Genetic Epidemiology of Major Depression: Review and Meta-Analysis

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Objective: The authors conducted a meta-analysis of relevant data from primary studies of the genetic epidemiology of major depression.

Method: The authors searched MEDLINE and the reference lists of previous review articles to identify relevant primary studies. On the basis of a review of family, adoption, and twin studies that met specific inclusion criteria, the authors derived quantitative summary statistics.

Results: Five family studies met the inclusion criteria. The odds ratios for proband (subjects with major depression or comparison subjects) versus first-degree relative status (affected or unaffected with major depression) were homogeneous across the five studies (Mantel-Haenszel odds ratio=2.84, 95% CI=2.31–3.49). No adoption study met the inclusion criteria, but the results of two of the three reports were consistent with genetic influences on liability to major depression. Five twin studies met the inclusion criteria, and their statistical summation suggested that familial aggregation was due to additive genetic effects (point estimate of heritability of liability= 37%, 95% CI=31%–42%), with a minimal contribution of environmental effects common to siblings (point estimate=0%, 95% CI=0%–5%), and substantial individual-specific environmental effects/measurement error (point estimate=63%, 95% CI=58%–67%). The literature suggests that recurrence best predicts the familial aggregation of major depression.

Conclusions: Major depression is a familial disorder, and its familiality mostly or entirely results from genetic influences. Environmental influences specific to an individual are also etiologically significant. Major depression is a complex disorder that does not result from either genetic or environmental influences alone but rather from both. These findings are notably consistent across samples and methods and are likely to be generally applicable.

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Major depression, a common (1–4), costly (5), and recurrent disorder (6), is associated with considerable morbidity (7–10) and excess mortality (11). Major depression has been projected to become the second leading cause of disability worldwide by 2020 (second to ischemic heart disease) (12). Moreover, major depression is of increasing importance in clinical psychiatry (13).

There are many primary studies of the genetic epidemiology of major depression, and a number of excellent reviews are available (14–17). However, to our knowledge, no single source has provided a quantitative summation of these data, which have been gathered through considerable effort by many teams of researchers worldwide over the past three decades. We believe that this area of research is sufficiently mature to warrant meta-analysis.

This synthetic meta-analysis addressed three questions. First, to what extent is major depression familial? Second, if major depression is familial, what are the relative contributions of genes and environment in the etiology of the disorder? Third, are there clinical features of major depression that predict familial aggregation?

Method

The key advantage of synthetic meta-analysis over traditional literature review is the potential to yield a less biased quantitative summary of the findings of many primary empirical studies (18–21). In performing this meta-analysis, we attempted to apply principles similar to those customarily applied to considerably larger bodies of literature (e.g., randomized clinical trials for common medical illnesses such as myocardial infarction).

First, to identify all relevant primary studies, we performed computerized MEDLINE searches for an inclusive list of descriptors and searched the reference lists of prior reviews of major depression to identify any reports that were not retrieved in the MEDLINE search. Second, we created an a priori set of criteria for studies' inclusion in the meta-analysis. To be included, a study had to possess features essential to interpretability, such as 1) explicit distinction between unipolar major depression and bipolar disorder, 2) systematic proband recruitment and ascertainment of relatives, 3) direct collection of diagnostic data from all or nearly all subjects (by using direct interview or, in one instance [22], by using questionnaires), 4) use of operationalized diagnostic criteria, and 5) diagnostic determination by assessors who were blind to ascertainment source and diagnoses of other relatives. For family studies, we also required a comparison group that was studied in a similar manner. For twin studies, we also required that zygosity was estimated with reasonable accuracy and blind to diagnoses.

More than half of the extant family and twin studies did not meet one or more of these criteria (most were unblinded and/or uncontrolled). If relative or co-twin diagnoses are assigned without "blindfolding," it is impossible to know the degree to which the results are contaminated by experimental bias. For archival purposes, we provide the citations for the family (23–30) and twin studies (31–34) that were not included.

We considered each family study as a two-by-two contingency table of proband diagnosis (major depression or comparison) versus relative diagnosis (affected or unaffected with major depression), with the odds ratio as a summary statistic (35). Assuming a fixed-effects model, each of the two-by-two tables for the five family studies forms a stratum. To pool these data, we used the Mantel-Haenszel method after first assessing the homogeneity of the data with the Breslow-Day chi-square test (21, 36).

No adoption study met our inclusion criteria, so the three published reports were considered qualitatively. We include these reports for three reasons. First, adoption studies have a fundamentally different set of assumptions than do twin studies. Consistent results from adoption and twin studies increase the likelihood that the conclusions more accurately reflect an underlying reality. Second, although adoption studies are theoretically elegant, they contain a host of practical and ethical difficulties: adoption studies are rather rare, and there may be few additional adoption studies of major depression in the future. Third, the results of adoption studies of major depression are often described in the literature as ambiguous or inconsistent with family and twin studies; we believe that this interpretation is incorrect.

For the twin studies, we first used structural equation modeling to perform univariate analysis of the primary studies (37). Briefly, by comparing the similarity of monozygotic twins with the similarity of dizygotic twins, it is possible to partition the variance in liability (38) to major depression into three components: additive genetic influences (a^2), environmental influences shared by members of a twin pair (c^2), and environmental influences specific to one or the other member of a twin pair (e^2). (The abbreviations a^2, c^2, and e^2 refer to quantitative estimates of the three components.) We used the structural equation modeling package Mx (39, 40) for these analyses. These statistical models can be fit to the raw contingency table data, and 95% confidence intervals (CIs) can be calculated for the relevant parameters (41). Mx is available on the World Wide Web at http://views.vcu.edu/mx.

After computing the estimates for each study, we created a more complex model that included the data from all of the twin studies. This model necessitated a series of assumptions: that prevalences of major depression were similar across studies, that the prevalences among monozygotic and dizygotic twins were similar, that the model parameters could be equated across studies, and that the data were similar across ascertainment methods and gender. We tested these assumptions by using the likelihood ratio chi-square difference test. For these tests, we in effect compared two models. For example, one model might allow a set of parameters to vary freely across studies, generating a goodness-of-fit chi-square with a certain number of degrees of freedom. A submodel might constrain these parameters to be equal, generating a goodness-of-fit chi-square with fewer degrees of freedom. The difference between the chi-square values of these two models is also a chi-square test. If the chi-square difference is large, the model fit worsens when moving from the unconstrained model to the submodel, indicating that the submodel provides a poorer representation of the data. On the other hand, a small chi-square difference suggests that the submodel provides a reasonable representation of the data.

On the basis of prior data about the biology of twinning (i.e., that monozygotic twins are, for most purposes, genetically identical and that dizygotic twins share half of their genes identical by descent) and assuming that etiologically relevant environmental factors are similar across monozygotic and dizygotic twins, a set of expectations can be generated. Comparing the experimental data to these expectations allows assessment of the goodness-of-fit of the observed data to the expectations.

Results

Familial Aggregation

Family studies can be conceptualized as a type of case-control study, as described in detail elsewhere (42, 43). In these studies, probands have major depression and comparison subjects have no history of major depression and are usually matched with probands on potentially confounding variables such as age and gender, and the outcome of interest is the prevalence of major depression in biological relatives (usually first-degree relatives).

Table 1 summarizes data from the five family studies of major depression that met our inclusion criteria for the meta-analysis (44–48). Only the study by Gershon et al. (44) did not match comparison subjects to probands by age and gender. All five studies showed evidence in support of the familial aggregation of major depression in probands, compared with comparison subjects. Across the five studies, there was strong evidence for an association between major depression in the proband and major depression in first-degree relatives (χ^2=97.7, df=1, p<0.00005). In addition, the hypothesis that the odds ratios were homogeneous across the five studies could not be rejected (Breslow-Day χ^2=5.22, df=4, p=0.27), and the summary Mantel-Haenszel odds ratio across the five studies was 2.84 (95% CI=2.31–3.49). Thus, in aggregate, these five studies provided strong and consistent evidence in support of the familiality of major depression.

These findings have two important potential limitations. First, all extant studies recruited most or all subjects with major depression from clinical sources. If having a family history of major depression increases the chance of clinical referral, then the overall odds ratio will be biased upward. One study did not find evidence for this potential bias (48), although two others did (49, 50). The overall impact of this potential bias is unclear, although it may not materially alter the conclusions (49).

Second, screening comparison subjects for the presence of psychopathology (other than major depression) generally leads to lower morbidity risks of major depression in first-degree relatives in comparison subjects and biases the overall odds ratio upward (51–53). This effect is evident in Table 1, which shows that the two studies with unscreened comparison subjects had lower odds ratios (45, 46) than the three studies with comparison subjects who were screened for psychopathology (44, 47, 48). When the data were analyzed more formally, there were indications (of marginal statistical significance) that the odds ratios from studies with screened and unscreened comparison samples were heterogeneous (Breslow-Day χ^2=3.75, df=1, p=0.053). However, it is critical to note that although the summary Mantel-Haenszel odds ratio from the studies

TABLE 1. Results of Family Studies of Major Depression

Study	Country	Subjects With Major Depression		Comparison Subjects			
		Source of Subjects	Morbidity Risk[a]	Source of Subjects[b]	Morbidity Risk[a]	Odds Ratio[c]	95% CI
Gershon et al., 1982 (44)	United States	Clinical setting	16.6	Screened medical patients	5.8	3.23	1.59–6.58
Maier et al., 1993 (45)	Germany	Clinical setting	21.6	Unscreened general population	10.6	2.32	1.62–3.33
Tsuang et al., 1980 (46)	United States	Clinical setting	15.2	Unscreened surgical patients	7.5	2.21	1.35–3.62
Weissman et al., 1984 (47)[d]	United States	Clinical setting	17.6	Screened general population	5.9	3.41	2.23–5.20
Weissman et al., 1993 (48)[e]	United States	Clinical plus general population	21.0	Screened general population	5.5	4.57	2.43–8.60

[a] Morbidity risk of major depression in first-degree relatives calculated by using the Strömgren method, except for studies by Maier et al. (45) and Weissman et al. (48), which used proportional hazards analysis.
[b] Screening excluded subjects with any diagnosed lifetime psychopathology.
[c] Summary Mantel-Haenszel odds ratio=2.84, 95% CI=2.31–3.49.
[d] Subjects with major depression included subjects with severe and mild major depression. Some subjects were also included in the group studied by Gershon et al. (44).
[e] Subjects had early-onset (age ≤30 years) major depression. Fifty-eight percent of subjects with major depression were drawn from the general population, and 42% from clinical sources.

with screened comparison samples was greater (odds ratio=3.62, 95% CI=2.65–4.97), the summary odds ratio from the unscreened studies (odds ratio=2.38, 95% CI=1.78–3.17) was still significantly greater than 1. Hence, even if screening comparison subjects for psychopathology results in bias toward greater familiality of major depression, the basic conclusion that major depression is familial appears to be correct.

Taken together, these methodologically rigorous studies demonstrate that major depression is a familial disorder (i.e., that it "runs" in families). Family studies cannot, however, distinguish genetic influences from environmental risk factors that are also familial. Accomplishing this aim requires other methodological approaches.

Genetic and Environmental Influences

Adoption and twin studies are the two principal approaches to delineating genetic and environmental effects in humans. Adoption studies are social quasi-experiments in which the offspring of one set of parents are reared from early in life by unrelated strangers. In contrast, twin studies are biological quasi-experiments that contrast genetically identical monozygotic twins with dizygotic twins who share many environment features while sharing half their genes on average. One analytic approach to adoption and twin data yields a partition of the etiological sources of variation into three types of causes. These are additive genetic effects, environmental effects common to both members of a twin pair, and environmental effects unique to an individual. The approach is described briefly (54) and in detail elsewhere (17, 37).

Adoption studies. The three adoption studies of major depression that we are aware of (55–57) did not meet our inclusion criteria for the meta-analysis, for the following reasons.

The study by von Knorring et al. (55) did not find evidence for a genetic influence on major depression. However, the diagnoses of major depression in that study were based on indirect sources (i.e., sick leave registrations and evidence of clinical treatment) that may underestimate the true lifetime prevalence of major depression, as only a subset of those with major depression seek treatment (58, 59). The odds ratio from this matched design was 0.71 (95% CI=0.16–2.94) (35, pp. 209–211).

The study by Cadoret et al. (56) had markedly limited data on biological parents and limited statistical power. This study is widely regarded as not supporting the hypothesis of genetic influences on major depression because the results were nonsignificant when they were analyzed separately by gender. However, the trend-level relationship evident in both genders became significant when the data were combined (χ^2=3.87, df=1, p=0.05; odds ratio=2.54, 95% CI=1.00–6.47, calculations ours).

The large study by Wender et al. (57) found evidence for a genetic effect on the transmission of major depression (χ^2=4.73, df=1, p=0.03; odds ratio=7.24, 95% CI=1.21–43.20). However, the diagnoses of major depression in that study were based on indirect sources rather than personal interviews.

In summary, two of these three adoption studies provided qualitative evidence consistent with the existence of significant genetic factors in the etiology of major depression.

Twin studies. The data from the twin studies of major depression that met our inclusion criteria are summarized in Table 2. At the time of this writing, the twin data and the principal Mx script are available on the World Wide Web at http://views.vcu.edu/pub/mx/examples/mdreview. More than 21,000 individuals have been included in these studies, and, notably, all of the studies used the DSM-III-R criteria for major depression. Four studies included community samples (22, 60–62), and two included clinical samples (22, 63). The original paper by Kendler and Prescott (61) has been amended (64), and the amended rather than the original data were analyzed for this report. Two published reports are not shown in Table 2. The limited data presented in one of those reports, by Andrews et al. (65), precluded critical evaluation of the claim that there were no important genetic effects for major depression. In addition, their sample partially overlapped with the larger

TABLE 2. Estimates of Concordance for Major Depression and of the Components of a Full Model of Variance in Liability to Major Depression From Studies of Male and Female Twins[a]

Source of Subjects	Study	Country	Subjects' Sex	Concordance[b]		Tetrachoric Correlation		Components of Full Model of Variance in Liability to Major Depression[c]					
				Monozygotic	Dizygotic	Monozygotic	Dizygotic	a^2	95% CI	c^2	95% CI	e^2	95% CI
Community	Bierut et al., 1999 (60)	Australia	Male	0.34	0.30	0.24	0.09	24	0–39	0	0–26	76	61–91
			Female	0.50	0.37	0.47	0.09	44	29–53	0	0–12	56	47–65
Community	Kendler et al., 1995 (22)[d]	Sweden	Male	0.40	0.33	0.57	0.39	57	0–96	2	0–73	41	4–100
			Female	0.67	0.32	0.82	0.24	78	18–94	0	0–42	22	6–55
Community	Kendler and Prescott, 1999 (61)	United States	Male	0.41	0.34	0.32	0.12	31	5–41	0	0–22	69	59–79
			Female	0.47	0.43	0.39	0.17	38	1–50	0	0–31	62	50–75
Community	Lyons et al., 1998 (62)[e]	United States	Male	0.23	0.14	0.37	0.13	36	11–47	0	0–20	64	53–75
Clinical setting	Kendler et al., 1995 (22)[d,f]	Sweden	Male	0.50	0.33	—	—	49	0–99	21	0–89	30	1–93
			Female	0.32	0.20	—	—	17	0–55	0	0–38	83	45–83
Clinical setting	McGuffin et al., 1996 (63)[f]	United Kingdom	Male	0.46	0.15	—	—	58	4–81	0	0–40	42	19–72
			Female	0.46	0.22	—	—	38	14–61	0	0–24	62	39–86
Summary[g]	Full model							37	31–42	0	0–5	63	58–67
	Best-fitting model							37	33–42	—	—	63	58–67

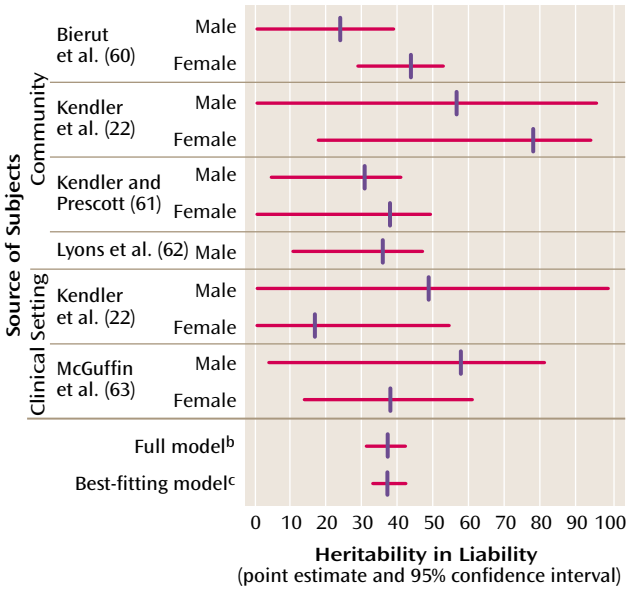
[a] These data are available on the World Wide Web at http://views.vcu.edu/pub/mx/examples/mdreview.
[b] Probandwise concordance in studies with community as source of subjects; pairwise concordance in studies with clinical settings as source of subjects.
[c] In the full model, a^2=proportion of variance due to genetic effects, c^2=proportion of variance due to shared environmental effects, and e^2=proportion of variance due to individual-specific environmental effects plus measurement error.
[d] Unipolar "intermediate" major depression diagnoses determined on the basis of responses to mailed questionnaire.
[e] Vietnam era twin registry, which included twin pairs concordant for military service from 1965 to 1975.
[f] Modeling assumes lifetime prevalence of major depression of 12.7% for males and 21.3% for females, as determined in the National Comorbidity Survey (4). Kendler et al. (22) and McGuffin et al. (63) used different lifetime prevalence estimates and reported different parameter estimates.
[g] Summary full model consists of the aggregate values across studies of a^2, c^2, and e^2. The best-fitting model consists of aggregate values across studies of a^2 and e^2.

sample studied by Bierut et al. (60). We present the most recent data from the longitudinal cohort first reported by Kendler et al. (3).

The results from the community and clinical studies summarized in Table 2 (also depicted in Figure 1) broadly support five conclusions. First, consistent with theoretical work on the statistical power of the classic twin study for discrete traits like major depression (66), the 95% CIs for the parameter estimates from these twin studies were fairly broad. One key purpose of a meta-analysis is to combine data across studies in an attempt to narrow the CIs on a parameter and thereby to increase precision. Second, the CIs for a^2 (heritability in liability) did not include 0 for seven of 11 of these studies, suggesting that the aggregate value of a^2 across the studies would be nonzero. Third, the 95% CIs for c^2 (proportion of trait variance due to shared environmental factors) included 0 in all of the twin studies, indicating that environmental influences shared by members of a twin pair are unlikely to have substantial impact on the liability to major depression. Fourth, heritability point estimates from community and clinically ascertained samples were not markedly discrepant. Finally, there were no consistent gender differences across the twin studies.

Before summary estimates of these twin data could be generated, it was necessary to test a number of critical hy-

FIGURE 1. Estimates of the Heritability in Liability to Major Depression in Studies of Male and Female Twins[a]



[a] Vertical bars indicate point estimates; horizontal bars indicate 95% confidence intervals.
[b] Aggregate values across studies of heritability in liability to major depression.
[c] Most parsimonious submodel, consisting of aggregate value across studies of a^2.

potheses and assumptions under which the data might be combined. First, it was necessary to allow the individual studies to have different major depression liability thresholds (i.e., prevalences) because equating the thresholds across studies led to an enormous worsening of the fit of the statistical model (χ^2=739.5, df=10, p≈0). Possible explanations for these differences include cross-cultural differences in major depression prevalence (67), age cohort effects (2), and differences in diagnostic approaches. Second, unexpectedly, it was necessary to allow same-sex dizygotic twins to have higher liability thresholds for major depression than same-sex monozygotic twins because equating the thresholds led to a worsening of the fit of the statistical model (χ^2=31.96, df=7, p=0.00004). Slight monozygotic-dizygotic differences have been observed for a number of traits; speculations about these findings generally focus on differential recruitment bias or a subtle protective effect of being a particular type of twin. Third, given the higher prevalence of major depression in women than in men, equating the thresholds for opposite-sex dizygotic pairs led to a considerable further worsening of fit (χ^2=47.13, df=2, p<0.0001). Fourth, when we tested whether the a^2, c^2, and e^2 parameters could be equated versus whether it was necessary for them to be free to vary across studies, we found that it was reasonable to equate the parameters (χ^2=7.86, df=8, p=0.45). This was a critical step in the goal of aggregating data from the published twin studies of major depression. Fifth, we also found that it was reasonable to equate the a^2, c^2, and e^2 parameters for studies from clinical and community sources (χ^2=5.10, df=4, p=0.28). Sixth and finally, it was reasonable to equate the a^2, c^2, and e^2 parameters across gender (χ^2= 3.23, df=2, p=0.20).

Although the principal reason for these comparisons was to establish the validity of our meta-analytic procedure, they also allow a substantiative conclusion that is important to our understanding of major depression. Despite the many differences across these twin studies in the prevalence of major depression, ascertainment, methods, ethnicity, and geographic location, the fundamental genetic architecture of major depression appears homogeneous across samples and across gender.

The next step was to generate the 95% CIs of the parameter estimates of the full model (bottom of Table 2 and Figure 1). These CIs suggest that the variance in liability to major depression is mostly due to individual-specific environmental effects (58%–67%) and additive genetic effects (31%–42%), with a negligible contribution by environmental effects shared by siblings (0%–5%). It is critical to note that the individual-specific environment includes the effects of measurement error and gene-environment interactions. As this meta-analysis had particular power to detect common environmental effects, it is notable that these effects accounted for a small proportion of variance.

In addition to estimating parameters under a full model, it is useful to investigate whether simpler models offer a more parsimonious explanation of the data (37). Fitting submodels reduces the number of parameters and leads to narrower CIs. As might be predicted from the summary results in Table 2, the best-fitting and most parsimonious submodel contained only additive genetic (a^2=37%, 95% CI 33%–42%) and individual-specific environmental effects (e^2=63%, 95% CI=58%–67%).

We investigated the heritability of major depression in community and clinical studies separately because of suggestions that clinically ascertained major depression might be "more genetic." Estimates of heritability were similar in subjects ascertained from community (a^2=37%, 95% CI=28%–42%) and clinical (a^2=43%, 95% CI=21%–58%) sources.

Gender. There is strong evidence that the risk of depression is greater in women than in men (67–69). These findings raise two questions. First, is the relative importance of genetic effects in the etiology of major depression the same in males and females? Four studies found no gender difference in heritability (22, 61–63), although one study did (60). Unsurprisingly, our meta-analysis did not find substantial differences in heritability in liability for major depression between men and women. In addition, the adoption study by Cadoret et al. (56) reported similar odds ratios in men (2.5) and women (2.4). Thus, the weight of the evidence suggests similar genetic effects on liability to major depression in males and females.

Second, even if genetic influences are equivalent in males and females, to what extent do these pools of genes overlap? One study estimated the correlation between genetic effects for males and females (r_a) to be 0.57 (61), and another study estimated the correlation to be 1.0 (22). Family data are consistent with partial overlap (70–72). Although the data are limited, the most parsimonious explanation appears to be that men and women share most but not all genetic influences for major depression. Possible reasons for these differences are discussed elsewhere (61, p. 43).

Assumptions. There are several potential threats to the interpretation of these studies. First, the critical equal-environment assumption posits that monozygotic and dizygotic twins are equally correlated in their exposure to environmental events of etiologic relevance to major depression. If this were not true, the greater similarity between monozygotic versus dizygotic twins for major depression could result from environmental and not genetic factors. The equal-environment assumption has been examined repeatedly, and there is considerable evidence supporting its validity for major depression (73, 74). Second, conclusions about major depression from twins may not generalize to singletons if there are protective or risk factors specifically associated with twins. Moreover, twins are distinctive from singletons in a number of potentially important ways (75); however, the incidence of treated major depression is similar in singletons, monozygotic

TABLE 3. Results of Studies of Clinical Indices Associated With Familial Aggregation of Major Depression[a]

Study	Significance of Clinical Index						
	Early Onset	Recurrent	Impairment	Duration	Number of Symptoms	Symptom Pattern	Comorbidity
Cadoret et al., 1977 (79)	*						
Gershon et al., 1986 (80)		*	*				
Kendler et al., 1994 (81)	n.s.[b]	**	*	n.s.	n.s.	n.s.	*[c]
Kendler et al., 1999 (82)	n.s.[b,d]	***	*	**	n.s.	**[e]	
Leckman et al., 1984 (83)						*[f]	
Leckman et al., 1984 (84)						*[g]	
Lyons et al., 1998 (62)	—[h]				—[h]		
McGuffin et al., 1987 (25)	n.s.						
McGuffin et al., 1996 (63)	n.s.	—[h]		—[h]		*[i]	
Mendlewicz and Baron, 1981 (85)	*						
Stancer et al., 1987 (29)	*						
Weissman et al., 1986 (86)	**[b]	n.s.[d]				n.s.	**[j]

[a] A blank cell indicates the study did not investigate the clinical index.
[b] Controlled for age at interview or year of birth.
[c] Bulimia and, separately, panic disorder.
[d] Clinical index was significantly associated with familial aggregation of major depression in univariate but not in multivariate analyses.
[e] Thoughts of death.
[f] Autonomous depression.
[g] Appetite change and guilt.
[h] Heritability in liability to major depression was greater when the study group was stratified by clinical index.
[i] Endogenous depression.
[j] Anxiety disorder and, separately, alcoholism.
*p<0.05. **p<0.01. ***p<0.0001.

twins, and dizygotic twins (see reference 76 for review), as are the mean levels of current depressive symptoms (77).

Finally, some unknown or poorly measured bias may be responsible for the results from twin studies. Estimates of heritability in liability from an alternative design can provide an important cross-check of this possibility. We computed tetrachoric correlations from the results of the controlled family studies of major depression in Table 1 (38). If a set of fairly restrictive assumptions are met, these tetrachoric correlations multiplied by 2 estimate heritability in liability to major depression (78). These assumptions are distinct from those of twin studies' design, and convergent results from different methodological approaches suggest that the assumptions of both methods are problematic or, more parsimoniously, that the results reflect the fundamental nature of major depression. From the family studies summarized in Table 1, the weighted mean heritability in liability to major depression was 58% (95% CI=42%–74%). Given that probands in all family studies were clinically ascertained, this result is in reasonable agreement with the heritability in liability from clinically ascertained twin studies (a^2=43%, 95% CI=21%–58%).

Without recourse to a more formal experimental design, it is not possible to prove that the results from twin studies are uncontaminated by all conceivable biases and violations of critical assumptions. However, given the available data, there is no reason at present to question the validity of the conclusions about major depression from twin studies.

Clinical Indices of Familial Aggregation

Table 3 summarizes data from studies of the clinical indices that predict familial aggregation of major depression (25, 29, 62, 63, 79–86). Given the biases possible with clinical ascertainment (87, 88), it is notable that only a few of these studies were based on community samples (62, 81, 82). Several of these reports are based on partially or wholly overlapping samples (80–84, 86).

Given the diversity of these studies and of the analytic methods used, we are limited to qualitative comparisons. The most widely studied clinical feature is early-onset major depression, although there are two critical conceptual difficulties. First, comparison across studies is problematic, as early onset has been defined in many different ways (e.g., onset at age <30, <32, <36, <40, or <52.2 years). Second, only a few studies (81, 82, 86) controlled for confounding between age at onset and age cohort effects for major depression (89), without which the analyses are difficult to interpret. Among the community-based studies we reviewed, a study of one twin cohort found that age at onset of major depression did not predict familial aggregation (81, 82), but another twin study found that age at onset was related to increased heritability (62). Early onset of major depression predicted increased familial risk in four other studies (29, 79, 85, 86) (only one of these controlled for year of birth [86]), but not in two others (25, 63).

The overall picture for recurrent major depression is clearer: recurrence has predicted familial aggregation in every study in which it was investigated (25, 63, 80–82, 86). In one study, however, recurrence was a significant predictor in univariate but not in multivariate analyses (86). It is critical to note, however, that groups defined by early onset of major depression and by recurrent major depression overlap considerably.

Other clinical features have been found to be associated with increased familiality of major depression. Impairment associated with major depression was a significant predictor of familial aggregation in the three studies in which it was examined (80–82). The duration of the longest

episode was associated with familiality of major depression in two studies (63, 82), but not in an overlapping cohort in a third report (81). Number of symptoms was associated with familiality in one study (62), but not in two others (81, 82). Finally, a number of specific depression symptoms and comorbid disorders have been investigated without the emergence of any clear pattern of results.

In conclusion, recurrent major depression appears to be the subtype of major depression that most consistently identifies increased familial risk. We are aware that early onset of major depression is prominently viewed as the clinical feature associated with familial aggregation (90), although this view is not entirely consistent with findings reported in the literature. Several other features warrant further investigation, including: 1) impairment associated with major depression, 2) atypical major depression with reversed vegetative features (91), 3) mood response to tryptophan depletion (92), and 4) several EEG sleep measures (93).

Discussion

The results of this synthetic meta-analysis of the literature on the genetic epidemiology of major depression support six conclusions.

Findings of the Meta-Analysis

Aggregation of major depression in families. Five large and carefully conducted family studies each demonstrated the familiality of major depression. Aggregating these data yielded a summary odds ratio of 2.84 (95% CI=2.31–3.49).

Genetic influences and familial aggregation. The conclusion that genetic influences are the most important contributor to familial aggregation is supported by two of the three adoption studies and all of the twin studies of major depression we reviewed. The heritability of major depression is likely to be in the range of 31%–42%. This is probably the lower bound, and the level of heritability is likely to be substantially higher for reliably diagnosed major depression or for subtypes such as recurrent major depression. In comparison, the heritabilities of schizophrenia and bipolar disorder are estimated to be approximately 70% (94).

Etiological importance of environmental influences. Environmental influences that are etiologically important appear to be specific to an individual. There was little evidence that environmental influences common to family members (e.g., general parenting style, socioeconomic status, or local environmental qualities) were important. The large sample size of the twin meta-analysis should have afforded reasonable power to detect common environmental effects. If these effects are in fact nonzero, their magnitude is quite small (less than 5%).

Major depression as a complex disorder. Data from the studies we reviewed are consistent with the conceptualization of major depression as a complex disorder (95) that does not result from either genetic or environmental influences alone but rather from both.

Consistency. The consistency of a finding across samples and methodologies is a key element for determining causation (96, 97). In psychiatric research, consistency of research findings has often been elusive. The four conclusions discussed above are remarkably consistent across three quite different methodological approaches (five of five family studies, two of three adoption studies, and all twin studies). In addition, the estimates of heritability in liability from clinically ascertained family and twin studies are quite similar.

Generalizability. The first three conclusions above are likely to generalize to groups other than those studied. The studies included in the meta-analysis used different methodologies and had as subjects men and women from diverse cultures. Yet nearly all supported the same conclusions. This finding is particularly relevant for heritability of liability to major depression, which is a population-specific statistic. When nearly all twin studies suggest essentially the same heritability figure, it is considerably more likely to reflect the fundamental nature of major depression.

Individual-Specific Environment

Measurement error inflates estimates of individual-specific environmental effects (e^2) at the expense of additive genetic (a^2) and/or shared environmental influences (c^2) (37). Measurement error was a concern for all the types of studies discussed here. The test-retest reliability (one type of measurement error) of a lifetime history of major depression has not been impressive in community samples (98, 99), although it has been somewhat higher in clinical samples (100). However, if two or more assessments are conducted over time, measurement error can be parsed out of the analysis (99, 101). In the longitudinal sample of female twins studied by Kendler et al. (3, 61, 99), the heritability of reliably diagnosed major depression was 66% (95% CI=53%–78%) (102). This finding strongly suggests that the true heritability of liability of major depression is substantially greater than the point estimate of 37% reported in Table 2.

Gene-environment interactions have been hypothesized to be of importance in the etiology of major depression. For example, a genetic vulnerability to major depression might be expressed only if an individual is exposed to stressful life events (103). Twin studies generally have poor power to resolve gene-environment interactions, and the presence of these interactions will lead to an increase in the estimate of individual-specific environmental effects. These more complex, but perhaps more likely, etiological pathways could lead to an overall underestimate of the importance of genetic effects in the etiology of major depression.

Clinical Implications

The results of this meta-analysis have implications for how clinicians conceptualize the etiology of major depression and how they might answer the question commonly encountered clinically, What causes major depression? The answer remains regrettably imprecise and has three components: 1) major depression results from both genetic and environmental factors, 2) major depression is heterogeneous, and 3) it is likely that a number of pathways lead to the common endpoint of major depression. Because of the astonishing complexity of major depression—and despite a broad array of research efforts—more precise explanations are not currently possible.

The second implication relates to how clinicians conceptualize the etiology of major depression in a particular patient, as exemplified by the question, Why do I have major depression? Overtly or covertly imbedded in this question is the complex question of who or what is to blame. Although the studies summarized here add weight to our understanding of the etiology of major depression at the level of large groups of individuals, the relevance of these findings to a particular patient is difficult to determine. Indeed, a key task in many types of clinical work—from pharmacological management to intensive psychotherapy—is to develop an individualized understanding of etiology. Our conclusions are relevant, but an important role for the clinician is to attempt to avoid a number of common misinterpretations (see reference 104 for review). The following points may help clinicians in their work with individual patients:

1. Heritability of liability applies to groups, not individuals. We cannot now state with confidence that a particular person's major depression is or is not genetic in origin, much less that some percentage of the disorder is "due to genes."

2. The causation of major depression is probabilistic, not deterministic. If we could measure liability to major depression directly, we would find substantial numbers of people with high liability who are not affected with major depression and people with low liability who are affected. Individuals' life experiences, intentions, choices, and actions are critically important.

3. Environmental influences are important. Even if heritability of liability to major depression is predominant in the etiology of the disorder, environmental events account for substantial portions of the variance in liability. The absence of shared environmental effects does not mean that the influences of parents and other family members are irrelevant. The most parsimonious explanation may be one that is familiar to clinicians: it is not the general qualities of some facet of the environment (e.g., a parent's rearing style, neighborhood, poverty) but rather how these qualities influence an individual and how he or she interacts with this part of the environment across developmental stages.

Research Implications

Although the conclusions summarized above constitute an important step in conceptualizing the nature of major depression, they do not immediately lead to the essential goal of a clear understanding of the pathophysiology of major depression. We submit, however, that these conclusions have the following implications for research on major depression:

1. These conclusions are consistent with efforts to identify susceptibility loci for major depression, as noted in an NIMH report on genetics and mental disorders (www.nimh.nih.gov/research/genetics.htm). We are aware of three major efforts to identify susceptibility loci that began in early 2000 and could yield results within 4–5 years.

2. If certain depressive features (i.e., recurrence) predict familiality of major depression, it may be useful to investigate the rationality of family-based screening as a primary and secondary preventive measure. Moreover, for clinical and biological studies, it may be possible to stratify heterogeneous samples to identify more homogeneous subsamples. Recurrence and family history of major depression are two variables that could be used to stratify samples. However, the most efficient means of obtaining these data (i.e., using the major depression proband as informant) may not be sufficiently sensitive (105–108) to be applied with confidence.

3. The finding that the prevalence of major depression was higher in dizygotic than monozygotic twins was unexpected but intriguing. Possible explanations include differential cooperation in monozygotic versus dizygotic twins in the presence of major depression, a protective effect of being a monozygotic twin, and/or a predisposing effect of being a dizygotic twin.

Limitations

This review has three general limitations. First, there may be published or unpublished family, adoption, or twin studies that were not included in this analysis. We attempted to limit the impact of this problem as described in the Method section. Second, the extant studies focused on predominantly Caucasian subjects from developed nations. It is not known whether the results generalize worldwide or across time cohorts. Third, although it is reassuring that the extant data support the validity of the equal-environment assumption in twin studies of major depression, it is impossible to prove that all potential violations have been assessed. Therefore, we cannot exclude the possibility that a cryptic violation of the equal-environment assumption could influence the results.

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