude of genetic or environmental effects in men and women and are detected from within-zygosity differences in the twin correlations obtained from same-sex male vs female twin pairs. Qualitative (also known as nonscalar) sex differences refer to differences in the actual genetic or environmental risk factors that contribute to variation in a trait and are detected from smaller twin correlations obtained from opposite-sex than from same-sex DZ twin pairs.

Ideally, one would combine the measurement model used in the measurement invariance analyses with the biometric models. [26] Unfortunately, the sparseness of some of the *DSM-IV* PG symptom data among some of the 5 sex/zygosity subgroupings precluded the implementation of this analytic approach.

RESULTS

Many of the participants were frequent gamblers. Nearly all of the participants had ever gambled, about one-half had gambled at least once a month, and about one-third had gambled at least once a week (Table 1). The overall lifetime prevalence of PG according to the *DSM-IV* was 2.2% (3.4% among men and 1.2% among women). The overall lifetime prevalence of ever experiencing 1 ormore *DSM-IV* PG symptoms was 12.5% (18.2% among men and 8.3% among women).

TESTS OF MEASUREMENT INVARIANCE

Of the 10 *DSM-IV* PG symptoms, 1 had to be excluded from the cross-sex measurement invariance analyses owing to low rates of endorsement in both sexes (committing illegal acts to finance gambling). The remaining 9 *DSM-IV* PG symptoms were factor analyzed, and the fit of the baseline single-factor model of these 9 symptoms, allowing all measurement parameters to differ for men and women, was quite good (comparative fit index= 0.99, Tucker Lewis Index=0.99, root mean square error of approximation=0.02). When the factor loading and threshold for a single symptom were allowed to differ for men and women, the fit of a constrained model no longer differed from the unconstrained model ($\Delta\chi^2_5$=4.29, *P*=.51, n=4764), suggesting partial measurement invariance of the *DSM-IV* PG symptoms across sex.

The measurement noninvariance of the single symptom “gambles to escape personal problems or to relieve a dysphoric mood” is consistent with significant differences in the prevalence of this individual *DSM-IV* PG symptom in men and women in general population surveys, [5] in treatment samples,[7] and with a previous analysis that also showed that this symptom functioned differentially for men and women.[31] This differential item functioning across men and women is an undesirable quality in a diagnostic criterion and warrants a reevaluation of the *DSM-IV* PG criteria set.

TESTS OF SEX DIFFERENCES

Prior to fitting biometric models, tests of the differences between the twin correlations for the different zygosity groups were conducted using Mx (Table 2). In these and all subsequent biometric models, thresholds (prevalences) for men and women were allowed to vary because they could not be constrained to be equal ($\Delta\chi^2_1$=92.4, *P*<.001, n=4758). The twin correlations from both the 2 MZ groups (male and female) and the 2 same-sex DZ groups (male/male and female/female) could be constrained to be equal ($\Delta\chi^2_2$=0.07, *P*=.97, n=4759), and the 3 correlations from the 2 same-sex DZ groups and the opposite-sex DZ group (male/male, female/female, and male/female) could also be constrained to be equal ($\Delta\chi^2_1$=0.00, *P*=.95, n=4760).

These results indicate that there is no evidence of quantitative sex differences or qualitative sex differences. Based on these findings, it would be appropriate to proceed with biometric modeling without allowing for sex differences in parameter estimates; but because there are so few data on the etiology of DG among women, we present results of fitting models to the male and female data separately in addition to fitting models to the pooled data from men and women.

BIOMETRIC MODEL FITTING

The best fitting model was one that included additive genetic and nonshared environmental sources of variation. Shared environmental or nonadditive genetic factors did not account for significant portions of variation in liability. The results of fitting a full univariate biometric model that included additive genetic, shared environmental, and nonshared environmental sources of variation are presented in Table 3 for the purpose of delineating the confidence bounds around the parameter estimates (of the nonsignificant as well as the significant parameters). For example, shared environmental factors were estimated at 0, but the narrow confidence interval (CI) around this estimate suggests that shared environmental factors could have accounted for only 4% of the variation in liability at best. Parameter estimates for men and women did not significantly differ from each other ($\Delta\chi^2_2$=0.1, *P*=.97, n=4760).

As a check on the validity of the underlying assumption of the liability-threshold model, we compared the heritability estimates obtained from fitting full univariate biometric models to the data from the full sample when the diagnostic cutoffs were set at 1 or more, 3 or more, or 5 or more symptoms (the latter cutoff corresponds to a diagnosis of *DSM-IV* PG). This yielded heritability estimates of 49% (95% CI, 28%–61%; Table 3), 58% (95% CI, 35%–78%), and 40% (95% CI, 9%–74%), respectively. These results are consistent with the hypothesis that the causes of variation in risk are similar at any point along the DG liability distribution and for any diagnostic cutoff imposed.

TESTS OF THE EQUAL ENVIRONMENTAL SIMILARITY ASSUMPTION

As a check on the underlying equal environment assumption of the twin method, we conducted logistic regressions predicting twin pair concordance for DG from childhood similarity of experiences (sharing the same friends, dressing alike, being in the same classes in primary school, and being in the same classes in high school) or frequency of contact as adults. After controlling for sex, age, and zygosity, neither childhood environmental similarity nor adult frequency of contact significantly predicted twin pair concordance for DG. This suggests that the equal environment assumption holds for DG in this study. The greater similarity of MZ than DZ twins is more likely attributable to greater sharing of genes rather than to greater sharing of environments.

COMMENT

There has been very little behavioral genetic research on DG to date. This investigation represents only the second twin study ofDGamong men and the first twin study of DG among women. The previous Vietnam Era Twin Registry study of DG[3] was based on a national US sample of men who were 42 years of age on average (range, 33–53 years) when the data were collected in 1991–1992; its assessment of DG was based on the *DSM-III-R* criteria.[33] The present study included a national Australian sample of men who were 38 years of age on average (range, 32–43 years) when the data were collected in 2004–2007 and used an assessment of DG based on the *DSM-IV* criteria. Eisen et al[3] also fit a liability-threshold model to the categorical DG diagnostic data and presented results based on using different cutoffs (ie, ≥1, ≥2, ≥3, and ≥4 *DSMIII-R* PG symptoms). The cutoff of 1 or more symptoms most closely matches the DG analyses in the present article. Based on this operationalization in the US study, the estimates of variation in DG liability due to additive genetic, shared environmental, and nonshared environmental influences were 48%, 0%, and 52%, respectively, which is nearly identical to the estimates for men in the present study (Table 3).

Neither the Vietnam Era Twin Registry study nor the present study obtained evidence of shared environmental influences contributing to variation in DG liability. This is similar to

the results obtained from metaanalyses of population-based twin studies of alcohol dependence[20,21] and major depression.[22] In fact, decades of quantitative genetic research on psychopathology, personality, and cognition have consistently found that shared environmental factors do not explain significant portions of phenotypic variation for most traits.[34]

This is not to say that shared family environmental factors may not be important in the development of DG. The effect of such environmental factors may be genotype dependent (ie, genotype × environment interaction),[35–37] or the exposure to such environmental factors may be correlated with genetic differences (ie, genotype × environment correlation),[37,38] and inmany instances these types of environmental effects will be apportioned to the genetic source of variation in biometric twin models.[36] An exemplar genotype × shared environment correlation for DG arises when a child is raised by a biological parent with a gambling problem. In this scenario, the child is potentially exposed to a problem gambling role model and inherits problem gambling susceptibility genes.

Women have been the focus of very little etiologic research on DG, and it is not clear the extent to which most DG research based upon men can be applied to women. In the present study, there was little evidence for sex differences, neither quantitative nor qualitative, in the sources of variation in liability to DG. The contribution of genetic, shared, and nonshared environmental factors to variation in DG liability did not significantly differ between men and women, and the estimated parameters of these effects were very similar. The genetic risk factors implicated in the liability to DG also did not significantly differ between men and women. The results of this study suggest that much of the existing literature on DG that has been based upon research with men might also be generalized to women.

There have been only 11 published molecular genetic studies of DG to date,[17] and the studies were based on only 4 independent samples. Altogether, only 518 individuals with DG (mostly men) have been included in molecular genetic investigations of DG. All of the studies have been candidate gene association studies; there has not yet been a genome-wide linkage or association study of DG. The focus of most of the association studies has been 1 or more of the dopamine receptor genes (including *DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5*) and the dopamine transporter gene (*DAT*), with at least 1 positive finding reported for *DRD1*, *DRD2*, and *DRD4*.[39–41]

Although it is difficult to draw firm conclusions from so few association studies[42] of dopamine genes and DG, there are at least 2 other lines of evidence that suggest that the dopamine genes are related to susceptibility for DG. First, meta-analyses of association studies of the *DRD2* gene and alcohol dependence[43] and the *DRD4* C521T polymorphism and novelty seeking[44] suggest that there are small but significant associations with these correlated traits. Second, there have been a series of reports on the incidence of DG among individuals with Parkinson disease[45–47] and restless legs syndrome[48] who were being treated with a dopamine agonist medication in combination with or without levodopa (an amino acid precursor of dopamine) and whose DG usually resolved with the discontinuation of the dopamine agonist therapy.[45,48]

In searching for susceptibility genes, it will be important to acknowledge the stage-sequential nature of DG.[49] Like other addictive disorders, DG requires that one pass through a series of stages, including the participation in gambling activities and progression to regular involvement, prior to the eventual development of DG symptoms. Thus, genetic susceptibility for DG will also include genes related to individual differences in these earlier stages. In a previous article from this sample, we presented evidence for significant genetic influences for a variety of indices of gambling involvement, including the number of

different gambling activities ever tried, the frequency of gambling, and the maximum amount ever bet, with heritabilities ranging from 43% to 56%.[24] It has not yet been established the extent to which the genes related to individual differences in gambling participation contribute to the genetic risk of DG, but it is likely that part of the answer will be found with such genes.

This study has a number of limitations. It is unclear how the results of this Australian twin study will generalize to other cultures. Australia was specifically chosen as the site for this study because it has a heavy gambling culture[23] and higher prevalences of PG. For example, the lifetime prevalences of *DSM-IV* PG in this Australian national survey were 3.4% and 1.2% among men and women, respectively, compared with 0.64% and 0.23% among men and women in a recent national US survey. [50] The univariate model-fitting results for men were similar to the results obtained from the all-male Vietnam Era Twin Registry study, but there are no similar twin studies among women with which to compare our results. Furthermore, like the Vietnam Era Twin Registry study, the age range of the sample was relatively narrow (32–43 years). The extent to which these results can be generalized to other age groups such as adolescents and older individuals remains an unanswered question.

Despite the higher prevalence of PG in this Australian twin sample, it still was necessary to broaden theDGphenotype to have adequate numbers of affected twins to fit sex-limitation models. Supplementary analyses using a diagnostic cutoff of 5 or more symptoms, corresponding to a diagnosis of PG, yielded a heritability estimate that was similar to the results obtained when using the lower DG cutoff of 1 or more symptoms. This supports the assumption of the liability-threshold model and suggests that the results apply to PG disorder as well as the broaderDGphenotype that was used throughout this article.

Despite limitations, this study represents a major step forward in that it establishes for the first time that genes are as important in the etiology of DG in women as they are in men. In addition to similar relative contributions of genetic vs environmental factors to variation in liability for DG, the results suggest that the susceptibility genes contributing to variation in liability forDGmay also overlap considerably in men and women. Twin studies can only indicate the importance of latent sources of genetic and environmental influence, but are mute concerning the specific genes or environments involved. The discovery of the specific genes and environments involved in the development of DG remains an important direction for future research.

Acknowledgments

Funding/Support: This work was supported by National Institutes of Health grant MH66206.

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Table 1

Lifetime Prevalence of Gambling Involvement and Disordered Gambling Classifications Among 4764 Adult Australian Twins

Characteristic	No. (%)		
	Full Sample (N=4764)	**Men (n=2037)**	**Women (n=2727)**
Frequency of gambling			
Ever	4663 (97.9)	2001 (98.2)	2662 (97.6)
Monthly[a]	2428 (51.0)	1138 (55.9)	1290 (47.3)
Weekly[b]	1714 (36.0)	796 (39.1)	918 (33.7)
Daily[c]	186 (3.9)	125 (6.1)	61 (2.2)
Disordered gambling			
PG, ≥5 *DSM-IV* PG symptoms	104 (2.2)	70 (3.4)	34 (1.2)
Problem gambling, 3–4 *DSM-IV* PG symptoms	79 (1.7)	49 (2.4)	30 (1.1)
At-risk gambling, 1–2 *DSM-IV* PG symptoms	412 (8.6)	251 (12.3)	161 (5.9)

Abbreviation: PG, pathological gambling.

[a] Ever gambled at least once a month for at least 6 months in a row.

[b] Ever gambled at least once a week for at least 6 months in a row.

[c] Ever gambled daily for a period of at least 2 weeks.

Table 2

Twin Correlations in Liability for Disordered Gambling

Zygosity Group	Twin Correlation (95% CI)[a]
Male MZ	0.49 (0.30–0.65)
Male/male DZ	0.21 (0.00–0.45)
Female MZ	0.55 (0.34–0.72)
Female/female DZ	0.21 (0.00–0.51)
Male/female DZ	0.22 (0.01–0.41)

Abbreviations: CI, confidence interval; DZ, dizygotic; MZ, monozygotic.

[a]Tetrachoric correlations.

Table 3

Parameter Estimates From Biometric Model-Fitting of Sources of Variation in Liability for Disordered Gambling

	Parameters (95% CI)		
Group	Additive Genetic	Shared Environment	Nonshared Environment
Full sample	49.2 (26.7–60.9)	0.00 (0.0–4.1)	50.7 (39.0–64.3)
Men	48.5 (10.3–64.1)	0.01 (0.0–46.1)	51.4 (35.8–70.6)
Women	51.8 (26.4–69.0)	0.00 (0.0–9.0)	48.2 (30.8–69.6)

Abbreviation: CI, confidence interval.