ORIGINAL ARTICLE

Major Depressive Disorder in a Community-Based Twin Sample

Are There Different Genetic and Environmental Contributions for Men and Women?

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Background: Depression affects more women than men and often aggregates in families. Using a community-based sample of twins, we examined the contributions of genetic and environmental factors to the risk of developing major depressive disorder and the effect of sex and different definitions of depression on the relative contributions of genetic and environmental effects. Sex differences in genetic effects were also studied.

Methods: A volunteer sample of Australian twins (2662 pairs) was interviewed using an abbreviated version of the Semi-Structured Assessment for the Genetics of Alcoholism, a semi-structured lay interview designed to assess psychiatric disorders. Depression was defined using 3 different criteria sets: *DSM-III-R* major depressive disorder, *DSM-IV* major depressive disorder, and severe *DSM-IV* major depressive disorder. Genetic and environmental contributions to the liability to develop depression were estimated using genetic model fitting.

Results: Lifetime prevalences were 31% in women and 24% in men for *DSM-III-R* major depressive disorder, 22% in women and 16% in men for *DSM-IV* major depressive disorder, and 9% in women and 3% in men for severe *DSM-IV* major depressive disorder. In women, the simplest model to fit the data implicated genetic factors and environmental factors unique to the individual in the development of depression, with heritability estimates ranging from 36% to 44%. In men, depression was only modestly familial, and thus individual environmental factors played a larger role in the development of depression. For *DSM-III-R* major depressive disorder, there were statistically different estimates for heritability for men vs women. For both sexes, the relative contributions of genetic and environmental factors were stable using different definitions of depression.

Conclusions: There was moderate familial aggregation of depression in women and this primarily was attributable to genetic factors. In men, there was only modest familial aggregation of depression. For both men and women, individual environmental experiences played a large role in the development of depression. Major depressive disorder as defined by *DSM-III-R* was more heritable in women as compared with men. The relative contributions of genetic and environmental factors in the development of depression were similar for varying definitions of depression, from a broad definition to a narrow definition.

Arch Gen Psychiatry. 1999;56:557-563

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MAJOR DEPRESSIVE disorder is one of the most common psychiatric illnesses and causes considerable impairment in social functioning, employment, and physical ability.[1] Estimates from the US National Comorbidity Survey indicate that 17.1% of the population suffers from a *DSM-III-R* major depressive episode at some point in their lifetimes, and 10.3% of the population has experienced a major depressive episode in the last 12 months.[2] Sex differences in rates of major depressive disorder have long been recognized; women are about twice as likely to suffer from a major depressive episode as men (21.3% of women and 12.7% of men).[2]

Depression is also an illness that aggregates in families. Family studies have observed an increase in the risk of developing major depressive disorder in the relatives of individuals with major depressive disorder, though the magnitude of risk has differed between reports.[3-6] To determine whether this clustering of depression in families is caused by genetic or environmental factors shared by family members, it is preferable to perform adoption and twin studies because these studies can separate genetic and common family environmental contributions related to the development of a disorder.

Results of adoption studies have not been consistent in either establishing or rejecting biologically heritable influences in the development of depres-

SUBJECTS AND METHODS

SUBJECTS

Subjects were drawn from the Australian National Health and Medical Research Council Twin Registry, a volunteer sample of twins. The cohort first completed a mailed questionnaire in 1980-1982 when they were 18 years or older, and the twins were subsequently followed up with a second mailed questionnaire in 1988-1990.[17,18] In 1992-1993, telephone interviews of twins were conducted, and this direct interview provided the data for analyses in this article.[19]

Data were obtained from both members of 2685 twin pairs. The mean age of the sample was 44 years (range, 28-89 years; SD, 12.35 years) in women and 42 years (range, 28-84 years; SD, 11.23 years) in men. Because this was a study of unipolar affective disorder, twin pairs were eliminated from analyses if one or both twins from a twinship screened positive for mania, which left 2662 twin pairs for the final analyses. Verbal informed consent was obtained from all subjects before the start of the interview.

ASSESSMENT

Subjects were interviewed by telephone using an abbreviated version of the Semi-Structured Assessment for the Genetics of Alcoholism,[20] a highly reliable, semi-structured interview designed to assess the lifetime prevalences of alcohol dependence, major depressive disorder, and other psychiatric disorders. Lay interviewers received intensive training in administering the interview, and when assessing a subject were blind to the results of a co-twin's assessment. Prior to data entry, an editor checked interview data for consistency and subjects were recontacted to clarify inconsistencies. (A fuller description is given elsewhere.[19])

DIAGNOSES

All diagnostic criteria were implemented using computer algorithms. Three different diagnostic criteria for depression were studied: *DSM-III-R* major depressive disorder, *DSM-IV* major depressive disorder, and severe *DSM-IV* major depressive disorder. Major depressive disorder as defined by the *DSM-III-R*, the broadest definition of depression, required 5 depressive symptoms occurring together during at least a 2-week period. Major depressive disorder as defined by the *DSM-IV* also required a clustering of 5 depressive symptoms during a period of 2 weeks or longer, and individuals must also report impairment in social relationships, work, or school or seek treatment for this depressive syndrome. Severe *DSM-IV* major depressive disorder was defined as 6 depressive symptoms during at least a 4-week period (instead of 5 symptoms for *DSM-IV* major depressive disorder). This narrower definition of depression is more likely to be reliably reported, since a depressive episode with more symptoms for a longer period is more often rereported at longitudinal follow-up.[21,22] Depressive syndromes were included in analyses regardless of whether a subject reported a concomitant factor for the depressive episode (medications, alcohol or other drugs, serious medical illness, childbirth, or death of a loved one).

An abbreviated assessment of mania was given. This section, though nondiagnostic, was considered "positive" for mania if the subject reported a week or more of euphoria and psychiatric treatment for this condition. Using these screening criteria, 23 subjects (0.4%) reported an episode consistent with mania. Clinician review of responses and

sion.[7-9] On the other hand, twin studies consistently have supported genetic effects in the development of depression.[10-14] A population-based sample of twins from Virginia showed modest genetic influence (heritability 39%-42%)[11,14] on the development of *DSM-III-R* major depressive disorder. A similar finding was seen in a sample of male twins recruited from members of the military during the Vietnam War era (heritability 36%).[12] Two studies of twins recruited from psychiatric treatment centers demonstrated strong genetic influences on the development of depression (*DSM-IV* major depressive disorder, heritability 70%[13] and *DSM-III-R* major depressive disorder, heritability 60%[10]).

The influence of genetic factors, however, may not be equal for men and women. As part of the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, subjects with depression and their first-degree relatives were studied[15] and the "transmissibility" of depression, which encompasses both environmental and genetic factors that are passed from parents to offspring, was examined. Women were found to have significantly greater transmissibility of depression than men.[16] However, twin studies[10,13,14] did not find any sex differences in the magnitude of genetic and environmental contributions to depression.

The purpose of this study is to examine the genetic and environmental contributions to major depressive disorder in a volunteer community-based sample of male and female twins to address the following questions. (1) Is there familial aggregation of depression in both men and women and, if so, is there a genetic contribution to the development of depression? (2) Is the genetic contribution to the development of depression similar in men and women? (3) Does the proportion of the genetic and environmental contributions to depression differ for broadly and narrowly defined depression?

RESULTS

The lifetime prevalences for the various definitions of major depressive disorder are presented in **Table 1**. The broadest definition of depression, *DSM-III-R* major depressive disorder, was common in this population and affected 23.9% of men and 31.2% of women. Major depressive disorder as defined by *DSM-IV*, which in addition to *DSM-III-R* criteria required impairment in functioning during the depressive illness or seeking treatment for the illness, was less common (15.7% of men and 22.4% of women). Severe *DSM-IV* major depressive disorder, which required 6 symptoms of depression and an episode lasting at least 4 weeks, was the narrowest definition of depression (3.4% of men and 9.2% of women). Also presented in Table 1 are the proportion of cases reporting impairment in functioning, treatment seeking,

interviewer notes confirmed that most of these subjects had a clear history of bipolar affective disorder.

ANALYSIS

Prevalences, probandwise concordance for monozygotic and dizygotic twins, and tetrachoric correlations were determined. The probandwise concordance is the proportion of co-twins of twins with depression who are also affected with depression; each affected twin is independently ascertained. Among men belonging to unlike-sex dizygotic twin pairs, probandwise concordance is defined as the number of affected brothers of affected women divided by the total number of brothers of affected women. A similar definition is used for women belonging to unlike-sex dizygotic twin pairs.

For genetic modeling analyses, the liability to develop depression is assumed to be a continuous normal distribution with a threshold above which individuals develop the disorder.[23] This liability distribution receives contributions from both genetic and environmental effects. Phenotypic variance can then be partitioned into the proportion due to genetic effects, shared familial environmental effects, and unique individual environmental effects.

Models were fitted using MX[24] to examine genetic and environmental contributions to the risk of developing depression. Thresholds for the underlying liability were allowed to differ for men and women, since there are prominent sex differences in the population prevalence of depression. The full model included additive genetic effects (A), unique (nonshared) individual environmental effects (E), and either shared family environmental effects (C) or dominant genetic effects (D), estimated separately for men and women. Simpler models were then fitted that included only additive genetic and individual environmental contributions (AE model), shared environmental and individual environmental contributions (CE model), or individual environmental contributions (E model) to depression. The fit of these models was assessed by a goodness-of-fit χ^2 test. Parameters for genetic and environmental contributions were estimated, and 95% confidence intervals (CIs) for these estimates were computed for the full model.[25]

After genetic and environmental contributions were estimated independently for men and women, parameters were constrained to be equal to test for differences in genetic and environmental contributions to the risk of developing depression by sex. Models were evaluated by a goodness-of-fit χ^2 test. This was done for each definition of major depressive disorder. Subsequently, we fit models for sex-specific gene effects, that is, for a genetic correlation between genetic effects in opposite-sex siblings for each definition of depression; however, the power to detect any differences was low and CIs ranged from 0 to 1.

Finally, depression was modeled as a single underlying liability to determine whether genetic and environmental effects contributed similarly to the risk of developing narrowly and broadly defined depression. Depression was modeled as a 4-point scale (unaffected, *DSM-III-R* major depressive disorder, *DSM-IV* major depressive disorder, and severe *DSM-IV* major depressive disorder) by setting a multivariate threshold model[26] with 3 different thresholds corresponding to the 3 different diagnostic criteria for depression. A poor fit of the model would be consistent with significantly different genetic and environmental influences contributing to the different definitions of depression. For example, a more severe disease may have a greater genetic contribution compared with a milder form of a disease. A goodness-of-fit χ^2 test was used to evaluate this model of multiple thresholds on a single liability scale.

Table 1. Characteristics of Major Depressive Disorder in Women (N = 3494) and Men (N = 1830)*

	DSM-III-R Major Depressive Disorder		*DSM-IV* Major Depressive Disorder		Severe *DSM-IV* Major Depressive Disorder	
	Women	Men	Women	Men	Women	Men
Lifetime prevalence, %	31.2	23.9	22.4	15.7	9.2	3.4
Cases reporting, %	n = 1090	n = 438	n = 784	n = 287	n = 320	n = 63
Any treatment	66.6	51.8	92.6	79.1	95.0	77.8
Impairment	33.2	40.6	46.2	62.2	50.0	66.7
Hospitalization	8.4	5.7	11.7	8.7	16.9	11.1
No concomitant factors	55.6	60.7	55.1	53.8	53.1	58.7
Concomitant factors	44.4	39.3	44.9	43.2	46.9	41.3
Types of concomitant factors, %	n = 484	n = 172	n = 352	n = 124	n = 150	n = 26
Alcohol use changes	8.2	46.6	18.5	41.9	22.0	38.5
Illicit drug use	4.1	14.5	4.6	14.5	7.3	23.1
Medication use	24.4	19.2	26.7	22.6	36.0	30.8
Serious medical problem	36.4	36.6	41.2	41.9	36.0	30.8
Bereavement	16.5	11.6	10.5	8.9	9.3	3.9
Childbirth	22.0	. . .	20.5	. . .	20.0	. . .

*Subjects can report more than 1 concomitant factor in a major depressive episode. Ellipses indicate not applicable.

and concomitant factors (eg, childbirth, bereavement) for each definition of depression.

Table 2 presents the prevalence and probandwise concordance for monozygotic and dizygotic twins. Tetrachoric correlations are also given. Female monozygotic twins had higher probandwise concordance rates than female dizygotic twins regardless of the diagnostic criteria used. Because monozygotic twins have the same genetic makeup whereas dizygotic twins share on average only half of their genes, a greater probandwise concordance rate in mono-

Table 2. Prevalence and Probandwise Concordance for Major Depressive Disorder

	Monozygotic Female Twins (N = 928 Pairs)			Dizygotic Female Twins (N = 527 Pairs)		
	Prevalence, %	Probandwise Concordance	Tetrachoric Correlation	Prevalence, %	Probandwise Concordance	Tetrachoric Correlation
DSM-III-R major depressive disorder	29.4	0.50	0.47	33.4	0.37	0.09
DSM-IV major depressive disorder	21.0	0.38	0.39	24.0	0.25	0.01
Severe *DSM-IV* major depressive disorder	9.2	0.26	0.41	8.4	0.09	0.03

	Monozygotic Male Twins (N = 395 Pairs)			Dizygotic Male Twins (N = 228 Pairs)		
	Prevalence, %	Probandwise Concordance	Tetrachoric Correlation	Prevalence, %	Probandwise Concordance	Tetrachoric Correlation
DSM-III-R major depressive disorder	23.4	0.34	0.24	26.3	0.30	0.09
DSM-IV major depressive disorder	15.3	0.20	0.12	17.3	0.23	0.14
Severe *DSM-IV* major depressive disorder	3.1	0.16	0.43	4.6	0.10	0.19

	Mixed-Sex Dizygotic Twins (N = 584 Pairs)				
	Males		Females		
	Prevalence, %	Probandwise Concordance*	Prevalence, %	Probandwise Concordance*	Tetrachoric Correlation
DSM-III-R major depressive disorder	22.8	0.29	32.9	0.42	0.18
DSM-IV major depressive disorder	14.9	0.22	24.1	0.36	0.22
Severe *DSM-IV* major depressive disorder	3.4	0.03	9.2	0.12	0.02

**Among men of the mixed-sex dizygotic twins, probandwise concordance is defined as the number of affected brothers of affected women divided by the total number of brothers of affected women. A similar definition is used for women of the mixed-sex dizygotic twins.*

Table 3. Estimates of Additive Genetic (A), Shared (C), and Nonshared (E) Environmental Variance Components for the Full Model of Major Depressive Disorder in Men and Women (95% Confidence Intervals)

	Women			Men		
	A	C	E	A	C	E
DSM-III-R major depressive disorder	0.44 (0.29-0.53)	0.00 (0.00-0.12)	0.56 (0.47-0.65)	0.24 (0.00-0.39)	0.00 (0.00-0.26)	0.76 (0.61-0.91)
DSM-IV major depressive disorder	0.36 (0.15-0.46)	0.00 (0.00-0.16)	0.64 (0.54-0.75)	0.18 (0.00-0.36)	0.00 (0.00-0.27)	0.81 (0.64-0.97)
Severe *DSM-IV* major depressive disorder	0.38 (0.00-0.52)	0.00 (0.00-0.34)	0.62 (0.48-0.78)	0.01 (0.00-0.68)	0.32 (0.00-0.60)	0.68 (0.32-1.00)

zygotic twins is consistent with a genetic contribution to the development of depression. Results were not as straightforward for male twins. Probandwise concordance rates were fairly similar for monozygotic and dizygotic twins, suggesting a smaller or even nonexistent genetic contribution to the development of major depressive disorder in men.

Full genetic and environmental models were fitted to these 3 definitions of depression, and results of the model fitting are displayed in **Table 3** and subsequent model fitting in **Table 4**. For *DSM-III-R* major depressive disorder, although the ACE and ADE models fit the data well, the simplest model to explain the data without a significant worsening of the fit of the model was the AE model for both men and women (likelihood ratio, AE vs ADE model: $\chi^2 = 2.40$, $df = 2$, $P = .30$; AE vs ACE model: $\chi^2 = 0.00$, $df = 2$, $P = 1.00$). The CE model, which postulates that the familial resemblance of twins is due to shared familial environment with no shared genetic effects, could be rejected (likelihood ratio, CE vs ACE model: $\chi^2 = 17.58$, $df = 2$, $P < .01$). Equal genetic and environmental effects for *DSM-III-R* major depressive disorder in men and women were then modeled by constraining parameter estimates to be equal across sexes. This model also could be rejected (likelihood ratio, separate parameter estimates for men and women vs equal parameter estimates for men and women, AE model: $\chi^2 = 5.0$, $df = 1$, $P = .03$). Thus the magnitude of the genetic and environmental contributions to the development of depression in men and women were significantly different.

Data for *DSM-IV* major depressive disorder also were fitted with the ACE and ADE models. The simplest model to explain the data was again the AE model; that is, a model with additive genetic and unique environmental effects contributing to the development of depression (likelihood ratio, AE vs ADE model: $\chi^2 = 1.51$, $df = 2$, $P = .47$; AE vs ACE model: $\chi^2 = 0.00$, $df = 2$, $P = 1.00$). Family resemblance was not solely explained by shared environmental influences (likelihood ratio, CE vs ACE model: $\chi^2 = 8.71$, $df = 2$, $P = .01$). Parameter estimates were again constrained to be equal for men and women. The model of similar genetic and environmental contributions for men and women to the development of *DSM-IV* major

Table 4. Model Fitting Genetic and Environmental Estimates of Additive Genetic (A), Dominant Genetic (D), Shared (C), and Nonshared (E) Environmental Variance Components for Major Depressive Disorder in Men and Women*

	Women				Men					
	A	C	D	E	A	C	D	E	χ^2	*df*
DSM-III-R major depressive disorder										
ACE Model	0.44	0.00	. . .	0.56	0.24	0.00	. . .	0.76	11.08	5
ADE Model	0.11	. . .	0.36	0.53	0.14	. . .	0.12	0.74	8.65	5
AE Model	**0.44**	. . .	. . .	**0.56**	**0.24**	. . .	. . .	**0.76**	11.05	7
CE Model	. . .	0.33	. . .	0.67	. . .	0.15	. . .	0.85	28.66	7
AE Model†	0.39	. . .	. . .	0.61	. . .	. . .	. . .	. . .	16.05	8
DSM-IV major depressive disorder										
ACE Model	0.36	0.00	. . .	0.64	0.18	0.00	. . .	0.81	11.71	5
ADE Model	0.10	. . .	0.29	0.62	0.12	. . .	0.06	0.81	10.19	5
AE Model	0.36	. . .	. . .	0.64	0.19	. . .	. . .	0.81	11.70	7
CE Model	. . .	0.26	. . .	0.74	. . .	0.14	. . .	0.86	20.42	7
AE Model†	**0.31**	. . .	. . .	**0.69**	. . .	. . .	. . .	. . .	14.31	8
Severe *DSM-IV* major depressive disorder										
ACE Model	0.38	0.00	. . .	0.62	0.01	0.32	. . .	0.68	6.22	5
ADE Model	0.00	. . .	0.40	0.60	0.41	. . .	0.01	0.58	4.53	5
AE Model	0.37	. . .	. . .	0.63	0.37	. . .	. . .	0.63	6.63	7
CE Model	. . .	0.29	. . .	0.71	. . .	0.19	. . .	0.81	12.55	7
AE Model†	0.37	. . .	. . .	0.63	. . .	. . .	. . .	. . .	6.63	8
AE Model Women/E Model Men	**0.38**	. . .	. . .	**0.63**	. . .	. . .	. . .	**1.00**	9.97	9

*The simplest model to explain the data is indicated in boldface type. Ellipses indicate not applicable.
†Equal estimates for men and women.

depressive disorder could not be rejected (likelihood ratio, separate parameter estimates for men and women vs equal parameter estimates for men and women, AE model: $\chi^2 = 2.61$, $df = 1$, $P = .11$).

The ACE and ADE models fit the data well for severe *DSM-IV* major depressive disorder. For both men and women, the AE model fit the data without a significant deterioration of the fit of the model (likelihood ratio, AE vs ADE model: $\chi^2 = 2.10$, $df = 2$, $P = .35$; AE vs ACE model: $\chi^2 = 0.00$, $df = 2$, $P = 1.00$) and the CE model was rejected (likelihood ratio, CE vs ACE model: $\chi^2 = 6.33$, $df = 2$, $P = .04$). The model could be further simplified and for men, a significant familial resemblance could not be detected though there was a trend for familial clustering (likelihood ratio, AE vs E model for men: $\chi^2 = 3.34$, $df = 1$, $P = .07$). However, the lifetime prevalence of a severe depressive syndrome was low in men, and the statistical power to model familial resemblance was weak. In fact, a model of equal genetic and environmental parameter estimates for men and women also could not be rejected (likelihood ratio, separate parameter estimates for men and women vs equal parameter estimates for men and women, AE model: $\chi^2 = 0.00$, $df = 1$, $P = 1.00$).

Finally, when depression was analyzed as a disorder with a normal liability distribution and thresholds corresponding to mild, moderate, and severe cases, there was a reasonable fit of the model ($\chi^2 = 47.17$; $df = 41$; $P = .23$). Thus, the assumption of equal genetic and environmental contributions to broad and narrow forms of depression was not rejected.

COMMENT

The purpose of this study was to examine the contributions of genetic and environmental influences in the development of major depressive disorder in a community-based sample of male and female twins.

IS THERE FAMILIAL AGGREGATION OF DEPRESSION FOR BOTH MEN AND WOMEN AND, IF SO, IS THERE A GENETIC CONTRIBUTION TO THE DEVELOPMENT OF DEPRESSION?

Using 3 different definitions, we examined the familial aggregation of major depressive disorder. In women, major depressive disorder, regardless of definition, aggregated in families and this familial clustering was best explained by shared genetic factors in the family as opposed to shared family environment. In men, there was also familial clustering of *DSM-III-R* and *DSM-IV* major depressive disorder; however, this clustering was not as pronounced as in women. This translated into lower concordance rates among male relatives, so that men related to an individual with major depressive disorder had a lower relative risk of developing major depressive disorder compared with women, even after taking into account sex differences in population prevalence. As in women, the familial aggregation of depression in men was best explained by shared genetic influences.

The narrowest definition of depression, severe *DSM-IV* major depressive disorder, showed no significant familial aggregation for men. That is, in our data set, the liability to develop a severe major depressive episode could be explained solely by unique environmental influences in men. However, this does not mean that there were no familial factors in the development of a severe major depressive episode in men. Instead, a more likely explanation is that our ability to detect familial influences, either genetic or environmental, was low given the decreased prevalence (3.4%) of severe depressive epi-

sodes in men. Twin studies have decreased in power when examining less-common disorders,[27] and the ability to accurately estimate heritability is low.

Regardless of the definition of depression, unique environmental experiences played the strongest role in the development of major depressive disorder for both men and women. However, the environmental parameter estimate included both an estimate of environmental influences on the development of depression and measurement (diagnostic) error, and measurement error can reduce heritability estimates. For example, Kendler et al[28] found that assessing subjects at 2 time points can reduce error in diagnosis and subsequent model fitting resulted in major depressive disorder having high estimates of heritability but moderate measurement reliability.

IS THE GENETIC CONTRIBUTION TO THE DEVELOPMENT OF DEPRESSION SIMILAR IN MEN AND WOMEN?

Though genetic factors contributed to the development of *DSM-III-R* major depressive disorder in both men and women, the magnitude of these contributions differed between sexes. Genetic factors accounted for a significantly greater proportion of the liability to develop *DSM-III-R* major depressive disorder in women compared with men. Genes also contribute to the development of *DSM-IV* major depressive disorder, and there was a trend for the relative contribution of genetic factors in the development of depression to be greater in women compared with men for *DSM-IV* major depressive disorder. However, the model of equal genetic contributions was not rejected.

For the most stringent definition of depression, severe *DSM-IV* major depressive disorder, there was evidence of genetic factors in the development of depression in women but not in men, also implicating that the magnitude of genetic contributions differs between sexes for this disorder. However, the model of equal genetic contributions again was not rejected.

DOES THE PROPORTION OF THE GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO DEPRESSION DIFFER FOR BROADLY AND NARROWLY DEFINED DEPRESSION?

When we examined the effect of narrowing the definition of depression on the magnitude of genetic and environmental contributions to the development of depression, there was little change in the heritability of major depressive disorder. Results of fitting a multiple-threshold model also did not suggest differential heritability or different genetic and environmental determinants of broadly and narrowly defined depression. In women, genetic effects explained between 36% and 44% of the variance. In men, the heritability estimates for depression had more variation, ranging from 1% for the narrowest definition of depression to 24% for the broadest definition. However, these estimates had extremely wide CIs owing to the lower prevalence of depression in men, and thus there may be no true differences in heritability for broadly or narrowly defined depression.

Overall, these results agree with those from the study by Kendler et al[11] of a general population of Virginia female twins. We obtained similar lifetime prevalences for major depressive disorder (31% for both studies) and estimates of heritability (42% heritability for Kendler et al vs 44% in this study). The extension of the Virginia twin study[14] to include male twins found a somewhat lower prevalence of major depressive disorder in men (16.4% for Kendler et al vs 24% in this study) and higher heritability (39% vs 24%, respectively). Although the Virginia twin study concluded that genetic risk factors were not the same for men and women, the magnitude of genetic effects was equal. This differs from our finding of a greater genetic influence in the development of depression in women as compared with men. Our findings were also consistent with a recent study by Lyons et al.[12] Though our population prevalences for *DSM-III-R* major depressive disorder in men differed (9% for Lyons et al vs 24% in this study), heritability estimates were reasonably similar (36% heritability for Lyons et al vs 24% in this study). Comparable methods were used in these studies—all studied community-based samples, used personal semi-structured interviews, and blinded interviewers for assessments.

These results more strongly differ from those reported in 2 clinically ascertained twin studies.[10,13] Both studies reported no sex differences in heritability and much higher estimates of heritability (60%[10] to 70%[13] heritability). Though both studies had a large number of clinically ascertained twin pairs (217 clinically ascertained pairs of 486 total pairs[10] and 177 clinically ascertained pairs[13]), their power to detect modest sex differences in heritability was likely low. Both studies had several important methodological differences from the current study that may contribute to differences in findings. In the study by Kendler et al,[10] twins were clinically ascertained and matched with a population-based control group, assessments were done by questionnaire, and both major depressive disorder and bipolar disorder were combined in the analyses. In the report by McGuffin et al,[13] twins were also clinically ascertained, population estimates of lifetime rates of major depressive disorder were used, assessments were a synthesis of personal interviews when available and medical records, and some assessments were not blinded. The simple explanation that twins recruited from a treatment setting for depression had a more severe syndrome and thus a more heritable syndrome cannot explicate the differences in heritability estimates, since we found no increase in heritability with a more stringent definition of depression.

An explanation for the difference in heritability between the McGuffin et al[13] study and the current report may be that different estimates of lifetime rates of major depressive disorder were used in the analyses. McGuffin et al used an estimated population prevalence of *DSM-IV* major depressive disorder of 8.4% for women and 3.5% for men. In contrast, this study used the prevalence derived from the sample for the genetic analyses (22.4% in women and 15.7% in men). As noted by McGuffin et al, when estimates of lifetime prevalences of major depressive disorder obtained in the US National Comorbidity Study were used (21% in women and 13% in men), the heritability of depression decreased to 48%.

Limitations of this study include that it is a volunteer sample of Australian twins, telephone interviews were done, and equal environment assumptions for monozygotic and dizygotic twins must be made. First, although this is a volunteer sample, it nonetheless contains individuals with a broad range of educational and socioeconomic levels. Our analyses did not include an assessment of the effect of these variables on development of depression; previous analyses showed no effect on other disorders such as alcohol dependence.[19] Telephone interviews were performed because of the large and geographically diverse population and several studies support the comparability of telephone and face-to-face interviews.[11,29] Finally, the classic twin study assumes that monozygotic and dizygotic twins are treated equally in their homes so that familial differences are related to genes alone. Another report studied this assumption of equal environments in the development of depression and found that it is unlikely to cause significant bias.[30]

In conclusion, major depressive disorder aggregates in families and this clustering is best explained by shared genetic factors and unshared family environment. Our results also suggest that, at least for a broad definition of depression, there are sex differences in the magnitude of genetic contributions to depression, with stronger genetic influences in the development of depression in women. Finally, depression can be viewed as a disorder along a liability continuum, with similar genetic and environmental factors effecting a broad to a narrow definition of depression.

Accepted for publication February 23, 1999.

This work was supported in part by grants MH14677, AA00231 (Dr Bierut), AA07535, AA07728, and AA10249 (Dr Heath) from the US Public Health Service, Washington, DC, and by grants 941177 and 971232 (Dr Martin) from the Australian National Health and Medical Research Council, Canberra.

Presented in part at the annual meeting of the American Psychiatric Association, San Diego, Calif, May 19, 1997.

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