

Research Article

SEX DIFFERENCES IN SYMPTOM PATTERNS OF RECURRENT MAJOR DEPRESSION IN SIBLINGS

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The objectives of this study were to examine sex differences in depressive symptom patterns in 475 sib pairs with well-defined recurrent major depression and to test the hypotheses that (a) symptom patterns show higher intraclass correlations within same sex sib pairs versus mixed sex sib pairs; and (b) symptoms more associated with women, e.g. atypical depressive and anxiety symptoms, account for differences between male and female siblings within the same family. A total of 878 individuals, with a past history of at least two depressive episodes, were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry interview and diagnosed according to DSM-IV using a computerized scoring program (CATEGO5). Intraclass correlations were compared between mixed and same sex sibs, and a conditional regression analysis in mixed sex sib pairs was performed to test whether specific symptoms account for differences between male and female siblings within the same family. Women showed a significantly earlier onset of depression compared with men (23.0 years, SD = 10.6 versus 25.5, SD = 12.5 years, $P = 0.0004$), and a significantly greater frequency of several aspects of depressed mood was found in women compared with men, including atypical depressive features of fatigability, appetite gain, weight gain and hypersomnia. Discordant sib-pair data analyses revealed five symptoms that accounted for the sex differences between siblings ($P = .000035$): phobia ($\exp(B) = 2.04$, $P = 0.017$), hypersomnia ($\exp(B) = 1.37$, $P = 0.055$), appetite loss ($\exp(B) = 1.38$, $P = 0.004$) and appetite

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gain ($\exp(B) = 2.19, P < 0.001$). Sex significantly modifies clinical features of depression and an earlier onset of depression and atypical depressive symptoms occur more frequently in women. *Depression and Anxiety* 25:527–534, 2008.

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INTRODUCTION

Depression is clinically heterogeneous and the aetiology comprises multiple genes of small effect interacting with environmental and developmental factors [Kendler, 1998; McGuffin et al., 2002; Sullivan et al., 2000]. Women are at greater risk than men for major depression [Kessler et al., 1993] and it has been suggested that genetic factors play a greater role in depression in women [Kendler et al., 2001]. However, there are only limited data available on sex differences in symptom patterns and familiarity of depressive symptoms.

Some studies have reported that women have an earlier onset of the first depressive episode [Kornstein et al., 2000; Marcus et al., 2005], as well as greater illness chronicity [Ernst and Angst, 1992] and impairment [Kornstein et al., 2000] compared with men. In other studies [Frank et al., 1988; Thase et al., 1994; Young et al., 1990], including a recent large epidemiological study of the US population [Hasin et al., 2005], no sex differences were found in age of onset, or number or severity of depressive episodes.

Similarly, there are varying reports of sex differences in depressive symptom patterns, with some finding no differences [Middeldorp et al., 2006] and others describing a female preponderance of weight change, sleep disturbance and feelings of worthlessness and guilt [Angst and Dobler-Mikola, 1984]. Atypical symptoms of depression, such as increased appetite and hypersomnia, are reported more commonly in women [Carter et al., 2000], whereas insomnia and agitation are more frequent in men [Angst et al., 2002; Khan et al., 2002; Matza et al., 2003; Marcus et al., 2005]. However, there is a controversy currently as to whether such atypical symptoms should be regarded as a specific sub-type of depression [Parker et al., 2002] or whether they are more closely linked to anxiety disorders, in particular social phobia [Parker and Hadzi-Pavlovic, 2004; Angst et al., 2005]. Women are more likely to have comorbid anxiety [Kessler et al., 1996, 2005] and Breslau et al. [1995] have proposed that the preponderance of depression in women is secondary to comorbidity with anxiety. However, this may be more representative of the different pathways that lead to depression in men (e.g. through prior alcohol or substance abuse) and women (e.g. through

anxiety) [Kessler, 2003; Kendler et al., 2002]. Although there is evidence for familial association and heritability of specific depressive symptoms and symptom dimensions [Korszun et al., 2004], there are few data available on sex-specific familial effects.

The objectives of this study were to examine sex differences in depressive symptom patterns in a large group of siblings with well-defined recurrent major depression. More specifically, we tested the hypotheses that (a) symptom patterns show higher intraclass correlations within same sex sib pairs compared with those within mixed sex sib pairs (indicating sex-specific familial effects) and (b) symptoms that are associated more with women, such as atypical depressive and anxiety symptoms, account for differences between male and female siblings within the same family.

METHODS

Sibling pairs from 403 families affected with recurrent unipolar depression were recruited as part of the Depression Network Study (DeNT) from eight clinical sites: Aarhus, Denmark; Bonn, Germany; Dublin, Ireland; Lausanne, Switzerland; St Louis, United States of America and London, Cardiff and Birmingham, United Kingdom. The rationale and design of this study has been detailed elsewhere [Farmer et al., 2004; Korszun et al., 2004]. Briefly, all sites obtained ethical approval for the DeNT study within their own countries and all study participants gave written informed consent for participation in the study. Subjects were identified from psychiatric clinics, hospitals, general medical practices and from volunteers responding to media advertisements. DeNT was a genetic linkage study limited to Caucasians and subjects were included if they were over the age of 18 and had experienced two or more episodes of unipolar depression of at least moderate severity separated by at least 2 months of remission as defined by the Diagnostic and Statistical Manual 4th edition operational criteria [American Psychiatric Association, 2003] or the International Classification of Diseases 10th edition operational criteria (ICD10) for unipolar depression [World Health Organization, 1992]. Proband was included in the study if they had at least one biological sibling, not a monozygotic twin,

over the age of 18 years meeting the same diagnostic criteria. Subjects were excluded if either sibling had ever fulfilled criteria for mania, hypomania, schizophrenia or if they had experienced psychotic symptoms that were mood incongruent or present when there was no evidence of a mood disturbance. Other exclusion criteria were intravenous drug use with a lifetime diagnosis of dependency, depression occurring solely in relation to alcohol or substance abuse or depression only secondary to medical illness or medication, and a clear diagnosis of bipolar disorder, schizophrenia, schizo-affective disorder or acute or transient psychotic disorders in first or second-degree relatives.

All subjects were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [Wing et al., 1990]. Items of psychopathology in the SCAN interview were rated for presence and severity according to the worst and second worst episodes of depression identified by the subjects. For the purposes of rating severity, subjects were asked to identify within each of these episodes of depression a 4–6 week period when their symptoms were at their worst (peak intensity). The majority of the SCAN items were coded 1–3 as follows: 0—indicates absence of the item, 1—the item was present but to a mild degree or intermittently throughout the peak intensity 4–6 weeks period, 2—item moderately severe and present for more than 50% of the peak intensity period or severe but present for less than 50% of the peak intensity period and 3—item severe for more than 50% of the peak intensity period. However, certain items are coded differently: general rating of anxiety, general rating of phobias, sleep problem with depressed mood, morning depression: 0/1; hypersomnia, appetite gain: 0–2 and suicide/self-harm: 0–4. Members from the same family were assigned a three-digit family number. In addition, body mass index was calculated from the self-reported current height and weight recorded in the SCAN interview.

All interviewers from each site attended a 4-day SCAN training course in the United Kingdom and interviewers from all sites took part in a joint inter-rater reliability exercise. Item by item κ statistics for SCAN items were calculated comparing each interviewer's ratings against a "master" rating. A mean item by item κ coefficient across all the sites of 0.77 (range: 0.63–0.89) was obtained indicating a substantial level of inter-rater agreement.

STATISTICAL ANALYSIS

Within individual subjects, correlations for all symptoms between worst and second worst episodes were highly significant ($P < 0.0001$) and thus analysis was carried out on 30 items from the SCAN interview reported for the worst episode of depression. These items represent a broad range of depressive symptoms

and four screening questions for the presence of anxiety symptoms. The analysis of variance was used to test for sex differences in symptoms. To remove the influence of latent dependencies between sib pairs stemming from being members of the same family and the effect of age, family effect was included into the model as a random effect and age was included as a covariate.

Most items in SCAN are coded on an ordinal scale indicating both presence and severity of items (general rating of anxiety, general rating of phobias, sleep problem with depressed mood, morning depression: 0/1; hypersomnia, appetite gain: 0–2; suicide/self-harm: 0–4; the remainder of items: 0–3). The frequency of a symptom was calculated as the proportion of individuals with a non-zero score divided by the total number of individuals with values available (i.e., not missing) for this symptom. Severity of these symptoms was calculated as the ratio of the average score to the maximum score for each item. The significance of differences in frequencies of each symptom between men and women was calculated using an odds ratio-based test statistic. Univariate analysis of variance was used to test for differences in severity, in which each symptom was included as a dependent variable with sex as the independent variable, as well as controlling for age and family random effects.

To identify the significance of the familial effect, intraclass correlations (ICC) were calculated for depressive symptoms, adjusted by age, between affected same and mixed sex sibling pairs. The depressive symptoms were adjusted for age by fitting a regression model with age as the independent variable. Then the residuals, being continuous variables, were used for ICC. In families with more than two members, each sibling pair contributed one independent pair, each trio (proband, sibling 1, sibling 2) contributed two independent pairs (proband—sibling 1 and proband—sibling 2), each quartet contributed three independent pairs and so on. Analysis was conducted on a total of 878 individuals comprising 403 families with 403 probands and 475 siblings yielding 475 sib pairs (236 female–female pairs, 187 male–female pairs and 52 male–male pairs).

Further analysis was performed on discordant (male–female) sib pairs. In this design, individuals of different sex are automatically matched by environmental (family) background so that we were able to concentrate on sex differences while minimizing the influence of the environment. Conditional logistic regression analysis was used to assess the sex differences, where sex was included as the dependent variable and symptoms as independent variables [Khan et al., 2002]. To determine which symptoms accounted for the sex differences, stepwise conditional logistic regression analyses were performed on discordant sib-pair data on the basis of all symptoms, which were considered in this study.

RESULTS

Analysis was conducted on a total of 878 individuals comprising 403 families with 403 probands and 475 siblings yielding 475 sib pairs. There were 270 (31%) men and 608 (69%) women and the overall age range at assessment was 18–80 years; mean age was 45, $SD = 12$ years. The mean age at onset of the first episode of depression was 24, $SD = 11$ years (range, 3–74 years) and the period between assessment and the worst episode of depression was 9.3, $SD = 9.8$ years.

Women showed an earlier onset of depression compared with men (23.0 years, $SD = 10.6$ versus 25.5, $SD = 12.5$ years, $P = 0.0004$). The age of onset of depression adjusted for sex and family effect showed a

positive correlation with age: Pearson's correlation coefficient (r) = 0.08, $P = 0.03$.

There was no difference in the number of episodes (median = 3) of depression reported by men and women but the duration of the worst episode of depression was greater in women. As the worst episode duration had a skewed distribution, the log transform was used in a subsequent analysis of variance (ANOVA), which also included age as a covariate, family number as a random effect and sex as the fixed effect. The results of this ANOVA showed a trend for women having longer worst episodes (median = 7 months) compared with men (median = 5 months) ($P = 0.06$). The (random) effect of family was significant ($P = 0.012$).

TABLE 1. Sex differences in frequency and severity of depressive symptoms

	Frequency				Severity			
	Male	Female	OR	<i>P</i> -value	Male	Female	B	<i>P</i> -value
Age of onset ^a	—	—	—	—	25.5	23.0	-1.84	0.0004
SCAN Section 3: Worrying and tension								
Worrying	74.1	76.0	0.90	0.544	0.61	0.64	0.04	0.458
General muscle tension	55.6	60.9	0.80	0.141	0.43	0.50	0.11	0.067
Localized tension pains	33.0	47.2	0.55	0.000	0.25	0.39	0.16	0.011
Restlessness	51.1	54.9	0.86	0.295	0.41	0.44	0.06	0.294
Fatiguability	63.7	72.9	0.65	0.006	0.54	0.64	0.13	0.034
Irritability	57.8	60.0	0.91	0.530	0.38	0.41	-0.07	0.217
SCAN Section 4: Panic, anxiety, and phobias								
General rating of anxiety	51.9	59.0	0.75	0.047	0.52	0.59	0.03	0.151
General rating of phobias	24.4	29.9	0.76	0.096	0.24	0.30	0.05	0.023
Free floating anxiety	33.3	39.5	0.77	0.083	0.26	0.30	0.06	0.293
Anxious foreboding	20.0	23.7	0.81	0.229	0.14	0.17	0.02	0.691
SCAN Section 6: Depressed mood and ideation								
Depressed mood	97.8	99.0	0.44	0.157	0.90	0.93	0.03	0.220
Tearfulness	77.0	86.0	0.55	0.001	0.57	0.75	0.21	0.000
Anhedonia	95.2	97.0	0.60	0.174	0.86	0.90	0.03	0.494
Loss of hope	88.9	90.8	0.81	0.383	0.79	0.83	0.00	0.909
Loss of feeling	42.2	50.7	0.71	0.021	0.32	0.42	0.09	0.116
Loss of reactivity	95.9	96.9	0.76	0.476	0.81	0.85	0.09	0.032
Morning depression	45.2	55.3	0.67	0.006	0.45	0.55	0.08	0.002
Suicidality	64.1	59.9	1.20	0.238	0.24	0.25	-0.05	0.390
Pathological guilt	49.6	60.2	0.65	0.004	0.35	0.47	0.09	0.180
Loss of self-esteem	83.0	89.5	0.57	0.008	0.72	0.80	0.10	0.050
SCAN Section 7: Thinking, concentration, energy, and interests								
Inefficient thinking	84.8	89.1	0.68	0.072	0.68	0.76	0.09	0.073
Feeling of retardation	53.3	63.7	0.65	0.004	0.39	0.52	0.12	0.060
Loss of energy (drive)	93.3	95.9	0.60	0.109	0.80	0.86	0.04	0.352
SCAN Section 8: Body functions								
Appetite loss	58.9	57.4	1.06	0.680	0.48	0.51	0.12	0.086
Appetite gain	6.7	16.6	0.36	0.000	0.06	0.15	0.1	0.003
Weight loss	47.8	52.5	0.83	0.200	0.20	0.24	0.06	0.283
Weight gain	14.1	22.5	0.56	0.004	0.09	0.16	0.05	0.073
Delayed sleep	62.2	59.9	1.10	0.510	0.56	0.54	-0.05	0.328
Early waking	46.3	51.3	0.82	0.170	0.35	0.40	0.00	0.942
Hypersomnia	27.8	31.9	0.82	0.221	0.22	0.25	0.11	0.006
Loss of libido	43.0	46.5	0.87	0.325	0.33	0.39	0.08	0.216
BMI ^a	—	—	—	—	26.3	26.4	-0.24	0.356

^aSeverity measure is given as mean of non-adjusted variables.

SCAN, Schedules for Clinical Assessment in Neuropsychiatry; BMI, body mass index.

Within individual subjects, correlations for all symptoms between worst and second worst episodes were highly significant ($P < 0.0001$). Table 1 shows the frequency and severity of depressive symptoms in male and female siblings, as well as the effect sizes and corresponding P -values in terms of odds ratio for the frequencies and the regression coefficient B for the severity measures. As this was an exploratory study and in large part was testing hypotheses derived from findings in previous literature, correction for multiple testing was not made.

There was a significantly greater frequency of several aspects of depressed mood in women compared with men.

In particular, women, compared with men, showed a significantly higher frequency and severity of localized tension pains and phobias, as well as the atypical depressive features of fatigability, appetite gain, weight gain and hypersomnia. Women also had a higher frequency and severity of tearfulness and loss of self-esteem and a greater frequency of pathological guilt as well as greater severity of morning depression and loss of reactivity.

There was no difference in the general rating of anxiety between men and women ($P = 0.293$).

There was no difference ($P = 0.356$) in body mass index (BMI) between men (26.3 $SD = 4.5$) and women (26.4 $SD = 6.7$) (57.8% of men and 48.1% of women

TABLE 2. Intraclass correlations

	Female-Female		Male-Female		Male-Male	
	ICC	Sig	ICC	Sig	ICC	Sig
Age of onset	0.18	0.01	0.26	0.00	0.12	0.21
SCAN Section 3: Worrying and tension						
Worrying	0.42	0.00	0.19	0.01	0.13	0.18
General muscle tension	0.4	0.00	0.14	0.03	0.08	0.278
Localized tension pains	0.28	0.00	0.2	0.00	0.1	0.243
Restlessness	0.35	0.00	0.24	0.00	0.37	0.003
Fatigability	0.22	0.00	0.25	0.00	0.19	0.097
Irritability	0.32	0.00	0.21	0.00	0.17	0.111
SCAN Section 4: Panic, anxiety, and phobias						
General rating of anxiety	0.25	0.00	0.3	0.00	0.12	0.196
General rating of phobias	0.22	0.00	0.12	0.04	0.02	0.439
Free floating anxiety	0.31	0.00	0.32	0.00	0.26	0.031
Anxious foreboding	0.26	0.00	0.21	0.00	0.09	0.268
SCAN Section 6: Depressed mood and ideation						
Depressed mood	0.3	0.00	-0.1	0.79	0.22	0.056
Tearfulness	0.18	0.00	0.07	0.16	0.27	0.029
Anhedonia	0.02	0.38	0.22	0.00	0.28	0.021
Loss of hope	0.13	0.02	0.03	0.33	0.36	0.004
Loss of feeling	0.3	0.00	0.34	0.00	0.13	0.179
Loss of reactivity	0.08	0.12	-0	0.58	0.29	0.019
Morning depression	0.27	0.00	0.01	0.44	-0	0.578
Suicidality	0.16	0.01	0.2	0.00	0.14	0.162
Pathological guilt	0.04	0.28	0.02	0.40	-0.2	0.952
Loss of self-esteem	0.02	0.41	0.1	0.08	0.41	0.002
SCAN Section 7: Thinking, concentration, energy, and interests						
Inefficient thinking	0	0.49	0.00	0.48	0.41	0.002
Feeling of retardation	0.21	0.00	0.15	0.03	-0	0.567
Loss of energy (drive)	0.03	0.31	0.09	0.12	0.13	0.172
SCAN Section 8: Body functions						
Appetite loss	0.13	0.03	0.08	0.16	0.09	0.269
Appetite gain	0.03	0.32	-0.1	0.91	0.13	0.194
Weight loss	0.13	0.03	0.11	0.07	0.17	0.134
Weight gain	0.23	0	-0	0.55	0.24	0.045
Delayed sleep	0.07	0.14	0.18	0.01	-0	0.562
Early waking	0.13	0.03	0.06	0.22	0.21	0.077
Hypersomnia	0.09	0.08	-0	0.68	0.29	0.018
Loss of libido	0.35	0.00	0.15	0.03	0.49	0.00
BMI	0.43	0.00	0.22	0.00	0.53	0.00

ICC, intraclass correlations; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; BMI, body mass index.

had a BMI >25), though there was a highly significant familial effect ($P < 0.001$).

INTRACLASS CORRELATIONS

Table 2 shows intraclass correlations for the range of symptoms in same and mixed sex siblings.

There were significant correlations between female–female siblings, but not between male–female or male–male siblings, for the following symptoms: depressed mood, morning depression, appetite loss, weight loss and early waking. Whereas male–male siblings exclusively showed significant correlations for hypersomnia and loss of reactivity, there was also a trend for these symptoms to be correlated in female siblings but no correlation was found in mixed sex siblings.

For depressed mood, weight loss and early waking there was also a trend in male–male pairs: the value of the correlation coefficient itself was quite large but not significant since the number of male–male pairs was 52 whereas the number of female–female pairs was 236.

CONDITIONAL LOGISTIC REGRESSION IN MIXED SEX SIBLINGS

This analysis confirmed the results of ANOVA.

Discordant sib-pair data analyses with the use of a stepwise procedure revealed five symptoms that accounted for the sex differences ($P = 3.5e-5$): phobia ($\exp(B) = 2.04$, $P = 0.017$), hypersomnia ($\exp(B) = 1.37$, $P = 0.055$), appetite loss ($\exp(B) = 1.38$, $P = 0.004$) and appetite gain ($\exp(B) = 2.19$, $P < 0.001$).

DISCUSSION

The participants in this study all had well-defined moderate to severe, recurrent major depression and the female:male ratio of 2:1 was representative of the sex distribution usually found in depressed populations [Kessler et al., 1993].

We found a significantly earlier age of onset of depression in men and women supporting the previous report of Marcus and colleagues [2005]. We also found a positive correlation of depression onset with age at interview, independently from any sex or familial effect. This could be for several reasons. First, menarche and puberty have been steadily occurring earlier over the last century [Blythe and Rosenthal, 2000] and as onset of depression in women is closely linked to puberty, this could explain the earlier female onset of depression in younger subjects. Secondly, there has been a 5-fold increase in lifetime prevalence of depression over the last 40 years [Kessler, 2003], which may be due to a progressively greater awareness of depression as a disorder resulting in earlier recognition and diagnosis. With the rapid increase in communication, later generations may also have greater life expectations and may be more likely to label themselves as “depressed”

when faced with normal responses to setbacks and life events. In the present study, diagnostic criteria were applied to the worst and second worst episodes only which may not necessarily be the first episode. Another factor may be the relationship with childhood trauma and neglect. In a related study, we have found that age correlated negatively with the level of reported childhood abuse and neglect [Moskvina et al., 2006]. Lastly, the possibility should be considered that the correlation may be due to artifact: (a) older individuals remember less well when their first episode of depression occurred, but this seems unlikely and studies have shown that retrospectively acquired data on depression are reliable and highly comparable to contemporary accounts derived from case notes [Kendler et al., 1993; McGuffin et al., 1986] and (b) older people have more years of risk.

There are some previous reports of greater severity of depression in women [Kornstein et al., 2000] though this is by no means a consistent finding [Frank et al., 1988; Hasin et al., 2005; Thase et al., 1994; Young et al., 1990]. In this study, we found no difference in numbers of episodes but a strong trend ($P = 0.06$) towards women reporting longer worst depressive episodes.

There was a high correlation in symptoms in worst and second worst episodes; therefore all analyses were carried out on symptoms reported in the worst episode. Despite criticisms that are made of the use of retrospectively acquired data, there is evidence that when the depression has been moderate to severe, as in this study, the symptoms are reported reliably [Kendler et al., 1993].

There were some notable sex differences in the frequency and severity of certain symptoms.

Whereas general muscle tension did not show any significant differences between men and women, there was a higher frequency and severity of local tension pain. This reflects the finding of a higher incidence of stress-associated chronic pain syndromes, such as temporomandibular disorder and fibromyalgia, in women [Korszun et al., 1998]. There is a significant overlap of these disorders with depression and dysregulation of the HPA axis occurs in both conditions and may represent the common underlying pathological mechanism [Crofford et al., 2004; Korszun et al., 2002].

As previously reported in other studies [Angst et al., 2005; Matza et al., 2003], the atypical depressive symptoms of fatiguability, appetite gain, weight gain and hypersomnia were significantly more frequent and severe in women. Although, women reported significantly more weight gain than men, there was no difference found in BMI between men and women. This could reflect either greater perception and focus on weight gain in women or it may merely be due to the fact that the weight gain was associated with active depressive episodes and most of the subjects in the study were not depressed at the time of reporting.

There was no sex difference in the general rating of anxiety. Prior anxiety increases the risk for major depression, and Breslau et al. [1995] have suggested that the higher prevalence of anxiety in women explains the preponderance of women with depression. However, others [Kessler, 2003; Parker and Hadzi-Pavlovic, 2004] have shown that preceding anxiety is similar in both men and women. Women did, however, show a higher frequency of phobias. In a study of the atypical features specified for major depression in DSM-IV, Parker and colleagues [2002] reviewed the earlier evidence of an association between phobic anxiety states and atypical depression, showing more symptoms of atypical depression in individuals with social phobia. However, we did not find any correlation between a general rating of phobias and atypical symptoms in the present study. The inclusion of mood reactivity in the definition of atypical depression does not show good specificity [Parker et al., 2002]; interestingly, we found a correlation between loss of reactivity and hypersomnia.

ICC between siblings provide information on the familial effect on symptomatology. If the same familial effect were operative for both male and female siblings, ICC would be similar in same and mixed sex sibs. However, if there is a familial effect that is sex-dependent, then a positive correlation would occur in same sex siblings but not in mixed sex siblings. Melancholic symptoms of depressed mood, tearfulness, loss of hope, morning depression, early wakening, weight and appetite loss showed a positive correlation in female–female siblings but not in mixed siblings. Tearfulness also showed positive correlation in male–male sibs but not in mixed sibs. Similarly, weight gain and hypersomnia showed positive correlations in same sex (female–female and male–male respectively) but not in mixed sex siblings. This suggests that there is either a genetic variation in the two sexes or other biological factors, e.g. reproductive hormones, mediate these differences. The familial effect can also be environmental, e.g. families with high emotional expression may encourage tearfulness when distressed and certain symptoms may be endorsed in female rather than male siblings. The conditional logistic regression in mixed sex siblings showed that sex differences are mostly explained by atypical symptoms.

As discussed in previous reports [Farmer et al., 2004; Korszun et al., 2004], this study was carried out on volunteers recruited in different ways from a variety of different sites across Europe and the United States of America. In some sites they were recruited from clinics and other sites relied heavily on recruitment through advertisement. Thus, findings cannot necessarily be generalized to all depressed individuals. Furthermore, all subjects in these primarily genetic studies were at least second generation Caucasians.

CONCLUSIONS

In conclusion, sex significantly modifies clinical features of depression and these data support previous findings that earlier onset, more severe (longer episodes) and atypical depressive symptoms occur more frequently in women.

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