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Sex Differences in the Pathways to Major Depression: A Study of Opposite-Sex Twin Pairs

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Abstract

Objective—The authors sought to clarify the nature of sex differences in the etiologic pathways to major depression.

Method—Retrospective and prospective assessments of 20 developmentally organized risk factors and the occurrence of past-year major depression were conducted at two waves of personal interviews at least 12 months apart in 1,057 opposite-sex dizygotic twin pairs from a population-based register. Analyses were conducted by structural modeling, examining within-pair differences.

Results—Sixty percent of all paths in the best-fit model exhibited sex differences. Eleven of the 20 risk factors differed across sexes in their impact on liability to major depression. Five had a greater impact in women: parental warmth, neuroticism, divorce, social support, and marital satisfaction. Six had a greater impact in men: childhood sexual abuse, conduct disorder, drug abuse, prior history of major depression, and distal and dependent proximal stressful life events. The life event categories responsible for the stronger effect in males were financial, occupational, and legal in nature.

Conclusions—In a co-twin control design, which matches sisters and brothers on genetic and familial-environmental background, personality and failures in interpersonal relationships played a stronger etiologic role in major depression for women than for men. Externalizing psychopathology, prior depression, and specific “instrumental” classes of acute stressors were more important in the etiologic pathway to major depression for men. The results are consistent with previously proposed typologies of major depression that suggest two subtypes that differ in prevalence in women (deficiencies in caring relationships and interpersonal loss) and men (failures to achieve expected goals, with lowered self-worth).

Because women consistently have a higher rate of major depression than do men (1–5), sex differences in the etiologic pathways to major depression have often been explored (2, 3, 6–10). Most studies have examined single risk factors, such as marital status or quality (5, 11, 12), stressful life events (7), prior anxiety disorders (13), personality (6), and ruminative propensity (9). Given the important etiologic role of genetic and environmental familial factors in major depression (14–18), delineating risk factors that differentiate the sexes would be facilitated by a design controlling for these background variables.

In this study, we examined sex differences in the etiologic pathway to major depression with a wide array of risk factors organized developmentally (19, 20), using a co-twin control

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design in opposite-sex dizygotic twin pairs—the optimal sample for studying sex differences.

Method

Sample

We examined data from a two-wave study of male-male and male-female pairs from the birth-certificate-based Virginia Twin Registry. Twins were eligible if one or both members could be located, were a member of a multiple birth that included at least one male, were Caucasian, and were born between 1940 and 1974 (21). Of 9,417 eligible individuals for wave 1, interviews were completed, typically by telephone, with 6,814 (72.4%). At least 1 year later, we recontacted these participants and completed a wave 2 interview, mostly face-to-face, with 5,629 individuals (82.6% of those eligible). Signed informed consent was obtained prior to all face-to-face interviews, and verbal consent prior to all telephone interviews. Interviewers were clinically trained. Each interview was reviewed twice for completeness. Members of a twin pair were interviewed by different interviewers. To assess reliability, 131 twins were reinterviewed 4.4 months (SD=1.1) after their initial interview.

This analysis is based on the 1,057 male-female pairs in which both members completed both interviews. At the wave 2 interview, the participants' mean age was 37.0 years (SD=9.2), and they had a mean of 13.5 years (SD=2.7) of education.

Outcome Variable

Our model predicted episodes of major depression in the year prior to the wave 2 interview. Major depression was treated as a dichotomous variable, assuming an underlying normal liability. In the wave 2 interview, twins were asked about the occurrence in the past year of 15 symptoms reflecting all DSM-III-R criterion A symptoms for major depressive episode. They then aggregated these symptoms in time, reported the total number of episodes, and dated, to the month, the onset and offset of each episode. We examined the first reported episode that met criteria unless there were multiple episodes and the first episode began in the first 2 months of the year. In that case, we took the next reported episode. Test-retest reliability for past-year major depression was good (kappa=0.74, SE=0.08; tetrachoric r=0.96, SE=0.03).

Model Variables

The variables examined paralleled those in our previous etiologic models for major depression in females (19) and males (20). As we did previously (19, 20), we organized our predictor variables into "tiers" approximating five developmental periods: childhood (familial risk, low parental warmth, childhood sexual abuse, and parental loss), early adolescence (neuroticism, low self-esteem, early-onset anxiety, and conduct disorder), late adolescence (low educational achievement, lifetime traumas, nicotine dependence, and alcohol and drug use disorders), adulthood (divorce, past history of major depression, and low social support), and past year (marital satisfaction, distal stressful life events, and dependent proximal and independent proximal stressful life events). Drug, alcohol, and nicotine dependence were interconnected by residual correlations, as were dependent and independent proximal stressful life events. All variables were treated as binary or ordinal, as the model was too complex to achieve convergence using a mixture of continuous and categorical variables. We defined the categories to maximize power. Details are provided in Appendix I in the data supplement that accompanies the online edition of this article.

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Statistical Methods

We maximized our ability to infer sex differences in the risk for major depression by taking advantage of the male-female paired structure of the data. Our model was constructed with two groups (male and female) so that one member of each complete pair was present in each group. As a result, unmeasured family-level influences, both genetic and environmental, were balanced across the two groups, using a quasi-random design. Therefore, family-level variables not included in our model were necessarily balanced in their effects and could not influence our evaluation of sex differences.

Model fitting was done using Mplus, version 6.11 (22), using weighted least squares. Fit was assessed by Akaike's information criterion (23), and the model was developed path by path, starting with paths from all variables to depressive onset and moving up the model. At each step, three tests were performed: Could the path be fixed to zero in males? Could the path be fixed to zero in females? If both paths were nonzero, could they be constrained to equality? Once every possible path in the model was tested, we repeated these same steps three more times. We utilized three fit indices: the Tucker-Lewis index (24) and the comparative fit index (25), with values ≥0.95 indicating a good fit, and the root mean square error of approximation (26), where ≤0.05 suggested a good fit.

Results

Of the 1,057 male-female twin pairs in our sample, 837 were concordant for no episodes of major depression in the past year. In 12 pairs, both members had depressive episodes. Of the 208 pairs discordant for major depression in the past year, the affected member was female in 130 (62%) and male in 78 (38%). Our best-fit model included 218 free parameters including paths (one-headed arrows in the figures) and correlations (two-headed arrows). It explained 44.5% (SE=3.9) and 48.2% (SE=3.9) of the variance in liability to major depression in females and males, respectively. The model fit indices were very good (comparative fit index=0.99, Tucker-Lewis index=0.99, root mean square error of approximation=0.01). Parameter estimates from the best-fit models are presented in Figures 1 and 2, for females and males, respectively. Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red, and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II in the online data supplement contains the best-fit model estimate for all these paths, along with their statistical significance and the equality or nonequality of that path across sexes. Twenty-eight paths were estimated at zero in males, and 16 in females. This explains the greater density of paths in Figure 1 relative to Figure 2.

Results of our model can be examined in several ways. We illustrate three levels of analysis focused on sex differences in 1) individual paths, 2) all outflow paths from risk variables, and 3) total effect of risk variables on liability to major depression.

Individual Paths

A number of individual paths stood out as having substantial sex differences. For example, the paths from childhood sexual abuse to both conduct disorder and early-onset anxiety disorders were much stronger in males than females (0.41 compared with 0.12, and 0.22 compared with 0.12). The paths from drug use disorders to distal and dependent proximal stressful life events were also much more robust in males than females (0.16 compared with zero, and 0.15 compared with zero). Also, the path from dependent proximal stressful life events to past-year major depression was considerably stronger in males than females (0.37 compared with 0.24).

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Paths from low parental warmth to early-onset anxiety disorders and prior history of major depression were both stronger in females than males (0.07 compared with zero, and 0.10 compared with zero, respectively). The paths from low marital satisfaction and social support to past-year major depression were both considerably more robust in females than males (0.20 compared with zero, and 0.12 compared with zero, respectively).

Risk Factors: Outflow

We next examined sex differences in the outflow of paths from individual risk factors. This is easy to do in the figures by comparing the number of red paths coming from each risk variable in females (Figure 1) with the blue paths coming from these same variables in males (Figure 2). We can simply classify variables into those with more red than blue paths and more blue than red paths emanating from them. Roughly, the former and latter are likely more important contributors to the etiologic pathway to major depression in females and in males, respectively. By this approach, low parental warmth, parental loss, neuroticism, lifetime traumas, divorce, social support, and marital satisfaction contribute more strongly to the pathway to major depression in females. Low self-esteem, drug use disorder, past history of major depression, and distal and dependent proximal stressful life events contribute more strongly to the major depression pathway in males.

Risk Factors: Total Direct and Indirect Paths to Major Depression

The most comprehensive way to compare the risk factors is to examine their total direct and indirect contribution to major depression in females and males. We do this in Table 1, which depicts the total effect of the 20 predictor variables on the liability to major depression in males and females. We divided the 20 variables into four groups. For nine variables, the absolute difference in their total direct and indirect impact on major depression was less than 0.02, which we considered to reflect *minimal* sex differences. For three variables, the absolute value of the difference was between 0.02 and 0.05, which we judged to reflect *modest* sex differences. Four of the variables had an absolute difference between 0.05 and 0.10, which we considered to demonstrate *moderate* sex differences. Finally, four of the variables had an absolute difference >.0.10, which we considered to reflect *strong* sex differences.

Of the three variables with modest sex differences, one had a stronger total effect in females (parental warmth) and two had stronger effects in males (childhood sexual abuse and past history of major depression). We can also trace the paths of these variables to risk for major depression in the two sexes, giving us insight into the differences in etiologic pathways. As seen in Table 1, the difference in the impact of parental warmth was driven by its stronger impact in females on a range of risk factors, including neuroticism, early-onset anxiety, conduct disorder, divorce, past history of major depression, and marital satisfaction. For childhood sexual abuse, the greater impact on risk for major depression in males results from its stronger effect on neuroticism, early-onset anxiety, and conduct disorder. The stronger effect of past history of major depression on males results, at least in part, from its greater effect on independent proximal stressful life events.

Of the four variables with moderate differences, two had stronger effects in females (neuroticism and divorce) and two had stronger effects in males (conduct disorder and drug use disorder). The greater effect of neuroticism on risk for major depression in females was largely mediated through its greater impact in women on risk for alcohol use disorders and dependent proximal stressful life events. The stronger impact of drug use disorder on risk for major depression in males occurred through its stronger effects on past history of major depression, distal stressful life events, and dependent proximal stressful life events. The greater effect of divorce on risk for major depression in females was mediated through its

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stronger impact on social support, marital satisfaction, distal stressful life events, and independent proximal stressful life events.

Four variables in the model had strong sex differences, two of which had more robust effects in females (social support and marital satisfaction) and two in males (distal and dependent proximal stressful life events). These four variables all came from later developmental stages of the model and thus largely had direct effects on risk for major depression.

Specific Classes of Stressful Life Events

The two factors with the strongest impact on males relative to females were dependent proximal and distal stressful life events. To understand in more detail the nature of these sex differences, we examined the impact of the specific categories of stressors in the affected and unaffected members of discordant pairs. We focused on the category of distal stressful life events because it contained the larger total number of events and hence the greater statistical power. Three event categories stood out as having the largest differences in effect size in the affected versus the unaffected twins in the male-affected versus female-affected discordant pairs: financial problems (0.17 and 0.08), work problems (0.12 and 0.03), and legal problems (0.08 and 0.03). That is, the event categories were much more likely to be reported by the affected twin in discordant pairs when it was the male who was affected rather than the female. Of note, two stressful life event categories had a comparable excess in the affected members of the female-affected versus male-affected discordant pairs: relationship problems and serious illnesses in individuals in the twin's close social network (0.24 compared with 0.13, and 0.11 compared with 0.01).

Discussion

We sought to clarify sex differences in the etiologic pathways to major depression as measured in the past year in a sample of 1,057 opposite-sex dizygotic twin pairs ascertained from a population-based registry. We studied a wide array of risk factors, assessed in two personal interviews at least 1 year apart. From these variables, we constructed a developmental path model with the goal of predicting the occurrence of major depression in the year prior to our second interview (19, 20). Most informative for our analyses were the 208 pairs discordant for a depressive episode.

Our best model fit the data very well and explained nearly half of the total variance in risk for major depression in males and females. Using statistical criteria, 60% of the paths in this model differed between the sexes. We suggested three levels at which the results of this model could be usefully examined. The first two utilized visual inspection to detect individual paths with clear sex differences or the risk factors themselves that originated paths with stronger overall effects in females or in males. By these methods it could be seen, for example, that in the earliest tier of developmental risk factors, childhood sexual abuse and low parental warmth had more potent downstream effects in males and females, respectively. In the third developmental tier, drug use disorders stood out as more strongly influencing other risk factors in males. In the fourth tier, divorce and low social support were more robust predictors in females. In the final tier, marital satisfaction had a stronger impact in females, and distal and dependent proximal stressful life events in males.

However, we focused more on a comprehensive statistical view of the individual risk variables that assessed their total direct and indirect contributions to liability to major depression. While producing results broadly similar to those obtained by more informal methods, this approach was both more global and more rigorous. Focusing on total effects, our 20 risk variables for major depression could relatively easily be divided into four groups with no, modest, moderate, and large sex differences. Nine of the variables fell into the first

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category, with quite similar total effects across the sexes. Of the 11 risk factors in the second, third, and fourth groups, five had a stronger total impact in females and six in males.

The five risk variables with a stronger total impact of liability to major depression in women reflected personality and interpersonal relationships. Neuroticism, a widely researched and robust risk factor for major depression (13, 27–30), was, in our sample, over 30% more potent in its impact on major depression in women than in men. Given that the genetic risk factors for major depression and neuroticism are strongly intercorrelated (30–32), our findings are consistent with previous results from this sample (33) and from a large Swedish twin sample (34) indicating that the heritability of major depression is higher in females than males. The other four variables that more potently had an impact on depressive risk in women all reflected the quality and continuity of intimate interpersonal relationships: parental warmth, divorce, social support, and marital satisfaction.

These results are consistent with an extensive literature in the social sciences demonstrating that compared with men, women derive a larger component of their sense of self and self-worth from interpersonal relationships (35–37). Compared with men, women have larger social networks, are more intimate with and emotionally involved with the members of their network, and are more sensitive to adversities experienced by their network (7, 38–40). This point was further supported by follow-up analyses showing that the stressful life events that most differentiated affected females from affected males in discordant twin pairs were events that involved their social network. Furthermore, a number of previous studies have found that the association between social support and psychopathology is stronger in women than in men (41–45).

The six risk variables with a stronger total impact on liability to major depression in men were divisible into three groups, reflecting externalizing psychopathology, prior depressive history, and greater sensitivity to specific stressors. Our results with externalizing psychopathology are consistent with a wide range of studies finding that men have higher rates than women of both conduct disorder and drug abuse (46) and that both of these disorders are associated with a higher risk for major depression (47–52). Our model showed that males had greater sensitivity than females to the depressogenic effects of childhood sexual abuse and stressful life events occurring in the past year. Sexual abuse in females is much more frequently researched than in males, with surprisingly few studies examining the pathogenic effects in males versus females (53–55). One of the few prospective studies of validated sexual abuse, in accord with our findings, reported a stronger association between abuse and major depression in men than in women (56). Males were also more sensitive to the depressogenic effects of recent stressful life events. When we examined the specific categories of these events, the greater male sensitivity was driven by stressors associated with financial, employment, and legal problems. These results are consistent with previous evidence indicating that compared with women, men are more emotionally involved in occupational and financial success (35, 36) and more likely to be both the perpetrators and the victims of crime (57, 58).

At face value, several of our findings are inconsistent with the bulk of previous studies. Most studies have reported either no sex difference in rates of recurrence (1) or a higher risk in females (59), whereas we found that past history was more predictive of risk for major depression in men. We did not replicate earlier evidence that a large proportion of the sex differences in major depression could be explained by prior anxiety disorders (13). Some (60) but not all (7) previous studies, contrary to our model-based results, found that divorce was more depressogenic for men than for women.

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However, our findings are not directly comparable to previous studies, because in our complex model, the impact of individual risk factors occurred in the context of all the other variables in the model. We give one example illustrating the importance of this context. In exploring the origins of the stronger effect in males of distal and dependent proximal stressful life events, we eliminated marital satisfaction from the model. In the full model, this variable much more strongly predicted risk for major depression in females. Its removal nearly equalized the impact of stressful life events on major depression in males versus females. This occurred because low marital satisfaction was strongly correlated with adverse marital stressful life events, especially in women. So with marital satisfaction in the model, the impact of the correlated marital stressful life events in females became much less potent. This in turn was responsible for why stressful life events proved in aggregate a stronger predictor of major depression in males.

Our findings are broadly congruent with a typology of major depression developed from a psychoanalytic perspective by Blatt (61), who noted similarities between his system and those proposed from cognitive-behavioral (62, 63), attachment (64), and interpersonal perspectives (65). Blatt proposed that major depression takes two forms: “anaclitic” and “introjective.” The former arises from deficiencies in caring relationships and unmet dependency needs (e.g., “I am unlovable”), and the latter emerges from the inability to meet internal demands for self-worth and achievement (e.g., “I am a failure”) (61). Males are substantially more likely to suffer from introjective depression and females from anaclitic depression (61). Consistent with our findings, anaclitic depression is strongly associated with parenting deficient in nurturance, and introjective depressions with externalizing psychopathology (61). Congruent with our results, anaclitic depressions are typically provoked by interpersonal difficulties involving rejection and/or failures to achieve expected intimacy, while introjective depressions are related to failures at key instrumental tasks, such as expected work achievements and failures to provide adequately for the family (61).

Limitations

These results should be considered in the context of four potential methodological limitations. First, our model assumes a causal relationship between predictor and dependent variables. The validity of this assumption varies across our model. Some of the intervariable relationships that we assume take the form of A→B may be truly either A←B or, more likely, A↔B.

Second, a number of our risk factors were assessed using long-term memory and may have been influenced by recall bias. Within the limits of a two-wave design with a cohort in mid-adulthood, we minimized this problem by using multiple reporters (i.e., reports from both co-twins on variables such as familial risk, parental warmth), using objective events less susceptible to recall bias (e.g., parental loss, divorce, educational level), assessing key variables prospectively (i.e., at our first interview), and measuring a number of key constructs over the past year (including stressful life events and depressive onsets), reducing the time frame of recall.

Third, our model assumes that multiple independent variables act additively and linearly in their impact on risk for major depression. This is unlikely to be true, as we have shown in this sample (66) that high levels of neuroticism increase sensitivity to the depressogenic effects of stressful life events.

Fourth, this sample consisted of adult white twins born in Virginia. With respect to the rates of psychopathology, twins are probably representative of the general population (67, 68). Our 1-year prevalence rates for major depression in females and males (13.4 and 8.5%,

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respectively) are quite similar to those reported in the National Comorbidity Survey (12.9% and 7.7%, respectively) (46).

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Fictional Cases to Illustrate Sex Differences in Risk Factors for Major Depression

"Mr. Jones" is a 37-year-old married man who in the past year developed his second episode of major depression. Earlier in the year, he had been fired from his job for problems related to his drug abuse. The depression began shortly after he and his wife were forced to file for bankruptcy because of the sharp reduction in family income. Mr. Jones had been sexually abused by a maternal uncle as a child, although he otherwise had a relatively stable upbringing. However, he had a range of conduct disorder symptoms starting in early adolescence. He dropped out of high school and has worked most of his life as a carpenter in a large construction firm. He has had intermittent problems with cocaine since his early 20s. His marriage has been relatively stable, with two children, and he has a good network of friends. His presenting complaints were a sad mood with a range of neurovegetative symptoms and deep feelings of guilt at having failed his family as a provider.

"Mrs. Hanson" is a 28-year-old separated woman who presented with her first episode of major depression in the setting of marital discord. She had a difficult childhood, with poor relationships with her parents, and she described herself as chronically nervous, moody, and "on edge." She first married at age 17 in part to escape from her conflictladen household. This relationship ended in a divorce a few years later. She moved to a new town with her second husband 2 years ago because of his job. She has felt socially isolated and has been unable to make friends. In recent months, her relationship with her husband has become very strained, and she suspects he is having an affair at work. He moved out 2 weeks ago for a "trial separation." Her sister, her closest "friend" and her only current source of support, just received a diagnosis of breast cancer. Her presenting complaints were a sad mood with a range of neurovegetative and anxiety symptoms, deep feelings of isolation and loneliness, and a sense of being unlovable.

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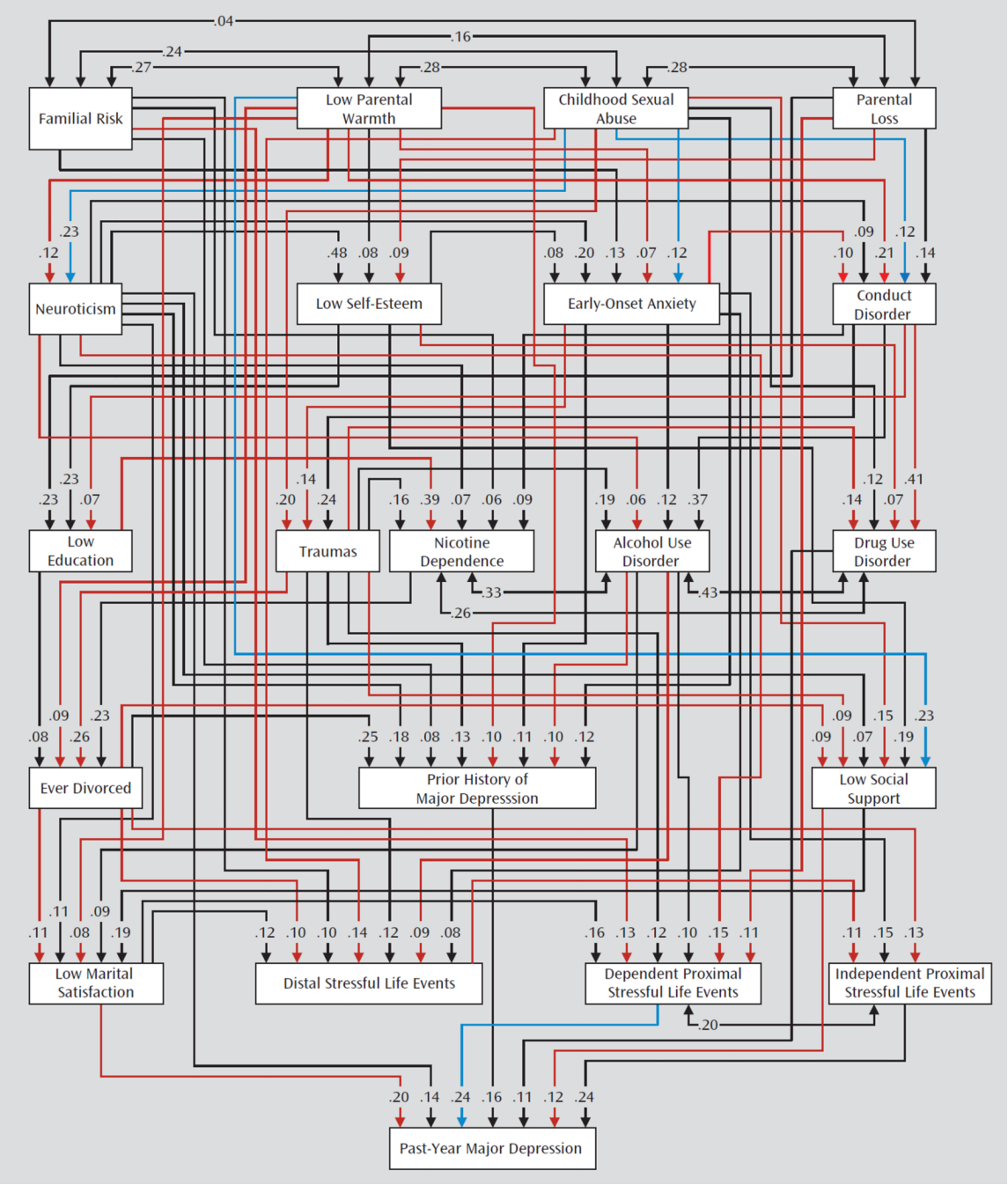

FIGURE 1. Path Estimates for Best-Fit Model for Causal Pathways to Major Depression in Femalesa

[a]Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red, and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II in the online data supplement contains the best-fit model estimates for all these paths, along with their statistical significance and the equality or nonequality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path

coefficients. Thus, paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

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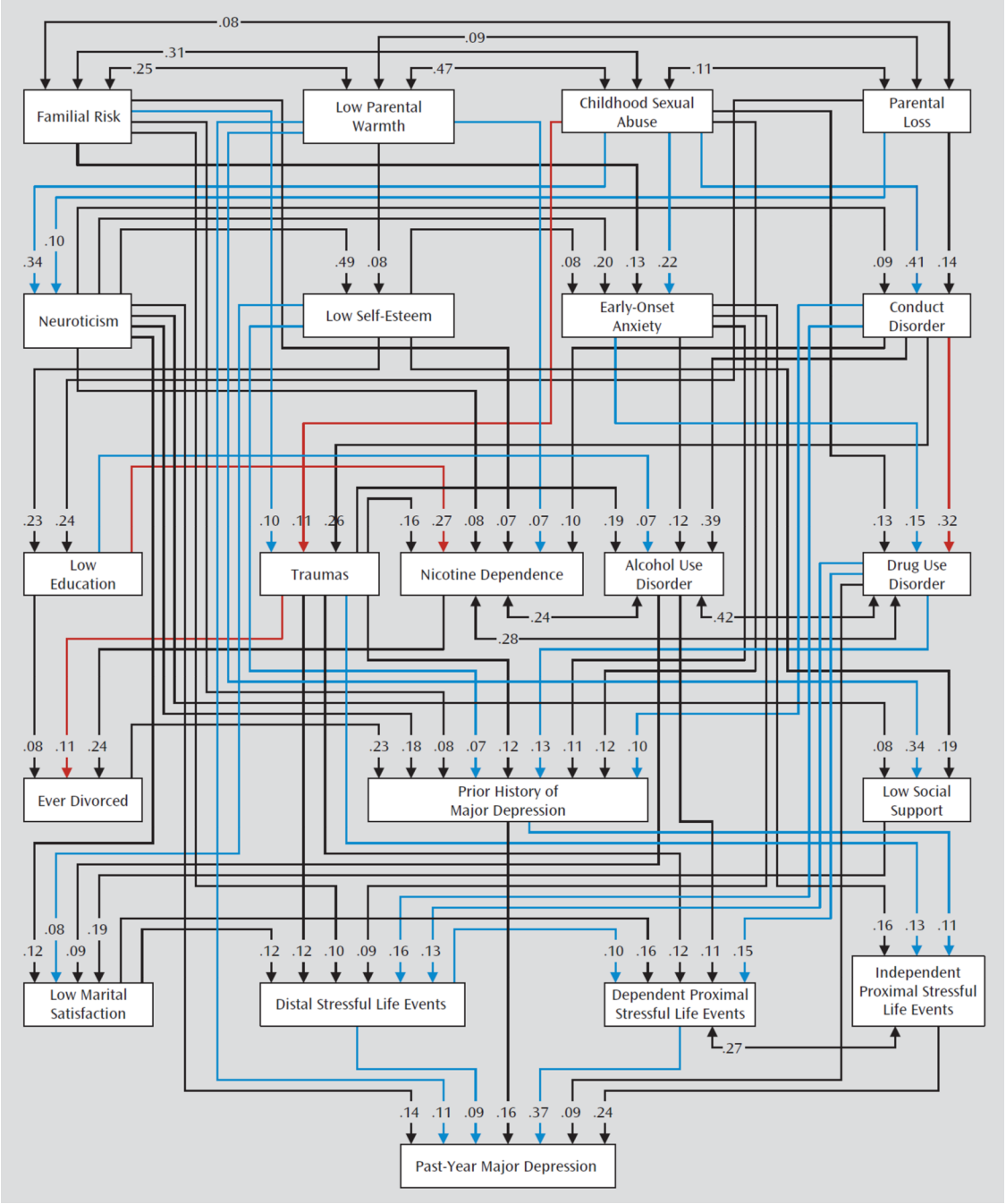

FIGURE 2. Path Estimates for Best-Fit Model for Causal Pathways to Major Depression in Malesa

[a]Parameters estimated to be equal across sexes, greater in females than males, and greater in males than females are depicted in black, red, and blue, respectively. If a path is not present between two variables, that is because it was estimated to have a zero value. Appendix II in the online data supplement contains the best-fit model estimates for all these paths, along with their statistical significance and the equality or nonequality of that path across sexes. The test of equality across sexes was based on raw path coefficients. However, for ease of interpretation and a consistent measure of effect size, we report standardized path

coefficients. Thus, paths that are depicted as equal (using raw coefficients) can differ slightly using standardized paths.

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TABLE 1

Summary of Results From a Model Predicting Sex Differences in the Risk for Major Depression in the Past Year From 20 Risk Factors Organized in a Developmental Cascade[a]

Variable	Total Effect on Males	Total Effect on Females	Difference	Magnitude of Sex Differences	Mediational Paths From the Variable for Which Effects in the Two Sexes Were:		
					Equal in Males and Females	Greater in Males	Greater in Females
Familial risk	0.052	0.059	F > M, 0.007	Minimal	EOAD, ND, PH, DSLE	LTR	DPSLE
Low parental warmth	0.122	0.151	F > M, 0.029	Modest	LSE	ND, LSS, MD	N, EOAD, CD, DIV, PH, LMS
Childhood sexual abuse	0.222	0.176	M > F, 0.046	Modest	DUD, PH	N, EOAD, CD	LTR, LSS, DSLE
Parental loss	0.045	0.050	F > M, 0.005	Minimal	CD, EDU	N	LSE, DPSLE
Neuroticism	0.231	0.300	F > M, 0.069	Moderate	EOAD, CD, ND, PH, LSS, LMS, MD		AUD, DPSLE
Low self-esteem	0.031	0.051	F > M, 0.020	Minimal	EOAD, EDU, LSS	PH, LMS	DUD,
Early-onset anxiety disorder	0.101	0.091	M > F, 0.010	Minimal	AUD, PH, DSLE	DUD	CD, LTR,
Conduct disorder	0.151	0.101	M > F, 0.050	Moderate	LTR, ND, AUD	PH, DSLE	EDU, DUD,
Educational attainment	0.009	0.019	F > M, 0.010	Minimal	DIV	AUD	ND
Lifetime traumas	0.126	0.127	F > M, 0.001	Minimal	ND, AUD, PH, DSLE, DPSLE	IPSLE	DUD, DIV, LSS,
Drug use disorder	0.187	0.103	M > F, 0.084	Moderate	MD	PH, DSLE, DPSLE	
Nicotine dependence	0.010	0.026	F > M, 0.016	Minimal	DIV		
Alcohol use disorder	0.045	0.065	F > M, 0.020	Minimal	LMS, DPSLE		PH, DSLE
History of divorce	0.043	0.114	F > M, 0.071	Moderate	PH		LSS, LMS, DSLE, IPSLE,
Past history of major depression	0.183	0.159	M > F, 0.024	Modest	MD	IPSLE	
Low social support	0.014	0.168	F > M, 0.154	Strong	LMS		MD
Low marital satisfaction	0.074	0.243	F > M, 0.169	Strong	DSLE, DPSLE		MD
Distal stressful life events	0.126	0.026	M > F, 0.100	Strong		DPSLE, MD	IPSLE
Independent proximal stressful life events	0.236	0.242	F > M, 0.006	Minimal	MD		
Dependent proximal stressful life events	0.366	0.239	M > F, 0.127	Strong		MD	

[a]AUD=alcohol use disorder; CD=conduct disorder; CSA=childhood sexual abuse; DIV=history of divorce; DPSLE=dependent proximal stressful life events; DSLE=distal stressful life events; DUD=drug use disorder; EDU=educational attainment; EOAD=early-onset anxiety disorder; F=female; IPSLE=independent proximal stressful life events; LMS=low marital satisfaction; LSE=low self-esteem; LSS=low social support; LTR=lifetime traumas; M=male; MD=major depression; N=neuroticism; ND=nicotine dependence; PH=past history of major depression; PL=parental loss.