Chapter 3

Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden Routine Outcome Monitoring Study

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Abstract

Background: Pre-adult onset of Major Depressive Disorder (MDD) may predict a more severe phenotype of depression. As data from naturalistic psychiatric specialty care settings are scarce, we examined phenotypic differences between pre-adult and adult onset MDD in a large sample of consecutive outpatients.

Methods: Altogether, 1,552 outpatients, mean age 39.2 ± 11.6 years, were diagnosed with current MDD on the Mini International Neuropsychiatric Interview-Plus (MINI-Plus) as part of the usual diagnostic procedure. A total of 1,105 patients (71.2%) had complete data on all variables of interest. Pre-adult onset of MDD was defined as having experienced the signs and symptoms of a first Major Depressive Episode before the age of 18 years. Patients were stratified according to the age at interview (20-40 / 40-65 years). Correlates of pre-adult onset were analysed using logistic regression models adjusted for age, age squared and gender.

Results: Univariable analyses showed that pre-adult onset of MDD had a distinct set of demographic (e.g. less frequently living alone) and clinical correlates (more comorbid DSM-IV-Text Revision diagnoses, more social phobia, more suicidality). In the multivariable model we found an independent association only for a history of suicide attempts (OR 3.15; 95% CI: 1.97-5.05) and current suicidal thoughts (OR 1.81; 95% CI 1.26-2.60) in patients with pre-adult versus adult onset MDD.

Discussion: Pre-adult onset of MDD is associated with more suicidality than adult onset MDD. Age of onset of depression is an easy to ascertain characteristic that may help clinicians in weighing suicide risk.

Introduction

Several studies suggest that pre-adult and adult onset major depressive disorder (MDD) are two distinct forms of MDD in terms of pathophysiology and phenomenology (see review by Kaufman et al., 2001). Diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) for MDD are independent of the age of onset of the first major depressive episode (MDE; American Psychiatric Association, 2000). This contrasts with dysthymic disorder, for which the DSM-IV-TR makes a distinction in age of onset before or after 21 years of age (early onset and late onset, respectively).

In previous studies, demographic characteristics of pre-adult versus adult onset MDD were female gender, being unmarried (Benazzi, 2000; Zisook et al., 2004; Zisook et al., 2007a), impaired social and occupational functioning (Zisook et al., 2007a), and lower education (Parker et al., 2003). The course of the depressive disorder also differed significantly in some studies, with pre-adult onset MDD being associated with more depressive episodes (Benazzi, 2000; Klein, 1999; Ramklint & Ekselius, 2003; Zisook et al., 2004; Zisook et al., 2007a) and more chronicity (Benazzi, 2000; Coryell et al., 2009; Klein, 1999; Parker et al., 2003; Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b). In addition, pre-adult MDD patients showed more suicidality (Benazzi, 2000; Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b; Thompson, 2008), a higher amount of medical comorbidity (Zisook et al., 2007a), more familiality of depression (Klein, 1999; Parker et al., 2003; Kendler et al., 2005; Zisook et al., 2007b), and more alcohol and drug abuse (Klein, 1999; Parker et al., 2003; Zisook et al., 2007b). Early childhood risk factors like motor skill deficits, perinatal insults and caretaker instability, criminality and psychopathology in the families of origin were associated with pre-adult onset MDD in a birth cohort that had been followed from childhood up to age 26 (Jaffee et al., 2002). Taken together, these data suggest that pre-adult onset MDD points towards a more severe form of illness.

Previous investigations have been undertaken in various study populations, using varying study designs. Prospective findings from a New Zealand birth-cohort suggested that both heritable and childhood psychosocial factors contributed to a pre-adult onset of depression (Jaffee et al., 2002). These findings were consistent with results from family studies which suggested that pre-adult onset MDD might be more strongly associated with genetic factors and early childhood psychosocial risk factors (Kovacs et al., 1997; Neuman et al., 1997; Klein et al., 2001). Several studies reported a different course of illness of pre-adult onset and adult onset MDD. Adolescent MDD has been associated with elevated rates of subsequent MDEs in early adulthood in prospective case control studies (Harrington et al., 1990; Weissman et al., 1999). Yet, most studies used cross-

sectional designs in selected populations. In three analyses in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study population (Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b), using data from over 4,000 selected MDD patients the most prominent findings in pre-adult onset MDD patients were more psychiatric comorbidity and more suicidality. These findings were largely consistent with the findings in a large US community sample of 9,282 people (Thompson, 2008).

It is well established that clinical treatment samples may be prone to selection bias, whereas population-based samples may not reflect a treatment seeking population either (Zimmerman et al., 2002). Since data on naturalistic patients are generally considered to represent 'real life patients' more closely than selected populations, naturalistic data on differences between pre-adult onset versus adult onset MDD would be of great value. Therefore, the aim of the present study was to evaluate differences in demographic correlates, comorbidity, symptomatology and general health status between pre-adult and adult onset MDD in a large naturalistic outpatient sample from psychiatric specialty care. We used the Leiden Routine Outcome Monitoring study baseline sample (de Beurs et al., 2011; van Noorden et al., 2010). We hypothesised that pre-adult onset MDD would be characterised by markers of greater severity as compared with adult onset MDD. Pre-adult onset of MDD was defined as first MDE before the age of 18 years.

Methods

Study design

The Leiden Routine Outcome Monitoring study baseline cohort sample comprised 3,798 adult outpatients who were referred for treatment of a mood, anxiety, or somatoform (MAS) disorder to the Dutch Regional Mental Health Provider (RMHP) Rivierduinen (RD) or the psychiatric outpatient department of the Leiden University Medical Center (LUMC) in the Western part of the Netherlands, between January 2004 until December 2006 (van Noorden et al., 2010; de Beurs et al., 2011). At baseline, subjects were assessed as part of the Routine Outcome Monitoring (ROM) procedure. In ROM, all patients referred to RD or LUMC for treatment of a MAS disorder are routinely assessed, at baseline and at fixed intervals during treatment, with an extensive battery of psychometric instruments administered by specially trained research nurses. ROM is a method for the systematic collection of data on the diagnostic status and severity of complaints to assess the effectiveness of treatments in everyday clinical practice. The only exclusion criteria for ROM are insufficient mastery of the Dutch language, and inability to perform the assessment

procedure due to severity of symptoms. In practice, more than 80% of the patients referred to the LUMC or RD for treatment of a MAS disorder are enrolled in ROM. During the first session, psychopathology was assessed with the Dutch translation of the Mini International Neuropsychiatric Interview-Plus 5.0.0.-R, structured diagnostic interview (MINI-Plus) developed to assess the presence of Axis-I disorders according to the DSM-IV-TR diagnostic criteria (Sheehan et al., 1998; van Vliet & de Beurs, 2007). The MINI-Plus has been validated with the Composite International Diagnostic Interview (CIDI; World Health Organisation, 1990) diagnoses and has good psychometric properties (Lecrubier et al., 1997). Patient data were stored anonymously in the Psychiatric Academic Registration Leiden (PAREL) database and were accessible for research purposes only. This procedure has been approved by the Medical Ethical Committee of the LUMC. For the present study, only the baseline ROM data were used.

Study population

In the present analyses all patients with a current DSM-IV-TR MDD diagnosis according to the MINI-Plus (age range 20-65) were included. We used only baseline ROM assessments, administered at intake. No distinction was made between MDD as principal or comorbid diagnosis. Concomitant current DSM-IV-TR disorders were recorded as well. The presence of DSM-IV-TR melancholic features of depression was systematically assessed with the MINI-Plus, whenever the DSM-IV-TR criteria for MDD were fulfilled. Patients with a bipolar disorder or lifetime psychotic illness were excluded, but a diagnosis of psychotic depression was allowed. Only patients with complete data on all variables of interest were included in the initial analyses. 1,552 (40.9%) of 3,798 patients fulfilled the DSM-IV-TR criteria of MDD, current episode on the MINI-Plus, and were aged 20-65. Of these 1,552 MDD patients, 1105 (71.2%) had complete data on all variables of interest and were included in the present analyses. The excluded 447 patients differed statistically significant in age (mean age 40.6, vs. 39.3 for included patients, respectively; $t = 2.06$, $p = 0.04$), age of onset (mean age 31.4 vs. 28.3 for included patients, respectively, $t = 4.21$, $p < 0.001$), MADRS score (mean score 24.2 vs. 25.5 for included patients, respectively; $t = -2.54$, $p = 0.02$), but not in gender, total BSI score, current suicidal thoughts or history of suicide attempts.

Age of onset

Age of onset of MDD was defined as the age at which the first MDE initiated, regardless of whether treatment was sought. In the MINI-Plus, when a current MDD was diagnosed, the age of onset of the first episode was assessed by the question: 'How old were you when you first experienced these symptoms of depression, for at least two weeks?' In our study

we defined pre-adult onset of MDD as an onset of MDD before age 18, in accordance with the existing literature on this subject. Various cut-off points to distinguish between pre-adult and adult onset MDD have been used in previous studies. Cut-off ages varied from 17 (Jaffee et al., 2002), 18 (Alpert et al., 1999; Benazzi, 2000; Fava et al., 1996; Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b), 21 (Klein, 1999), 25 (Parker et al., 2003) and 26 (Ramklint and Ekselius, 2003) to 30 (Thompson, 2008), and despite the lack of widely accepted consensus most authors use a cut-off age of 18 years. In sensitivity analyses we re-analysed our data with a cut-off age of 25 years (see statistical analyses).

Other variables

Demographic variables were obtained using a self-report questionnaire that assessed ethnic background, marital status, housing situation, educational status, and employment status. A Dutch ethnic background was assumed when the patient and both parents were born in the Netherlands.

Depression severity was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery, 1979), a 10-item observer-rated scale that measures symptoms of depression on a 7-point Likert-scale. The MADRS has a good internal consistency and reliability (Montgomery, 1979). In addition to the continuous measure, three categories were distinguished; a MADRS score of <20 for mild depression, 20-35 for moderate depression, and ≥35 for severe depression (Muller, 2003; Snaith, 1986). Post-hoc, we analysed MADRS item 10, that assesses suicidal thoughts. We dichotomised in symptom absent, if the score was 0 or 1, and symptom present if the score was 2 or higher. The Brief Anxiety Scale (BAS), an observer-rated scale that measures symptoms of anxiety, was used to assess severity of anxiety (Tyrer et al., 1984). General psychopathological symptoms were scored on the Brief Symptom Inventory (BSI). The BSI is a short version of the Symptom Checklist (SCL-90), a self-report instrument that measures psychopathological symptoms in several domains, e.g. somatic symptoms, depressive symptoms, anxiety symptoms and hostility on a 5-points Likert-scale (de Beurs & Zitman, 2006; Derogatis & Melisaratos, 1983). The BSI has shown good internal consistency, reliability and validity (Derogatis, 1977). In addition to the BSI-total score we studied presence of specific symptoms on the depressive and anxiety subscales of the BSI. A score of 0 or 1 on each individual item was defined as the absence of a symptom, whereas a score of 2, 3 or 4 was defined as the presence of a symptom. A history of suicide attempts and current suicidal thoughts were assessed with the MINI-Plus. In section C of the MINI-Plus, the following questions were asked respectively: "Did you ever in your life try to commit suicide?" and "During the past month, did you ever think about suicide?"

Comorbid DSM-IV-TR disorders, e.g. anxiety disorders, somatoform disorders and alcohol or drug related disorders were also assessed with the MINI-Plus. Generic health status was assessed with the Dutch version of the Short-Form-36 health survey (SF-36), a 36-item self-report questionnaire that measures health status in eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (Aaronson et al., 1998; Ware, Jr. & Sherbourne, 1992).

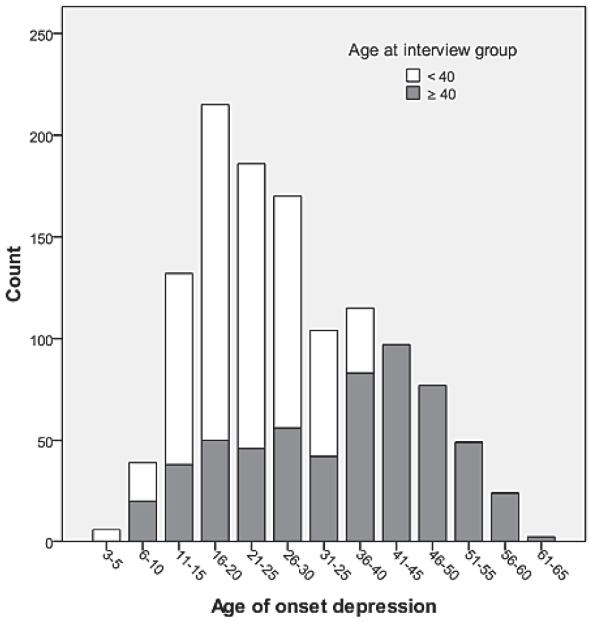

Figure 3.1. Distribution of age of onset of depression in 1,105 outpatients with MDD

Statistical analyses

All group comparisons were made between pre-adult onset (age<18 years) and adult onset (age≥18 years) MDD-groups. T-tests for independent samples were used for continuous data, while categorical data were analysed with χ^2 tests. In all previous cross-sectional studies, the pre-adult onset MDD patients were younger than adult onset MDD patients at the time of assessment. Despite the fact that many studies adjusted for age, residual confounding by age at interview is possible as several demographic factors are highly associated with age (e.g., marital status, duration of disease, and comorbidity).

Therefore, we stratified the study population into two age strata (20-40 and 40-65 years of age at interview). If both age strata would yield similar associations and odds ratios, the confounding effects by age are likely to be small. Stratification based on the age of 40 years was chosen because this age is generally considered to be the beginning of middle age, and it was close to the median age of the sample (i.e., 38 years). Also, it was assumed that the associations between the clinical characteristics and age of onset would vary by gender. Therefore we also made adjustments for gender and current age by including these characteristics in a logistic regression model with forced entry (adjusted analysis). To account for the potential curvilinear confounding effects of age, a quadratic term (age-squared) was added to the model. In the logistic regression model, we analysed the univariable findings with a $p<0.1$ in the two age strata and the combined group. Sensitivity analyses were performed in which patients with an age at interview of 20-25 years were excluded from the analyses, to rule out the possibility that any differences in outcome could be explained by the very short disease duration. Sensitivity analyses were subsequently performed on the complete sample of 1,552 MDD patients while using multiple imputations of missing data. Finally, sensitivity analyses were performed in which a cut-off age of 25 instead of 18 years was used to distinguish between pre-adult onset and adult onset MDD. The statistical significance was set at $p<0.05$. When appropriate, Bonferroni correction for multiple testing was applied. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) 17.0 for Windows.

Results

Sociodemographic characteristics

The sample consisted of 711 women and 394 men (35.7%). The mean age of the subjects was 39.2 (SD 11.6) years (range 20-65). Figure 3.1 illustrates the distributions of age of onset of MDD and age at interview of the 1,105 patients. In table 3.1 the sociodemographic characteristics of the study population are presented. In total, 246 patients (22.3%) had an early-onset form of MDD. These patients were younger than adult onset patients at the time of interview in both strata (in 20-40 group: median age 25 vs. 31 years, respectively [$p<0.001$], in 40-65 group: median age 46 vs. 49 years [$p=0.03$]). No difference in ethnic background was found between pre-adult and adult onset groups.

Table 3.1. Sociodemographic characteristics according to age of onset in 1,105 outpatients aged between 20 and 65 with MDD

	Age 20-40 years			Age 40-65 years		
	Pre-adult onset <18 (n =172)	Adult onset ≥18 (n =410)	p-value	Pre-adult onset <18 (n =74)	Adult onset ≥18 (n =449)	p-value
Female gender (n, %)	119 (69.2)	295 (72.0)	0.50	49 (66.2)	248 (55.2)	0.08
Age at interview (median, p25-p75)	26 (22-32)	31 (26-36)	<0.001 [a]	46 (43-53)	49 (44-55)	0.03 [a]
Ethnic background (n, %)			0.27			0.40
Dutch	134 (77.9)	293 (71.5)		60 (81.1)	373 (83.1)	
Other	38 (22.1)	117 (28.5)		14 (18.9)	76 (16.9)	
Marital status (n, %)			0.006			0.83
Married	62 (36.0)	187 (45.6)		44 (59.5)	250 (55.7)	
Divorced/ widowed	10 (5.8)	42 (10.2)		21 (28.4)	137 (30.5)	
Never married	100 (58.1)	181 (44.1)*		9 (12.1)	62 (13.8)	
Housing situation (n, %)			0.05			0.02
Living alone	59 (34.3)	106 (25.9)		11 (14.9)	129 (28.7)*	
Living with partner	63 (36.6)	191 (46.5)		45 (60.8)	250 (55.7)	
Living with family	50 (29.1)	113 (27.6)		18 (24.3)	70 (15.6)	
Educational status (n, %)			0.28			0.85
Lower education	59 (34.3)	160 (39.0)		40 (54.1)	248 (55.2)	
Higher education	113 (65.7)	250 (61.0)		34 (45.9)	201 (44.8)	
Employment situation (n, %)			0.05			0.05
Working full-time	36 (20.9)	82 (20.0)		8 (10.8)	78 (17.4)	
Working part time	27 (15.7)	83 (20.2)		19 (25.7)	63 (14.0)	
Retired/unemployed	59 (34.3)	98 (23.9)		21 (28.4)	123 (27.4)	
On sick leave	50 (29.1)	147 (35.9)		26 (35.1)	185 (41.2)	

MDD denotes Major Depressive Disorder ; * Indicates significant difference post-hoc with chi-squared test after Bonferroni correction.
[a] Mann-Whitney non-parametric test.

Table 3.2. Rating scale scores and subtype of depression according to age of onset in 1,105 outpatients aged between 20 and 65 with MDD

	Age 20-40 years			Age 40-65 years		
	Pre-adult onset <18 (n =172)	Adult onset ≥18 (n =410)	p-value	Pre-adult onset <18 (n =74)	Adult onset ≥18 (n =449)	p-value
MADRS score (mean ± SD)	24.2 (7.8)	25.0 (7.8)	0.28	26.0 (8.4)	26.1 (7.6)	0.97
MADRS categories (n, %)			0.28			0.65
MADRS <20	44 (25.6)	84 (20.5)		13 (17.6)	81 (18.0)	
MADRS 20-35	117 (68.0)	289 (70.5)		50 (67.6)	318 (70.8)	
MADRS ≥35	11 (6.4)	37 (9.0)		11 (14.9)	50 (11.1)	
BAS score (mean, ± SD)	17.0 (6.3)	17.4 (6.7)	0.59	18.0 (6.5)	17.4 (6.5)	0.43
BSI total score (geometric mean, p5-p95)	1.6 (1-3)	1.4 (0-3)	0.41	1.5 (0-3)	1.4 (0-3)	0.11
Suicidality						
Current suicidal thoughts (n, %)	77 (44.8)	140 (34.1)	0.02	35 (47.3)	153 (34.1)	0.03
History of suicide attempt (n, %)	53 (30.8)	76 (18.5)	0.001	27 (36.5)	87 (19.4)	0.001
MADRS item 10 ≥2 (n,%)	81 (47.1)	155 (37.8)	0.04	34 (45.9)	200 (44.5)	0.82
Depression subtype						
without comorbidity						
(pure depression) (n, %)	74 (43.0)	193 (47.1)	0.37	36 (48.6)	40 (53.5)	0.44
melancholic depression (n, %)	81 (47.1)	166 (40.5)	0.14	41 (55.4)	221 (49.2)	0.32

Abbreviations: MDD: Major Depressive episode ; MADRS: Montgomery-Åsberg Depression Rating Scale; BAS: Brief Anxiety Scale; BSI: Brief Symptom Inventory.

Univariable analyses

Table 3.2 shows the relationship between age at onset and rating scale scores and subtype of depression. The main difference was that patients with pre-adult onset MDD had significantly more often a history of suicide attempts (in 20-40 group 30.8% vs. 18.5% [p<0.001]; in 40-65 group 36.5% vs. 19.4% [p<0.001]). No differences between the groups were found in MADRS continuous scores, nor in MADRS categories. Only in the 20-40 group, pre-adult onset patients more often had a positive score on the MADRS suicidality item (47.1% vs. 37.8% [p=0.04]). No significant differences were found between the early- and adult onset groups on the BSI or BAS scores, nor in the presence of subtypes of depression.

Furthermore, we analysed the differences between pre-adult onset and adult onset groups on the symptom level, by focusing on the anxiety and depression subscales of the BSI. Significant differences in univariable analyses were found for the following two items only: "thoughts of ending your life" and "feeling hopeless about the future". Consistent with "suicidal thoughts" on the MINI-Plus, these affirmative answers from the depression subscale were more prevalent in patients with pre-adult onset than adult onset MDD (data not shown).

Table 3.3. Current comorbidity according to age of onset in 1,105 outpatients with MDD

	Age 20-40 years			Age 40-65 years		
	Pre-adult onset <18 n =172	Adult onset ≥18 n =410	p-value	Pre-adult onset <18 n =74	Adult onset ≥18 n =449	p-value
Any Anxiety disorder (n, %)	79 (45.9)	165 (40.2)	0.21	28 (37.8)	155 (34.5)	0.58
Posttraumatic stress disorder	34 (19.8)	69 (16.8)	0.40	9 (12.2)	57 (12.7)	0.90
Panic disorder	267 (15.1)	44 (10.7)	0.14	8 (10.8)	40 (8.9)	0.60
Generalised anxiety disorder	5 (2.9)	17 (4.1)	0.47	4 (5.4)	23 (5.1)	0.92
Social phobia	31 (18.0)	45 (11.0)	0.02	12 (16.2)	40 (8.9)	0.05
Obsessive compulsive disorder	12 (7.0)	24 (5.9)	0.61	5 (6.8)	16 (3.6)	0.20
Any Somatoform disorder (n, %)	9 (5.2)	28 (6.8)	0.47	6 (8.1)	36 (8.0)	0.98
Hypochondria	2 (1.2)	8 (2.0)	0.50	2 (2.7)	4 (0.9)	0.18
Body dysmorphic disorder	5 (2.9)	12 (2.9)	0.99	0 (0)	3 (0.7)	0.48
Both somatoform and anxiety						
disorder (n, %)	10 (5.8)	24 (5.9)	0.99	4 (5.4)	18 (4.0)	0.60
Alcohol dependence / alcohol abuse (n, %)	13 (7.6)	20 (4.9)	0.20	8 (10.8)	39 (8.7)	0.55
Drug dependence / drug abuse (n, %)	14 (8.1)	19 (4.6)	0.09	5 (6.8)	11 (2.4)	0.05
Number of comorbid MAS disorders (n, %)			0.02			0.04
0	65 (37.8)	187 (45.6)		30 (40.5)	240 (53.5)*	
1	62 (36.0)	157 (38.3)		27 (36.5)	149 (33.2)	
≥2	45 (26.2)	66 (16.1)*		17 (23.0)	60 (13.4)	

Abbreviations: MDD: Major Depressive disorder ; MAS: Mood, anxiety and somatoform; * Indicates significant difference post-hoc with chi-squared test after Bonferroni correction.

Table 3.3 summarises the presence of comorbid DSM-IV-TR disorders according to age of onset in each group, in univariable analyses. Pre-adult onset individuals had increased rates of comorbid social phobia, but no differences were found in the rates of other DSM-IV-TR anxiety disorders.

Patients with a pre-adult onset MDD were more likely to be dependent on drugs or to abuse drugs and had a higher number of comorbid MAS disorders.

No differences were found for any of the SF-36 subscale scores between pre-adult onset and adult onset MDD patients (data not shown).

Table 3.4. OR for outcomes according to pre-adult age of onset of MDD in 1,105 outpatients aged between 20 and 65 with MDD

	Age 20-40 years		Age 40-65 years		Both groups combined	
	No. of patients	OR for pre-adult onset (95% CI)	No. of patients	OR for pre-adult onset (95% CI)	No. of patients	OR for pre-adult onset (95% CI)
Marital status						
Married	249	1	294	1	543	1
Divorced/widowed	52	0.84 (0.28 – 2.54)	158	1.17 (0.30 – 4.55)	210	1.06 (0.47 – 2.38)
Never married	281	1.01 (0.44 – 2.63)	71	1.26 (0.29-5.44)	352	1.21 (0.57 – 2.59)
Housing situation						
Living alone	165	1	140	1	305	1
Living with partner	254	0.90 (0.35 – 2.28)	295	2.55 (0.59 – 10.92)	549	1.27 (0.58 – 2.75)
Living with family	163	0.58 (0.34 – 0.96)	88	2.51 (1.05 – 6.01)	251	0.93 (0.61 – 1.42)
History of suicide attempts						
No	453	1	409	1	862	1
Yes	129	**4.17** (2.25 – 7.72)	114	**2.52** (1.12 – 5.67)	243	**3.15** (1.97 – 5.05)
Current suicidal thoughts						
No	365	1	335	1	700	1
Yes	217	**1.92** (1.22 – 3.01)	188	1.59 (0.84 – 3.01)	405	**1.81** (1.26 – 2.60)
Number of comorbid MAS disorders						
0	252	1	270	1	522	1
1	219	0.99 (0.64 – 1.54)	176	1.30 (0.72 – 2.35)	395	1.14 (0.81 – 1.61)
≥2	111	1.58 (0.89 – 2.81)	77	1.20 (0.53 – 2.73)	188	1.55 (0.98 – 2.46)
Comorbid social phobia						
No	506	1	471	1	977	1
Yes	76	1.28 (0.72 – 2.31)	52	1.76 (0.78 -3.95)	128	1.36 (0.85 – 2.17)
Comorbid drug dependence / abuse						
No	549	1	507	1	1056	1
Yes	33	1.22 (0.54 – 2.77)	16	2.63 (0.80 – 8.59)	49	1.59 (0.82 – 3.08)

Abbreviations: OR: Odds Ratios; MDD: Major depressive Disorder ; CI: Confidence Interval; Reference =adult onset MDD
Data adjusted for age at interview and gender with forced entry in logistic regression models. Bold denotes statistical significant difference at $p<0.05$.

Multivariable and sensitivity analyses

The results of the multivariable analyses are presented in table 3.4. After adjusting for age at interview and gender, in both strata pre-adult onset MDD patients significantly more often had a history of suicide attempts compared to adult onset MDD patients (OR in 20-40 group: 4.17; 95% confidence interval [CI]: 2.25-7.72; OR in 40-65 group: 2.52; 95% CI: 1.12-5.67). Furthermore, pre-adult patients in the 20-40 group and in the combined groups more often had current suicidal thoughts. In the 40-65 group, a non-significant

trend was found. In the combined groups, the OR for having a history of suicide attempts in pre-adult onset MDD patients was 3.15 (95% CI: 1.97-5.05), and the OR for having current suicidal thoughts was 1.81 (95% CI: 1.26-2.60). Results of sensitivity analyses as described in the methods section were as follows: In a first sensitivity analysis when excluding all patients between 20 and 25 years, the odds ratio's for a history of suicide attempts and current suicidal thoughts remained largely unchanged (2.75 and 1.66, respectively, for the combined group). In our second sensitivity analysis we aimed to impute missing data and to analyse the complete sample of 1,552 MDD patients in the multivariable model. However, no variables used in the multivariable model were missing, so the analysis could be performed in 1,552 patients without imputation. Odds ratio's for a history of suicide attempts and current suicidal thoughts were 2.71 and 1.52 respectively, for the combined group. In the third sensitivity analysis we used a cut-off age of 25 instead of 18 years to distinguish between pre-adult and adult onset MDD. In this analysis, OR were again largely comparable to the original analysis (2.78 and 1.94, respectively for the combined group).

Discussion

In our naturalistic patient sample we found that patients with pre-adult onset MDD, defined as an onset before age 18, more often had a history of suicide attempts and current suicidal thoughts compared to patients with adult onset MDD. We found no differences in severity of depression measured with the MADRS, nor differences in the presence of comorbid anxiety disorders or differences in self-reported generic health status.

The main finding of more previous suicide attempts and current suicidal thoughts after adjusting for age at interview and gender in multivariable models in patients with pre-adult onset MDD, is in accordance with the results of several studies in different populations and settings. In three studies of Zisook et al. (Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b), the STAR*D population was used to investigate factors that differentiate early and later onset MDD. The most prominent finding of the first two studies in 1,500 and 2,541 patients, respectively, was a higher rate of suicidality and more previous suicide attempts in the pre-adult onset MDD group (Zisook et al., 2004; Zisook et al., 2007b). In the third study on the combined sample the study population was divided into five age-at-onset groups. Earlier onset was again associated with more suicidality in multivariable analyses adjusted for age at interview, duration of illness and gender (Zisook et al., 2007a). Most other findings of the first study, like more anxiety disorders in the pre-adult onset group, and greater depressive symptom severity could not be replicated in the

second and third study. Our results are also in line with those of the National Comorbidity Survey, a large representative US population study in 9,289 respondents, where a higher degree of suicidal intent was associated with early onset MDD (Thompson, 2008).

In our study, there were no significant differences in a number of clinical characteristics, such as symptom severity or comorbid anxiety disorders, which were found previously in several clinical trial samples to differ between pre-adult and adult onset MDD (Benazzi, 2000; Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b). For example, after adjusting for age at interview and gender, pre-adult onset was found to be associated with more social and simple phobias and more alcohol abuse or dependence in a sample of 381 adult MDD patients who were recruited for outpatient clinical trials (Alpert et al., 1999). In a study of 269 MDD outpatients, partly consecutive referrals and partly recruited patients, patients with an MDD-onset before age 25 showed more irritability, anxiety, and more alcohol and drug use in multivariable models adjusting for age at interview (Parker et al., 2003). The fact that earlier cross-sectional studies identified other clinical differences between pre-adult onset and adult onset MDD patients might be explained by the differences in study design and populations. These clinical studies often used selected groups of patients that had been recruited for clinical treatment trials. It is known that clinical treatment studies, particularly Randomised Controlled Trials (RCTs), use stringent criteria for patient selection which may reduce the generalisability to routine clinical practice. For example, patients with suicidality, comorbidity or unsuccessful previous treatments are often excluded from RCTs (Zetin & Hoepner, 2007; Zimmerman et al., 2002; Zimmerman et al., 2005). If suicidal patients are excluded, finding an association between suicidality and age of onset would be impossible. (e.g. Alpert et al., 1999; Klein, 1999) On the other hand, one would expect to validate previous findings from more selected populations in a replication study with a naturalistic design. Since the results of studies carried out in naturalistic patient samples are more applicable to 'real-life' patients, the probability of finding 'true effects' is higher in these studies. Indeed, the finding of more suicidality in pre-adult onset MDD was the main finding of the three STAR*D trials, with a design that aimed to have maximum generalisability of patients in both specialty and primary care.

Another remarkable difference between previous cross-sectional studies and our study is the proportion of MDD patients that reported a pre-adult onset of MDD. The percentage (22%) of MDD patients that reported a pre-adult onset MDD in our study is lower than the 35-40% found in other studies (Alpert et al., 1999; Fava et al., 1996; Zisook et al., 2007a) also using a cut-off age of 18. Since both our study and these earlier studies obtained the age of onset retrospectively, this cannot explain the observed differences.

Hence, the differences are probably the result of differences in study design and study samples.

We found no differences between the groups in rates of patients with melancholic depression. The overall rate of 46.1% (509 from 1,105 patients, see table 3.2) is in line with previous prevalence estimates of melancholic depression in psychiatric specialty care outpatients, that vary from 16% to 67% (Mallinckrodt et al., 2005) depending on definitions being used.

The finding that patients with a pre-adult onset MDD are more likely to have attempted suicide and to have current suicidal thoughts could have several explanations. First, the increased occurrence of suicidality in pre-adult onset MDD could point towards a different variant of MDD, with a different genetic and familial load or other childhood experiences. Indeed, previous studies on suicidality in depression found that genetic factors and familial loading were risk factors for suicide attempts in depression as were early traumatic experiences (Malone et al., 1995). Unfortunately, no information about familial status or early trauma was ascertained in ROM in the study period. Second, MDD with an onset before age 18 could reflect a more severe variant of MDD. Suicidality and suicide attempts generally occur in severely depressed patients and hence can be interpreted as a marker of severity of psychopathology (Forman et al., 2004). However, this explanation is not supported by the results of our study as we did not find differences between the pre-adult and late-adult onset MDD patient on global measures of severity, e.g. MADRS scores or BSI total scores. A third explanation for the increased suicidality could be found in the time passed by since the onset of MDD as patients with pre-adult onset of MDD generally have been depressed longer or more often. Because we adjusted for current age and stratified in two age groups, we did not adjust for the highly correlated disease duration variable. Furthermore, in a sensitivity analysis in which we excluded all patients aged 20-25, the odds ratio's remained largely unchanged. Hence, we believe that our data do not support the explanation of the increased suicidality being the result of the longer disease duration or in patients with pre-adult onset MDD. A final explanation could be that the increased suicidality is a chance finding. However, the use of stratification with the consistent findings within each stratum, as well as the consistency with previous similar findings (Zisook et al., 2004; Zisook et al., 2007a; Zisook et al., 2007b; Thompson 2008) reduce the probability that this was a chance finding.

Strengths and limitations

Our study has several strengths. First, to our knowledge, few previous studies investigated the differences between pre-adult MDD and adult MDD in a naturalistic sample of secondary and tertiary care MDD outpatients. More than 80% of the patients referred for treatment of a MAS disorder between 2004 and 2007 in RD or the LUMC were included in the ROM-database. The external validity of these findings from real-life patients is likely higher than findings in samples from RCTs. Second, the reliability of the results was enhanced by replication of the findings in the two age group samples, ruling out the confounding of age. Most previous studies adjusted for current age (Parker et al., 2003; Ramklint & Ekselius, 2003) or age and duration of illness (e.g. Zisook et al., 2004; Zisook et al., 2007b), which may still leave room for residual confounding. Third, in addition to using a cut-off age of 18 years like in most previous studies, we performed a sensitivity analysis in which we used a cut-off age of 25 years to distinguish between pre-adult and adult onset MDD. This analysis yielded largely comparable results.

A limitation of our study is the fact that the initial onset of MDD was assessed retrospectively, by using self-report estimates, which limits the reliability. This was also the case in many previous studies. This method is more prone to measurement error and bias than assessment through medical records, e.g., a current depressive state can cause recall bias regarding the exact age of onset of the first depressive episode. In addition, the retrospective assessments did not allow for more subtle distinctions, such as the between the onset of first symptoms and the onset of the full syndrome. However, as other studies also assessed age of onset retrospectively, this limitation is not restricted to our study. Other possible limitations include the fact that not all patients were included in the ROM database (e.g. due to language problems) and the fact that excluded patients with missing variables had different mean age, age of onset and MADRS score than included patients. Furthermore, no data regarding familial status, somatic comorbidity, Axis II disorders and information about (pharmacological) treatment was ascertained. Finally, by using the MINI-Plus diagnostic interview we were not able to make a distinction between principal and comorbid diagnoses.

Conclusion

Overall, our findings in a large naturalistic cohort of outpatients with MDD confirm earlier studies that found pre-adult onset MDD associated with more suicidality. Our study stresses the importance of taking the age of onset of MDD in account in clinical decision making and suicide risk assessment.

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