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ORIGINAL PAPER

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Familiality of major depressive disorder and patterns of lifetime comorbidity. The NEMESIS and GenMood studies

A comparison of three samples

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Abstract *Background* Major depressive disorder (MDD) aggregates in families and is associated with high rates of lifetime axis-I comorbidity. This study examined whether familiality of MDD is associated with the presence of specific comorbid disorders, which might be an important factor to be taken into account in MDD treatment and research into MDD etiology. *Methods* A population sample was divided into subjects with familial (f-MDD; $n = 432$) and nonfamilial MDD (nf-MDD; $n = 454$). Since, more comorbidity was expected in clinical cases, a clinical sample with f-MDD ($n = 120$) was also studied. Subjects were assessed with the Composite International Diagnostic Interview and family history methods. Binary logistic regression analyses were carried out to examine the influence of familiality of MDD on comorbidity. Analyses were adjusted for potential confounders, including MDD characteristics such as severity and age of onset. *Results* Dysthymia, anxiety disorders, and alcohol use disorders were significantly more prevalent in subjects with f-MDD than in subjects with nf-MDD. Clinical f-MDD was associated with more anxiety disorders and fewer alcohol use disorders than population f-MDD. After adjustment for MDD characteristics including age at onset, severity, and disease course, comorbid disorders remained more prevalent in f-MDD than in nf-MDD. *Limitations* The instruments used in the population and the clinical samples were not identical, however, they were comparable to a substantial degree. *Conclusions* F-MDD, especially in clinical cases, appears to increase the risk of development of comorbid disorders, regardless of MDD characteristics. The link between familiality and comorbidity is important because it will aid a better understanding of the MDD phenotype, and it contributes to planning of effective treatment and to molecular genetic studies.

Key words major depressive disorder · familiality · comorbidity · clinical features

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Background

Major depressive disorder (MDD) is one of the most common psychiatric disorders and causes impairment in several areas. The lifetime prevalence of MDD is estimated at 15–17% [6, 23, 24]. Family studies have shown an average risk ratio of 2.8 for major depression among the first-degree relatives of probands with major depression compared with the relatives of controls, indicating moderate familial aggregation of unipolar mood disorders [42]. MDD characteristics, such as age of onset and recurrence of episodes, each increase the risk of the disorder in relatives [27, 32, 45, 46, 51]. Twin studies estimate

the heritability of MDD to be moderate, in the range of 35–40% [40, 42].

In most studies MDD is treated as a homogeneous disorder even though there are considerable differences in syndrome characteristics and in MDD subtypes. Moreover, MDD is associated with high rates of lifetime psychiatric comorbidity, which also contributes to heterogeneity in expression of MDD. MDD with comorbid disorders causes more functional disabilities than pure MDD [6, 21, 25, 37]. The National Comorbidity Survey-Replication (NCS-R) observed that 72.1% of subjects with lifetime MDD had more than one axis-I disorder [21], with anxiety disorders, in particular generalized anxiety disorder (GAD), and dysthymia being found to frequently occur with MDD [36, 37]. Although twin and family studies indicate that MDD and anxiety disorders are distinct entities and not alternative phases of one disease [36], common genetic risk factors might explain the high rate of comorbidity. Most epidemiological studies, except for the Netherlands Mental Health Survey and Incidence Study (NEMESIS), found MDD to be associated with alcohol use disorders [17, 37].

Factor analytic studies focusing on the clustering of axis-I disorders have repeatedly revealed a three-factor model of disorders. This model is composed of two internalizing factors, "anxious-misery" (MDD, dysthymia, and GAD) and "fear" (panic disorder, agoraphobia, social and simple phobias), and an externalizing cluster, composed of alcohol dependence, drug dependence, and antisocial personality [19, 26, 44]. This three-factor division is observed in both males and females [19, 26]. Interestingly, GAD coincides more frequently with depression and dysthymia than with other anxiety disorders [26, 44]. Apparently, these three latent dimensions reflect core psychopathological processes underlying different mental disorders over time [44], with the common psychopathological variance being possibly due to shared genetic factors [26]. The finding of this three-factor model is supported by findings from studies investigating genetic factors for axis-I disorders. In a female-twin study by Kendler et al. [20], MDD and GAD loaded on the same genetic factor, whereas other anxiety disorders clustered together on another genetic factor. This suggests that GAD and MDD are different manifestations of the same underlying genetic vulnerability. The genetic influences on alcohol dependence were largely disorder-specific and independent of those influencing susceptibility to major depression [20].

Despite the frequent presence of comorbid disorders in MDD, the observed axis-I clusters in factor analytic studies, and the considerable differences in syndrome characteristics, MDD is still often considered a single disorder with regard to treatment and studies aiming at identifying the (genetic) etiology of the disorder. This might explain the large variability in response to treatment and probably leads to underestimation of the heritability of MDD [5, 15]. While diagnostic and genetic boundaries between the subtypes of MDD and other psychiatric disorders are still unclear [16], it may be important to recognize the expression of different subtypes and the accompanying comorbid lifetime psychiatric disorders.

In this study, we examined the relationship between MDD familiality and patterns of comorbid axis-I disorders. More specifically, we tested whether familial MDD (f-MDD) and nonfamilial MDD (nf-MDD) are associated with different patterns of comorbidity. We also investigated whether MDD characteristics, such as age of onset, disease course, and severity, influence the association between familiality of MDD and comorbidity patterns.

Methods

Samples

Two samples of subjects with lifetime MDD were included in this study. Inclusion criteria were age 18–64 years at the time of interview, first episode of MDD between 12 and 50 years, and being of Dutch descent (participant and both parents born in the Netherlands). Subjects with a lifetime diagnosis of comorbid bipolar disorder or schizophrenia were excluded.

The first sample was drawn from a longitudinal prospective study (NEMESIS) of the prevalence, incidence, course, and determinants of psychiatric disorders in a representative sample of Dutch adults. NEMESIS had three measurement phases. The first involved 7,076 individuals (69.7% response) and took place in 1996. These data were used in the current study. To select a representative population, households in 90 different Dutch municipalities were identified and subjects with the most recent birthday were invited for participation. To correct for differing response rates in different population groups, post stratification weighting was applied to the NEMESIS database (gender, age, marital status, and urbanization). For a more detailed description see Bijl et al. [7].

The second sample was collected in the context of a clinical study into the genetics of MDD. Recruitment started in 2004 in the Netherlands and is still continuing (GenMood study). The Dutch central medical ethics review board and local ethics boards approved the study. Individuals with major depression and a familial vulnerability to depression (having at least one first-degree relative with a history of MDD) were recruited through psychiatric treatment settings and advertisements on Internet, in local newspapers, and in popular magazines. After providing written informed consent, eligible participants were (endo)phenotyped on the basis of diagnostic, temperamental, cognitive, endocrinological, and lifestyle measures. The clinical GenMood sample used in this study consisted of 120 subjects.

Diagnostic assessment and procedures

The Composite International Diagnostic Interview (CIDI) was used for diagnostic assessment. The CIDI is a structured interview developed by the World Health Organization (WHO) that can be administered by trained interviewers who are not clinicians. The CIDI has acceptable interrater reliability and test–retest reliability for most diagnoses including major depression [48]. DSM-III-R lifetime diagnostic reliability was found to be acceptable to good with Kappa values well above 0.5. Although few studies have validated the CIDI, it is considered to have acceptable validity [48].

Subjects in the population sample (NEMESIS study) were interviewed at home using the computerized CIDI 1.1 (DSM-III-R) [41, 49], and those in the clinical sample (GenMood study) were interviewed when in remission at the Department of Psychiatry of

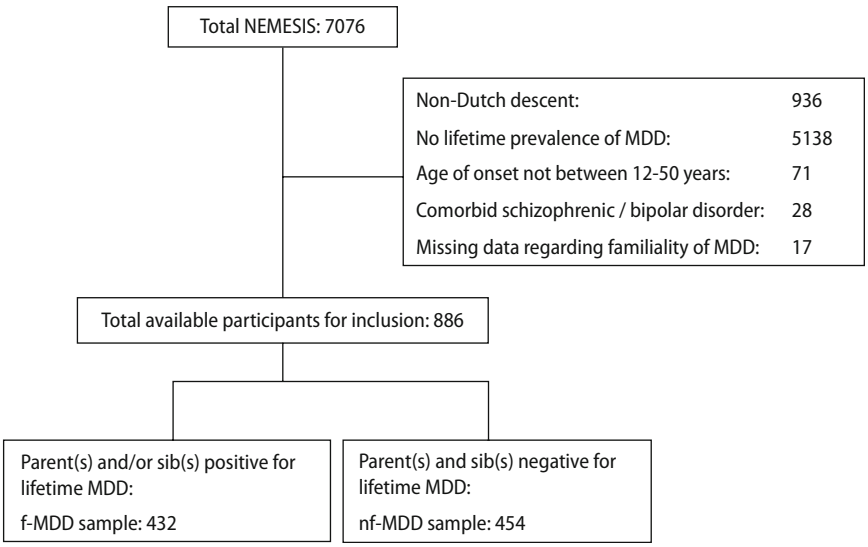

Fig. 1 Flowchart of NEMESIS samples and reasons for exclusion of subjects

the Radboud University Nijmegen Medical Centre or at home, by means of the computerized CIDI 2.1 (DSM-IV) [47]. For the current study, the following CIDI sections were of interest: the lifetime presence of mood disorders (dysthymia, major depression, bipolar disorder), anxiety disorders (panic disorder, agoraphobia, generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), social phobias, simple phobias), schizophrenia and other non-affective psychotic disorders, and alcohol abuse and dependence. We used the CIDI diagnostic information to estimate comorbidity and to exclude subjects with lifetime bipolar or schizophrenic disorder.

In the population sample, information on family history was obtained by questioning subjects about the presence of axis-I disorders in first-degree relatives: had relatives ever been hospitalized in a psychiatric setting, ever received medical care for psychiatric disorders, or ever had a psychiatric disorder? If, based on a single question, participants reported major depression in a first-degree relative, they were classified as f-MDD (positive family history for MDD, $n = 432$); otherwise, they were classified as nf-MDD (negative family history, $n = 454$, see Fig. 1). In a subsample consisting of 323 relatives of 51 clinical subjects, a high level of agreement was found between this single question and a more elaborate family history method based on the Family Interview for Genetic Studies (FIGS; 33) and the Family History Research Diagnostic Criteria (FH-RDC; 11) (kappa = 0.78).

In the clinical sample, a family history method based on a combination of the FIGS [33] and the FH-RDC [11] was used. With the use of a drawn family tree showing all first-degree relatives, the lifetime presence of MDD, bipolar disorders, anxiety disorders, and alcohol use disorders was evaluated for each first-degree relative individually. A best-estimate diagnosis was made using criteria from the FH-RDC. Subjects were positive for f-MDD if the proband reported at least one first-degree relative to have been diagnosed with MDD and to have received treatment (or to have ever been hospitalized for the disorder). Family members positive for lifetime MDD were contacted and asked to participate in the GenMood project. To estimate the reliability of this family history method, we checked 50 random pedigrees. In 50.5% of the relatives we were able to verify MDD status by using information obtained from the CIDI or a telephone interview. In 92.2% of the relatives depression was confirmed. Unfortunately, we were unable to assess MDD status in the remaining 49.5% of the relatives because subjects had died or were unwilling/unable to participate in GenMood.

Dependent variables

As dependent variables we used lifetime comorbid diagnoses of dysthymia, anxiety disorders (panic disorder with and without agoraphobia, agoraphobia, social phobia, simple phobia, GAD, and OCD), and alcohol use disorders (alcohol abuse and dependence). We used the following definition of comorbidity: "Comorbidity is the presence of more than one disorder in a person in a defined period of time, regardless of the association between those disorders" [8]. For this study the "defined period of time" was lifetime. This means that comorbid disorders did not necessarily co-occur with MDD.

Independent variables

Subjects were classified according to MDD characteristics including age of onset (early vs. late onset), disease course (single episode vs. recurrent MDD), and disease severity (mild vs. severe) on the basis of CIDI diagnostic scores. The age of onset dichotomy distinguished early onset MDD (first episode of MDD ≤25 years) from late onset MDD (first episode of MDD >25 years) [30, 32, 50, 51]. Single MDD was defined as a single episode of MDD during life (DSM classifications 296.20, 296.21, 296.22, 296.23, 296.24), and recurrent MDD was defined as more than one episode of MDD, at least 2 months apart in which criteria for MDD were not met (DSM classifications: 296.30, 296.31, 296.32, 296.33, 296.34). Severity of MDD was categorized as mild (mild and moderate episodes; DSM classifications 296.21, 296.22, 296.31, and 296.32) and severe (severe episodes of MDD and MDD with psychotic features; DSM classifications 296.23, 296.24, 296.33, and 296.34).

Statistical analyses

Sociodemographic and clinical characteristics of the samples were compared. For categorical variables, contingency tables were created and Pearson's χ^2 were calculated. For continuous variables, independent T tests were performed. All tests were two-tailed. For each sample, the frequency of overall comorbidity and of each single comorbid disorder was calculated. We investigated whether the samples differed from each other with respect to the lifetime prevalence of comorbid disorders using logistic regression analyses. P values below 0.05 were considered statistically significant.

To study the effect of familiality of MDD on the presence of lifetime comorbid disorders, binary logistic regression analyses were performed. Dependent variables were comorbid dysthymia, anxiety disorders, and alcohol use disorders (0 = absence; 1 = presence). Analyses were adjusted for gender, age at the time of interview, and educational attainment. These factors have been found to be associated with depression in community samples [6, 22]. In the next step, MDD characteristics such as age of onset (early vs. late), course (recurrent vs. single), and severity (severe vs. mild MDD) were added

Table 1 Descriptive and clinical characteristics of the population (NEMESIS) and clinical (GenMood) samples

	Population nf-MDD, $n = 454$	Population f-MDD, $n = 432$	Clinical f-MDD, $n = 120$	Statistics
Gender (% females)	312 (68.7%)	302 (69.9%)	85 (70.8%)	NS
Age in years, mean (SD)	39.9 (10.1)	39.3 (10.1)	45.6 (10.8)	$F(2; 1{,}003) = 18.5$, $P < 0.001$
Marital status *N* (%)				
Married	223 (49.1%)	224 (51.7%)	73 (60.3%)	NS
Previously married	77 (17.0%)	71 (16.4%)	17 (14.0%)	
Widow(er)	26 (5.6%)	13 (3.0%)	2 (1.7%)	
Never married	128 (28.2%)	124 (28.7%)	28 (23.3%)	
Educational level *N* (%)				
Low	131 (28.9%)	102 (23.6%)	10 (9.2%)	$\chi^2 = 33.59$, $df = 6$, $P < 0.001$
Medium	173 (38.1%)	179 (41.4%)	35 (32.1%)	
High	118 (26.0%)	117 (27.1%)	54 (49.5%)	
University	32 (7.0%)	34 (7.9%)	10 (9.2%)	
MDD characteristics *N* (%)				
Early onset[a]	156 (34.4%)	193 (44.7%)	60 (50.0%)	$\chi^2 = 14.69$, $df = 2$, $P < 0.01$
Recurrent MDD[b]	153 (33.7%)	192 (44.4%)	70 (58.3%)	$\chi^2 = 26.95$, $df = 2$, $P < 0.001$
Severe MDD[c]	135 (29.7%)	169 (39.1%)	60 (50.0%)	$\chi^2 = 15.17$, $df = 2$, $P < 0.01$

[a]Early onset versus late onset
[b]Recurrent MDD versus single MDD
[c]Severe MDD versus mild MDD

to the logistic regression analyses to see whether apparent differences in comorbid disorders between samples were due to familial factors and not actually due to MDD characteristics. Covariates were entered simultaneously.

Associations between variables were expressed as odds ratios (ORs) and 95% confidence intervals (95% CIs). Differences between odds ratios were considered statistically significant if the confidence intervals of a risk factor mutually excluded the point estimates in one or both of the other categories [13]. Analyses were performed using SPSS 12.0.

Results

Descriptive and clinical characteristics of the samples

The demographics of the population (NEMESIS study) and clinical (GenMood study) samples are summarized in Table 1. Both samples consisted of about 70% women, but the clinical sample was significantly older, on average 5 years, and had a higher educational status than the population sample. There were no significant differences in marital status.

The nf-MDD sample differed significantly from the f-MDD samples with regard to age of onset (there were fewer cases with an early onset), course (there were fewer cases with recurrent MDD), and severity (more subjects had mild MDD) (Table 1). The clinical f-MDD sample had more recurrent cases than the population f-MDD sample.

Comorbid disorders in the samples

Significantly more subjects in the clinical f-MDD sample than in population f-MDD sample or in the nf-MDD sample had at least one comorbid disorder (89.2, 74.3, and 66.7%, respectively). The presence of comorbid disorders was significantly higher in population f-MDD than in population nf-MDD (OR 1.5, 95% CI 1.1–2.0). In the clinical f-MDD sample, comorbid disorders were also significantly more prevalent than in population nf-MDD cases (OR 5.1, 95% CI 2.7–9.7: see Table 2 "Any disorder"). The difference in prevalence of comorbidity between both familial samples was also significant, since the confidence intervals mutually excluded the point estimates from the other category. Figures 2 and 3 show the rates of the different comorbid disorders in each sample. The most frequent comorbid disorders were anxiety disorders, in particular GAD and phobias.

Familiality of MDD and prevalence of comorbid disorders

Table 2 (columns labeled with[a]) presents the results of the binary logistic regression analyses examining whether familiality of MDD influenced the presence of comorbid disorders. Since the subjects in the population f-MDD and nf-MDD samples were significantly younger than the subjects in the clinical f-MDD sample, age was used as a covariate. Other covariates were gender and educational status. We found that subjects in the population f-MDD sample had significantly more often dysthymia and alcohol use disorders than the subjects in the nf-MDD sample. There was no difference in the overall prevalence of anxiety disorders, though, OCD was significantly more prevalent in the subjects in the population f-MDD sample (Table 2, population f-MDD[a]). Almost all disorders, except for agoraphobia and alcohol use disorders, were more common in the subjects in the clinical f-MDD sample than in the subjects in the nf-MDD sample (Table 2, clinical f-MDD[a]).

Comparison of the population and clinical samples of f-MDD showed that anxiety disorders, especially

Table 2 Odds ratios and 95% CIs for the presence of lifetime comorbid disorders in clinical f-MDD and population f-MDD with nf-MDD as the reference group

	Population f-MDD[a]	Clinical f-MDD[a]	Population f-MDD[b]	Clinical f-MDD[b]
Dysthymia	1.7 (1.2–2.2)**	2.1 (1.3–3.4)**	1.6 (1.2–2.2)**	1.7 (1.0–2.8)*
Any anxiety disorder	1.2 (0.9–1.6)	6.6 (3.8–11.4)***	1.1 (0.8–1.4)	5.3 (3.0–9.4)***
Panic disorder	1.0 (0.7–1.5)	5.0 (3.0–8.3)***	0.9 (0.6–1.3)	4.2 (2.4–7.3)***
Simple phobias	1.1 (0.8–1.5)	2.1 (1.3–3.4)**	1.0 (0.7–1.4)	1.6 (1.0–2.6)
Social phobia	1.3 (1.0–1.8)	2.0 (1.2–3.3)**	1.2 (0.9–1.7)	1.6 (1.0–2.7)
GAD	1.1 (0.8–1.6)	4.4 (2.7–7.0)***	1.0 (0.7–1.4)	4.0 (2.4–6.5)***
Agoraphobia	1.2 (0.8–1.9)	1.0 (0.4–2.1)	1.2 (0.7–1.9)	0.8 (0.4–1.9)
OCD	2.9 (1.0–8.3)*	9.9 (3.1–32.0)***	2.7 (0.9–7.6)	6.8 (2.0–23.3)*
Alcohol use disorder	1.5 (1.1–2.2)*	0.8 (0.4–1.6)	1.5 (1.0–2.1)*	0.7 (0.3–1.4)
Any disorder	1.5 (1.1–2.0)**	5.1 (2.7–9.7)***	1.3 (1.0–1.8)	3.9 (2.0–7.7)***

Results from logistic regression analyses
[a]Adjusted for age, gender, and educational attainmen
[b]Additionally adjusted for age of onset, disease course, and severity of MDD
*$P < 0.05$, ** $P < 0.01$, ***$P < 0.001$

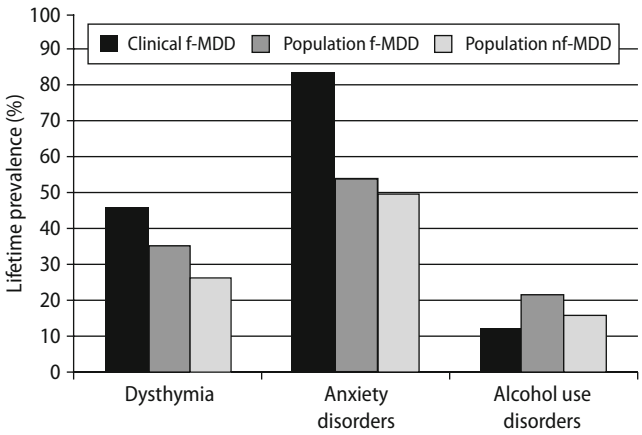

Fig. 2 Lifetime prevalence of comorbid dysthymia, anxiety disorders and alcohol use disorders in the samples. Anxiety disorders include simple phobia, social phobia, GAD, OCD, panic disorder with and without agoraphobia, and agoraphobia. Alcohol use disorders include alcohol abuse and alcohol dependence

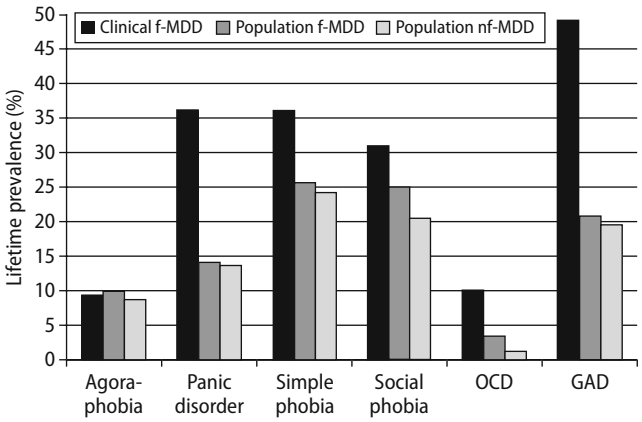

Fig. 3 Lifetime prevalence of comorbid specific anxiety disorders in the samples. Panic disorder includes both panic disorder with and without agoraphobia

panic disorder, simple phobias, social phobias, GAD, and OCD were more often present in the clinical f-MDD sample than in the population f-MDD sample, whereas alcohol use disorders were less prevalent in the clinical f-MDD sample than in the population f-MDD sample (Table 2; columns labeled with[a]).

Characteristics of MDD and prevalence of comorbid disorders

Overall, more comorbidity was observed in the subjects with f-MDD (clinical and population samples) with early onset compared with late onset MDD (OR 1.7, 95% CI 1.3–2.3), and in nf-MDD subjects with severe MDD compared with those with mild MDD (OR 2.3, 95% CI 1.7–3.1). Disease course influenced the presence of comorbidity only at a trend level. Binary logistic regression results showed that adjustment for these MDD characteristics did not lead to major changes in the odds ratios for comorbidity. Odds ratios for dysthymia and alcohol use disorders remained significantly higher in the population f-MDD sample than in the nf-MDD sample (Table 2; population f-MDD[b]), whereas dysthymia and anxiety disorders, especially panic disorder, GAD, and OCD, remained significantly more prevalent in the clinical f-MDD sample than in the nf-MDD sample (Table 2; Clinical f-MDD[b]). Minor changes were observed for OCD (Table 2; compare population f-MDD[a] and f-MDD[b]) and social and simple phobias (Table 2; compare clinical f-MDD[a] and f-MDD[b]). There were significant differences in comorbid disorders between the clinical f-MDD sample and the population f-MDD sample after controlling for age of onset, disease course, and severity of MDD (Table 2; columns labeled with [b]). Anxiety disorders, in particular panic disorder, simple phobias, and GAD, were significantly more prevalent in the clinical f-MDD sample than in the population f-MDD sample, whereas alcohol use disorders were significantly more prevalent in the population f-MDD sample.

Discussion

The present report is one of the first to investigate the presence of lifetime comorbid disorders in f-MDD versus nf-MDD. The findings lend support to our hypothesis that the rate of lifetime comorbid dysthymia, anxiety disorders, and alcohol use disorders is higher in f-MDD than in nf-MDD. In addition, subjects from the clinical f-MDD sample reported significantly more anxiety disorders (especially GAD) and fewer comorbid alcohol use disorders than subjects from the population f-MDD sample. These effects of familiality on comorbidity patterns largely remained after correcting for MDD characteristics, such as age of onset, disease course, and severity. That the association between familiality and comorbidity patterns was independent of disease severity is contrary to the generally held belief that more severe forms of illness are accompanied by more comorbidity. This finding has not been reported earlier.

Comorbid disorders in the samples

In MDD, comorbidity seems to be rule rather than exception [1, 10, 28], with dysthymia, anxiety disorders, and alcohol abuse and dependence frequently co-occurring with MDD [35, 39]. This was also the case in our samples, with anxiety disorders showing higher comorbidity with MDD than alcohol use disorders. This difference in anxiety- and alcohol use disorder comorbidity accompanying MDD is consistent with findings from other studies [3, 25]. Epidemiological studies have indicated that of the anxiety disorders, panic disorder and GAD are most often comorbid with MDD [20, 34]. In the population samples, however, panic disorder was less prevalent than social and simple phobias. In the clinical sample, panic disorder was as often present as social and simple phobias. GAD was most prevalent.

Familiality and comorbidity

That comorbidity is less common in nf-MDD than in f-MDD might indicate that familial vulnerability for MDD is expressed as MDD with comorbid disorders rather than as pure MDD. This is in accordance with family studies showing that comorbid disorders in a proband with MDD significantly increase the risk of MDD in relatives [4, 14, 18, 45]. However, it is not clear which lifetime comorbid disorders influence the risk of MDD in relatives [14, 18, 29, 45]. Weissman et al. [45] found that comorbid anxiety disorders and secondary alcoholism increased the risk of MDD in relatives, whereas Kendler et al. [18] found comorbid panic disorder and bulimia to increase the risk of MDD in the co-twin. In the latter study, however, only female twins were included and it is unclear how many of them actually had bipolar disorder. The significantly higher prevalence of comorbid anxiety disorders in the clinical sample in this study might be explained by treatment or referral bias [12]. This is in line with findings that clinical cases of MDD are more socially incapacitated than population cases of MDD [9]. In the latter study [9], the presence of comorbid disorders was not taken into account, which could have made the association even stronger.

Contrary to our expectation, alcohol use disorders were not more prevalent in the clinical f-MDD sample than in the nf-MDD sample. This is probably due to selection bias; the clinical sample had a higher educational attainment. It is also possible that subjects with alcohol use disorders are more easily reached in population surveys than in psychiatric clinics, since alcohol use disorders are mostly treated in specialized treatment settings.

Strengths and limitations

The findings of this study should be interpreted in the light of its strengths and limitations. A strength of this study is that we included both population and clinical samples of f-MDD and a control sample without f-MDD. In fact, this is one of the first studies to investigate the effect of familiality of MDD on comorbidity in a large, representative population sample. However, due to differences in samples, study design, and methodologies between the population (NEMESIS) and clinical (GenMood) studies there are some limitations. CIDI 1.1 (DSM-III-R) was used for diagnostic assessment in the population study, whereas CIDI 2.1 (DSM-IV) was used in the clinical study. However, the differences between these instruments would not affect diagnostic outcomes. Furthermore, the family history method used for the assessment of MDD in relatives differed between the two studies. Both studies were similar in relying solely on proband knowledge. Although the family history method has been criticized because of its susceptibility to bias [38], it is known that familiarity of the informant with manifestations of psychopathology increased the reporting accuracy for relatives, which is also the case in our study. We were able to show a relatively high agreement between the single family history question for the assessment of familiality of MDD and the more elaborate family history method. Further, the reliability of the family history method approach used in the clinical study was very high [43]. Altogether, we believe that the different family history methods will identify familial cases comparably well.

Another limitation is the use of retrospective reports of axis-I disorders. This can be subject to recall bias, although studies suggest that it is possible to collect reliable lifetime diagnoses [2, 31]. However, we do not think that this has biased our findings in a

serious way since this possible influence from memory is operating in all three samples.

Implications

The present study shows that it is important to include comorbid disorders in the phenotypic description of MDD in addition to MDD characteristics, such as age of onset, disease course, and severity of MDD. A better understanding of the phenotype of MDD is of importance for the clinical assessment, treatment, and prevention of MDD, and for etiological (genetic) studies. Treatment often focuses on one condition, thereby possibly neglecting other concurrent conditions [28, 35], whereas all disorders, primary as well as comorbid, should be treated. The confirmation in this study that f-MDD is associated with an earlier onset of disease, more recurrence, and more severe episodes of MDD should be considered with regard to prevention as well. Individuals with these characteristics may be particularly vulnerable to the development of comorbid psychiatric disorders.

A better insight into the relevant phenotype of MDD, i.e. the frequent presence of comorbid disorders, could lead to more accurate phenotyping in molecular genetic studies. This is essential since it may otherwise result in misleading association findings, such as an association between a candidate locus and the phenotype of interest (i.e. MDD) that may actually be attributable to an association between that locus and the comorbid phenotype, or results that are not reproducible in other studies.

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