Differences Between Early and Late Onset Adult Depression

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Abstract: *Background:* It is unclear, whether age-of-onset identifies subgroups of depression.

Aim: To assess the clinical presentation of depression with onset in the early adult age (18-30 years) as compared to depression with later onset (31-70 years).

Method: A total number of 301 patients with first episode depression were systematically recruited. Characteristics including psychiatric co-morbidity, personality disorders and traits, stressful life events prior to onset, family history, and treatment outcome were assessed by structured interviews and compared by chi-square tests for categorical data, t-tests for continuous parametric data and Mann-Whitney U-test for continuous nonparametric data. Logistic and multiple regression analyses were used to adjust the analyses for potentially confounding variables.

Results: Patients with early onset of depression were characterised by a higher prevalence of co-morbid personality disorders, higher levels of neuroticism, and a lower prevalence of stressful life events preceding onset compared to patients with later age-of-onset. There were no differences in severity of the depressive episode, treatment outcome or family loading of psychiatric illness.

Conclusion: Early adult onset of depression is associated with co-morbid personality deviances, whereas late onset is associated with environmental risk factors.

Keywords: Depression, age-of-onset, stressful life events, neuroticism, personality disorder.

INTRODUCTION

Age-of-onset has been suggested as a valid alternative to recurrence and polarity for classifying mood disorders [1]. However, it is not clarified, whether age-of-onset identifies subgroups of affective disorders or how to define the cut-off age. The majority of previous studies on characteristics of depression according to age-of-onset fall in two categories: Studies that have evaluated childhood or adolescent onset depression in comparison with adult depression (typically cut-off of 18-21 years) [2-5] and studies that have compared patients with late-life onset of depression to patients with earlier onset (typically a cut-off of 55-65 years) [6-10]. The age groups used in these studies are motivated by hypotheses of different aetiologies of depression, for example an increased familial loading for depression among patients with pre-adult depressions [5] and more vascular risk factors among patients with late-life depressions [11]. In contrast, there is a paucity of investigations of the impact of age-of-onset among patients with onset of depression in the ages between these extremes [12]. Moreover, previous studies have included mixed samples of patients with single and recurrent depressions. Consequently, age–of-onset has been assessed retrospectively among patients who might have experienced a number of episodes in the intervening time period between onset and assessment. This method implies a risk of confounding, since, as stated by the authors of the STAR*D study, "some of the factors ostensibly related to age of onset might actually be accounted for by current age, duration of illness and gender" [4]. Additionally, recall bias may influence the assessment of a number of variables, for example the experience of stressful life events prior to onset, due to the long time intervals between the time of onset and the time of the examination.

The present study aimed to assess the validity of a phenomenological distinction between depression with age-of-onset between 18 and 30 years (hereafter designated early adult depression (EAD)) and depression with later ages at onset (31-70 years, hereafter designated late adult depression (LAD)) by comparing a range of clinical and socio-demographic characteristic between these two groups. There is no consensus about the appropriate cut-off ages in previous studies assessing the impact of age-of-onset. In one study of 198 non-psychotic and non-melancholic outpatients [31], the median age at onset of the first depressive episode (29 years) was used to define early onset as compared to late onset depression. The clinical differences between the two groups (early onset depressions had significantly more recurrences, atypical features, irritability, interpersonal sensitivity and more frequently a family history of mood disorders) gradually disappeared as the age cut-off was increased to 40, 50 and 60 years, respectively, thereby providing some evi-

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dence for a cut-off age around 30 years. Hence, this was also used in the present study. In order two reduce recall bias and confounding by the history of depression among participants, we included only patients with a recent onset of the first lifetime depressive episode, sytematically recruited by means of the Danish Psychiatric Central Research Register [13], which was also used to characterise non-participants in the study.

MATERIALS AND METHODOLOGY

The Register

The Danish Psychiatric Central Research Register is a nation-wide registration of all psychiatric hospitalisations and outpatient contacts (patients in ambulatory care or community psychiatry centres) in Denmark [13]. The register comprises information on treatment settings, duration of contact to psychiatric care, and psychiatric diagnoses (from 1994 January 1 according to The International Classification of Diseases, 10th Revision, ICD-10 [14]. The registration is based on a unique person identification number assigned to all inhabitants in Denmark (Civil Person Registration number), thus previous contacts to psychiatric services can be established with great certainty irrespective of changes in names or addresses. General practitioners and psychiatrists in private practice do not report to the register. No private psychiatric hospitals are operating in Denmark.

The Sample

The study sample was defined as all outpatients (patients in hospital ambulatory care and community psychiatry centres) and inpatients (patients admitted during daytime or overnight to a psychiatric hospital) with the diagnosis of a single depressive episode (ICD-10, code DF32-32.9) reported to the Danish Psychiatric Central Research Register following the first contact ever to a psychiatric hospital in eastern Denmark (Sealand (Sjælland)) and aged 18-70 years at the time of discharge. This area comprises approximately 2.4 million inhabitants corresponding to 44% of the total Danish population. Patients were sampled consecutively from the register every second month in a period from 2005 June 1 through 2007 May 31 and invited to participate in the study 1-3 months after discharge. In order to obtain a homogeneous sample, we included only individuals of Danish ethnicity (the proband as well as both parents were born in Denmark and no grandparents were born outside Europe). Since we intended to evaluate response to antidepressant treatment, individuals who never received antidepressant medication (for at least one week), were excluded. The only exclusion criteria were significant physical illness, dementia or mental retardation.

The Danish Ministry of Health, The Danish Ethic Committee (KF 01.209/04) and the Data Inspection approved the study. The investigation was conducted in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent.

Interviews and Questionnaires

The interviews were conducted by two experienced medical doctors (CB and JDB) using standardized semi-structured interviews. The interviewers conducted co-ratings of 10 interviews in a pilot study and of additional 16 interviews during the 2-year inclusion period.

In order to validate the clinical diagnoses reported to the register, psychiatric diagnoses according to ICD-10 criteria were obtained using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [15]. The diagnostic evaluation was based on the interview with the patient and data from case reports, which were available for 79.1 % of the participants. ICD-10 diagnoses according to the SCAN interview were established for the episode leading to psychiatric hospital contact and for the lifetime before. Both interviewers followed a WHO-certified course in the use of the SCAN. The reliability coefficient (agreement of the diagnosis of a single depressive episode) was 1.0. Atypical features were established in terms of reversed vegetative symptoms (overeating and oversleeping), which has been proposed as a simple definition of atypical depression [16].

Diagnoses of personality disorders (PD) were assessed according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) [17]. The reliability coefficient (agreement of the diagnosis of a personality disorder of any kind) was 0.76.

The presence of life events in a period of six months prior to onset of the depressive symptoms was assessed by means of the Interview for Recent Life Events (IRLE) [18], which specifies 64 different life events in nine areas comprising work, education, financial conditions, health, bereavement, migration, courtship and cohabitation, legal matters, family and social affairs, and marital relations. For each life event, detailed information was recorded in order to assess the time of occurrence, the independency of the depressive state (rated from almost certainly independent to almost certainly dependent on a five point scale) and the negative impact of the event (rated from no negative impact to severe negative impact on a five point scale). In line with the guidelines for the use of IRLE, the evaluation of negative impact was based on an objective judgement made by the interviewer taking into account the individual and contextual circumstances. Stressful life events (SLE) were defined as those events, which were rated certainly or most likely independent of the depression (an independency score of 1-2 in IRLE) and of moderate to severe negative impact (an impact score of 1-3 in IRLE). The reliability coefficient between the to interviewers (agreement of the presence of one or more stressful life events) was 0.82.

A complete medical treatment history was evaluated using the Treatment Response to Antidepressants Questionnaire (TRAQ) [19]. Each antidepressant medication and each combination of different antidepressants or add-on treatments with other classes of drugs (lithium, anticonvulsants or neuroleptics) were assessed as separate antidepressant trials. For each trial the duration, dosages, setting, compliance and outcome (rated from no effect to very good effect on a five-point scale) were recorded.

The family history of psychiatric illness, substance abuse and suicide among first and second-degree relatives were evaluated using a modification of the Family History Method [20]. The reliability coefficient (agreement of a family history of depression among first-degree relatives) was 0.91.

Severity of depressive symptoms at the time of the interview was assessed using the 17-item Hamilton Depression Rating Scale (Ham-D 17) [21] and the 21-item Beck Depression Inventory (BDI 21) [22]. Moreover, the participants completed questionnaires regarding personality traits (Eysenck Personality Questionnaire, EPQ [23]) and anxiety symptoms (the 14-item Anxiety Subscale of the Symptom Rating Scale for Depression and Anxiety [24]). Only complete answers of the questionnaires were included in the analyses (BDI: N=285, Anxiety Subscale: N=290, EPQ: N=243).

Outcome was assessed in two levels: 1) remission following the first adequate antidepressant trial and 2) Ham-D 17 score and BDI 21 score at endpoint (the time of examination), that is the final outcome of the overall treatment as given in clinical practice. An adequate antidepressant trial was defined in accordance with the Antidepressant Treatment History Form (ATHF) by Sackheim [25] as treatment with an antidepressant drug for $\geq$ 4 weeks in a sufficient dosage (corresponding to a score of 3 or above in ATHF) and in addition with $\geq$ 85% compliance (corresponding to a score of 4 in the TRAQ). Remission was defined as a HAM-D 17 score $\leq$ 7 at the interview as well as a response score of 4 or above in TRAQ. Non-remission was established, when the initial antidepressant treatment has been discontinuated because of insufficient effect. Discontinuation was defined as either a shift to another antidepressant or add-on treatment with lithium, another antidepressant drug (except for mianserin in doses not higher than 20 mg and amitriptylin or nortriptylin in doses not higher than 25 mg per day), or an antipsychotic drug in a dosage equivalent to 100 mg chlorpromazine per day or above.

Onset of depression, defined as the time point, when the patient first experienced significant depressive symptoms, was established during the SCAN interview. If it was impossible to determine a more precise date of onset, onset was defined as the time, when the patient was seeking professional care because of depressive symptoms for the first time.

Non-Participants

Register information on age, gender, treatment settings (inpatient/outpatient), diagnoses, and the duration of psychiatric hospital contact was available for all participants as well as non-participants in the study. Additional information was collected for non-participants on ethnicity, adverse life events prior to onset of depression, treatment with antidepressants, and overall subjective improvement during the treatment period (in three categories "yes", "no", and "unsure/perhaps") by a structured telephone interview or alternatively by a questionnaire including the same questions, which was posted to all non-participants.

Statistical Analysis

Patients with EAD and LAD were compared with regard to demographic and clinical variables using chi-square tests for categorical data, t-tests for continuous parametric data and Mann-Whitney U-test for continuous nonparametric data. We used logistic and multiple regression analyses to test the effects of age-of-onset adjusted for the effect of gender, and other potentially confounding variables on categorized and continuous outcome variables, respectively.

Because of the large number of variables tested in univariate and adjusted analyses, p-values (two-sided) $\leq$ 0.005 were regarded to indicate statistical significance, and p-values (2-sided) between 0.005 and 0.05 were regarded to indicate a trend. The tests were performed with SPSS 15.0 for windows (Release 15.0.0 (6 sep 2006)).

RESULTS

Participants and Non-Participants

In total, 1486 individuals with the main diagnosis of a single depressive episode were sampled from the register, 480 individuals were excluded (owing to data protection (N=78), non-pharmacological treatment (N=78), non-Danish ethnicity (N=291), death (N = 9), disability (N = 14), or migration (N = 10)), 399 participants took part in the full face-to-face interview (participation rate 39.7%) and 238 individuals (39.2% of the non-participants) completed the short questionnaire or telephone interview. The participants did not differ from the non-participants with respect to age at discharge, severity of depression (mild, moderate or severe according to register diagnoses), setting (in- or outpatients), duration of hospital contact, prevalence of SLE or overall subjective improvement during treatment (p>0.1). An excess of women participated in the study (64.9% *vs.* 58.5%, p=0.04). Among the 399 participants, the diagnosis of a single depressive episode according to ICD-10 was established by the SCAN interview for 301 individuals, who constituted the sample for further analyses. The remaining participants obtained diagnoses of recurrent depression (11.0%), bipolar disorder (3.3 %), dysthymia (0.5%), schizophrenia (1.0 %) and various other diagnoses (8.8 %)).

Socio-Demographic Characteristics According to Age of Onset

Ninety-nine of the 301 participants (33%) had onset of the first depressive episode at the age of 30 or below. Table **1** presents socio-demographic characteristics according to age of onset. As can be seen, more females presented with EAD compared to male patients. There was a higher proportion of the patients with EAD who were employed or students and a higher proportion who were living alone as compared to patients with LAD.

Treatment Characteristics According to Age of Onset

The majority of participants had received more than one antidepressant trial defined as treatment with different antidepressants, different combinations of antidepressants, or different add-on treatments with lithium, anticonvulsants or neuroleptics. There were no significant differences between the patients with EAD and LAD in the total number of antidepressant trials (1 trial: 48.5% *vs.* 38.6%, 2 trials: 25.3% *vs.* 23.3%, 3 trials: 14.1% *vs.* 20.8%, $\geq$4 trials: 12.2% *vs.* 17.3%, p=0.4), in the type of drug given as first-line treatment (selective serotonin reuptake inhibitors: 76.8% *vs.* 62.9%, serotonin and norepinephrine reuptake inhibitors: 12.1% *vs.* 14.4%, noradrenergic and specific serotonergic antidepressant: 8.1% *vs.* 19.2%, tricyclic antidepressants: 1.1% *vs.* 2.0%, other or unknown treatment 2.0% *vs.* 1.5%, p=0.4), or

Table 1. Socio-Demographic Characteristics of the Participants, Totally and by Age-Of-Onset

Characteristic	Total (N=301)	Age ≤ 30 Years (N=99)	Age > 30 Years (N=202)	P [1]
Gender (female), N (%)	199 (66.1)	84 (84.8)	115 (56.9)	<0.0005
Work status[2], N (%) Unemployed, sick leave or retired Employed or student	 67 (24.2) 210 (75.8)	 7 (7.6) 85 (92.4)	 125 (67.7) 60 (32.4)	<0.0005
Marital status[3], N (%) Married/living together Living alone	 148 (54.2) 125 (45.8)	 31 (36.0) 55 (64.0)	 117 (62.6) 70 (37.4)	<0.0005

[1)] P-values (2-sided) in analyses comparing patients with early and late onset (χ^2-test).

[2)] Data missing from 24 patients.

[3)] Data missing from 28 patients.

Table 2. Clinical Characteristics of 301 Patients with First Episode Depression, Totally and by Age-of-Onset

Characteristic	Total (N=301)	Age ≤ 30 Years (N=99)	Age > 30 Years (N=202)	P [1]	B /OR (95% CI) [2] Early *vs* Late Onset (Adjusted for Gender)	P [3]
Severity of depression[4], N (%) Mild Moderate Severe	 73 (24.3) 161 (53.5 67 (22.3)	 19 (19.2) 56 (56.6) 24 (24.2)	 54 (26.7) 105 (52.0) 43 (21.3)	 0.4	 0.6 (0.3-1.2) 0.8 (0.4-1.5) 1	 0.1 0.5
Melancholic features[4], N (%)	196 (65.1)	58 (58.6)	138 (68.3)	0.1	0.7 (0.4-1.2)	0.2
Psychotic features[4], N (%)	13 (4.3)	4 (4.0)	9 (4.5)	0.9	1.4 (0.4-5.0)	0.6
Suicidal ideations[4], N (%)	194 (64.5)	69 (69.7)	125 (61.9)	0.2	1.6 (0.9-2.7)	0.09
Atypical features[4], N (%)	11 (3.7)	10 (10.1)	1 (0.5)	<0.0005	15.4 (1.9-122.9)	0.01
Psychiatric co-morbidity[4], N (%) Anxiety/OCD Alcohol abuse Drug abuse Somatoform/eating disorders	 143 (47.5) 45 (15.0) 22 (7.3) 14 (4.7)	 53 (53.5) 7 (7.1) 14 (14.1) 8 (8.1)	 90 (44.6) 38 (18.8) 8 (4.0) 6 (3.0)	 0.1 0.007 0.001 0.05	 1.2 (0.7-2.0) 0.4 (0.2-0.9) 4.1 (1.6-10.8) 2.1 (0.7-6.4)	 0.4 0.03 0.004 0.2
Personality disorders[5], N (%) Any personality disorder Cluster A Paranoid Schizotypal Schizoid Cluster B Antisocial Borderline Histrionic Narcissisitic Cluster C Evasive Dependent Obsessive-compulsive Depressive	 96 (31.9) 3 (1.0) 3 (1.0) 3 (1.0) 9 (3.0) 35 (11.6) 0 1 (0.3) 30 (10.0) 12 (4.) 19 (6.3) 26 (8.6)	 55 (55.6) 2 (2.0) 2 (2.0) 2 (2.0) 5 (5.1) 26 (26.3) 0 0 14 (14.1) 9 (9.1) 10 (10.1) 14 (14.1)	 41 (20.3) 1 (0.5) 1 (0.5) 1 (0.5) 4 (2.0) 9 (4.5) 0 1 (0.5) 16 (7.9) 3 (1.5) 9 (4.5) 12 (5.9)	 <0.0005 0.2 0.2 0.2 0.1 <0.0005 - 0.5 0.09 0.002 0.06 0.02	 4.8 (2.8-8.3) 2.8 (0.2-31.1) 8.2 (0.7-105.7) 4.8 (0.4-62.1) 3.5 (0.1-1.8) 6.2 (2.7-14.2) - - 1.6 (0.7-3.4) 9.8 (2.3-41.0) 3.4 (1.2-9.4) 2.0 (0.9-4.7)	 <0.0005 0.4 0.1 0.2 0.09 <0.0005 - - 0.3 0.002 0.02 0.1
Personality traits[6], mean (SD) Neuroticism-score Extroversion-score	 11.6 (6.3) 11.5 (5.4)	 14.0 (5.5) 11.4 (5.7)	 10.5 (6.3) 11.5 (5.3)	 <0.0005 0.9	 -2.7 (-4.4- -1.0) -0.05 (-1.6-1.5)	 0.002 1.0
Anxiety score[7], mean (SD)	10.2 (6.2)	10.7 (5.7)	10.0 (6.4)	0.4	0.1 (-1.4-1.7)	0.9
Family history of psychiatric illness in 1. generation, N (%) Depression Any psychiatric illness	 87 (28.9) 199 (66.1)	 33 (33.3) 67 (67.7)	 54 (26.7) 132 (65.3)	 0.2 0.7	 1.4 (0.8-2.5) 1.0 (0.6-1.6)	 0.20 0.9

Table 2. cont…..

Characteristic	Total (N=301)	Age ≤ 30 Years (N=99)	Age > 30 Years (N=202)	P [1]	B /OR (95% CI) [2] Early *vs* Late Onset (Adjusted for Gender)	P [3]
Family history of suicide in 1. generation, N (%)	10 (3.3)	2 (2.0)	8 (4.0)	0.4	0.5 (0.1-2.3)	0.3
One or more stressful life events[8], N (%)	189 (62.8)	46 (46.5)	143 (70.8)	<0.0005	0.4 (0.2-0.7)	0.001

[1)] P-values (2-sided) in univariate analyses comparing patients with early and late onset (χ^2-test categorical data and t-test for continuous data).

[2)] Correlation coefficients in multiple regression models / odds-ratios in logistic regression models; the effect of age-of-onset adjusted for the affect of gender.

[3)] P-values (2-sided) in the regression models.

[4)] According to Schedules for Clinical Assessment in Neuropsychiatry (SCAN).

[5)] According to The Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).

[6)] According to Eysenck Personality Questionnaire (EPQ).

[7)] According to Symptom Rating Scale for Depression and Anxiety, Anxiety Subscale.

[8)] According to Interview of Recent Life Events (IRLE).

in total duration of treatment (median duration: 8.0 month (quartiles 5.0-13.8) *vs.* 7.5 month (quartiles 5.3-13.0), p=0.7), but there was a trend for more patients with LAD being treated in inpatient settings (inpatients: 52.5% *vs.* 64.9%, p=0.04).

Clinical Characteristics of Patients According to Age-of-Onset

Table **2** presents clinical characteristics according to age at onset, unadjusted and adjusted for the effect of gender. Comparison of patients with EAD and LAD revealed several significant differences between the groups. As can be seen from Table **2**, the patients with EAD were characterized by a substantial higher prevalence of any co-morbid personality disorder (PD), also when adjusted for the effect of gender. This difference between the age groups reached significance in separate analyses comparing the prevalence of dependent PD (adjusted p = 0.002) and borderline PD (adjusted p < 0.0005), respectively. Also, there was a trend for a higher prevalence of obsessive-compulsive PD among patients with EAD when adjusted for the effect of gender (adjusted p = 0.02). Further, a higher level of neuroticism characterized EAD. Drug abuse (of any kind inclusive cannabis) was more frequent among patients with EAD; on the other hand, there was a trend for less prevalent alcohol abuse among patients with EAD. The experience of stressful life events prior to the onset of depression was significantly less prevalent among patients with EAD compared to patients with LAD. Severity of depression as reflected in the ICD-10 diagnoses obtained by SCAN interview did not differ between patients with EAD and LAD, and subdivisions according to symptomatology revealed differences neither in melancholic or psychotic features, nor in the prevalence of suicidal ideations, though there was a trend for more patients with EAD presenting atypical features. Moreover, there was no gender difference in family history of psychiatric illness or suicide.

In order to examine the positive findings in more details, we performed additional multivariate analyses. Even though the severity of depressive symptoms was rather low at the time of interview (mean Ham-D 17 score was 9.3 (S.D. 6.2), and 44.5% of the participants had a Ham-D 17 score ≤ 7), remaining depressive symptoms could have influenced the assessment of PD and the reporting of stressful life events. Thus, we analysed the combined effects of age-of-onset, gender, and Ham-D score at the time of interview on the prevalence of PD and SLE, respectively, in logistic regression analyses, which revealed only minor changes in the effects and significance levels (results not presented). Since impulsive behaviour, e.g. by drug abuse, is a criterion for borderline PD, we tested whether the excess of drug abuse among young patients was independent of this diagnosis. Including co-morbidity of borderline PD in the regression analysis together with age-of-onset and gender as independent variables revealed a smaller and non-significant effect of age-of-onset on the prevalence of drug abuse (OR=2.8, 95%CI: 1.1-7.1, p=0.03), indicating that the excess of drug abuse among patients with EAD was partly attributable to more prevalent borderline PD in this group.

Clinical Outcome According to Age-of-Onset

Among the non-remitters, 28 individuals had never received an adequate antidepressant trial according to the definition used, and consequently they were excluded from the analyses of remission following the first-line treatment. Two patients, who initially got ECT, were also excluded, leaving a total number of 271 individuals for these analyses. All of the 301 participants were included in the analyses of the final outcome expressed as Ham-D 17 score at endpoint (the time of the interview), and all of the 285 participants, who completed the BDI 21, were included in the analyses of outcome expressed as BDI score. As can be seen from Table **3**, age-of-onset did not influence the rate of remission on first-line treatment. Patients with EAD reported more depressive symptoms at endpoint as measured on BDI, though when adjusted for gender this difference only reached borderline significance (p = 0.008). In contrast, the symptom severity as measured on HAM-D did not differ between the two age groups.

Because of the difference in symptom severity as assessed by BDI and HAM-D, respectively, we considered that the reporting of subjective symptoms in BDI could reflect personality traits rather than a state phenomenon. Therefore, we included neuroticism-score together with age-of-onset and gender in a multiple regression analyses with BDI-score as the dependent variable. In this model, the effect of age-of-onset on BDI-score was no longer significant (B= -1.2, 95% CI –3.4-1.0, p=0.3).

Table 3. Outcome of First Episode Depression, Totally and by Age-Of-Onset

Characteristic	Total (N=301)	Age ≤ 30 Years (N=99)	Age > 30 Years (N=202)	P [1]	B /OR (95% CI) [2] Early *vs* late Onset (Adjusted for Gender)	P [3]
Remission on first-line treatment, N (%)	79 (29.2)	27 (31.8)	52 (28.1)	0.5	1.3 (0.7-2.4)	0.4
Mean Ham-D 17 score at endpoint (S.D.) [4]	9.3 (6.2)	8.9 (5.8)	9.4 (6.3)	0.5	0.6 (-0.9-2.2)	0.4
Mean BDI 21 score at endpoint (S.D.) [5]	15.3 (9.9)	18.4 (10.3)	13.8 (9.4)	**<0.0005**	-3.4 (-5.8- -0.9)	**0.008**

[1)] P-values (2-sided) in univariate analyses comparing patients with early and late onset (χ^2-test categorical data and t-test for continuous data)

[2)] Correlation coefficients in multiple regression models / odds-ratios in logistic regression model; the effect of age-of-onset adjusted for the affect of gender

[3)] P-values (2-sided) in the regression models

[4)] 17-item Hamilton Depression Rating Scale (Ham-D 17)

[5)] 21-item Beck Depression Inventory (BDI 21)

DISCUSSION

Main Results

Patients with onset of depression in the early adult age (<30 years) were characterised by a substantially higher prevalence of co-morbid dependent PD and borderline PD, a higher level of neuroticism, a lower prevalence of stressful life events experienced during a six month period preceding onset, and, further, a trend towards a higher prevalence of atypical features compared to patients with later age-of-onset. The patients with early onset reported more subjective depressive symptoms (BDI 21 score) after treatment, however this difference disappeared after adjustment for the effect of gender and neuroticism. Further, there was no difference in the rate of remission following first-line antidepressant treatment and no difference in the symptom severity at endpoint assessed with Ham-D 17. Moreover, age-of-onset did not have any impact on severity of the depressive episode or on the prevalence of a family history of psychiatric illness. Patients with early onset had more drug abuse, but this difference seemed to be – at least in part – attributable to a higher prevalence of co-morbid borderline PD in this group.

Advantages of the Study

The inclusion of patients with recent onset of a single depressive episode, exclusively, is an important advantage. Further, the study participants were systematically recruited and register data on all non-participants plus additional information from questionnaires or telephone interviews on 39 % of the non-participants was included. Based on these data, our sample seems to be representative for a Danish population of patients in psychiatric hospital care diagnosed with a single depressive disorder. It is often supposed, that the estimated prevalence of PD among patients with depression may be influenced by the presence of depressive symptoms [26], even though this has not been found by all authors [27]. The same concern may apply to the evaluation of life events due to recall bias. We conducted the interviews some time following discharge (median 147 days, quartiles 119-184 days), that is to say, apart from the acute depressive state, thereby probably reducing this source of error. Further, we adjusted the regression analyses for the effect of Ham-D 17-score at the time of the interview. Treatment outcome was assessed in two stages: Outcome on first line antidepressant treatment as well as the final outcome following one or several antidepressant trials. These outcome measures reflect clinical reality and could be regarded as more relevant to clinical practice than the short-term outcome of randomised, controlled trials. Finally, we used comprehensive interviews to ensure a high validity of our data and a multidimensional approach, which enabled us to characterise the depressive disorder on a broad range of clinical variables and to adjust positive associations for the effects of potential confounders.

Limitations of the Study

Even though we included the participants shortly after onset of depression, SLE and personality factors were still assessed retrospectively and recall bias cannot be excluded. Remission on first-line treatment was also evaluated retrospectively. Further, the interviewers were not blinded to the age of the participants. We considered only recent SLE, since it has been shown, that the effect of environmental adversities is quickly declining with time [28]. More distant SLE, chronic stress, childhood adversities, social support or positive life events, which might also be associated with age-of-onset, were not evaluated. SLE were assessed in a wide sense. It is possible that age-of-onset is more or less associated with specific subtypes of SLE. The group of patients with LAD represent a larger age span than the EAD group and might be more heterogeneous than the younger patients, since the older patients in the LAD group probably present greater brain atrophy and poorer physical health and also face the psychosocial factors of old age. Finally, and probably most importantly, we investigated a sample of patients referred to psychiatric hospital care, and consequently our findings cannot be generalized to patients with milder depressions treated in primary care.

Methods of Previous Studies

All studies of clinical differences between early and late onset depression have included mixed samples of patients with various numbers of subsequent depressive episodes. This method implies three important limitations. Firstly, determining the onset of the first depressive episode retrospectively is uncertain due to the time interval between age at onset and current age and there seems to be a substantial risk of recall bias. Secondly, since the participants with earlier onset are usually younger at entry into the studies [12, 29-31] and have a longer total length of illness and more depressive episodes [12], it becomes difficult to distinguish the effect of current age and different courses of illness from differences related to age-of-onset *per se*. Thirdly, there is no control of selection, when patients are included at some later point in the course of illness. This will inevitably result in

selection bias; for example, it seems reasonable to believe, that patients with many recurrences, a poor response to treatment, more pronounced co-morbidity or more serious psychosocial consequences of the illness have a higher tendency to seek professional care and therefore a higher chance of being enrolled in clinical investigations. None of the studies has presented data on non-participants. Thus, the influence of selection on the findings cannot be further estimated. The present study was designed to oppose these methodological problems by using a systematic recruitment procedure and by investigating depression at onset (i.e. patients with first lifetime depressive episode).

Results of Previous Studies

The majority of studies on age differences in the phenomenology of depression have focused either on childhood and adolescent depression (onset before 18-21 years) (e.g. [2-5]) or on late-life depression (onset after 55-65 years) (e.g. [6-10]). A few studies have used a cut-off age of 25-35 years, hence grouped some cases of early adult onset depression together with the childhood / adolescent onset group [29-33]. These studies have reported a higher prevalence of co-morbid PD [29, 30] and anxiety [29], a poorer response to treatment [29], more atypical features [31], higher levels of suicidal ideation [33], and more frequent family history of mood disorders [29, 31] among patients with early onset compared to later onset of depression. Further, the group of patients with onset of depression before the age of 25-35 years seems to be characterized by female gender [32, 33] and more severe and recurrent courses of illness [29, 31, 32]. However, all of the above-mentioned studies included pre-adult depressions in the early onset group, hence it is difficult to determine, how far the characteristics of this age group derived from patients with childhood or adolescent depression or from patients with early adult depression. Only one large study [12] has divided the age of onset further into pre-adult (age < 18 years), early adult (age 18-44), middle adult (45-59) and late adult (age 60 +). In this study, there were fewer clinical differences between the adult age groups than between pre-adult and adult depression, though the authors still found early adult onset depression to be associated with higher family loading for affective disorders, more prevalent co-morbid anxiety and greater symptom severity and suicidal ideation as compared to those with middle and late adult onset. This might be due to the exclusion of patients with pre-adult onset from the early adult group, or it could be a consequence of the rather broad age category defining early adult depression compared to other studies. We did not replicate the findings of a poorer treatment outcome, increased suicidality and greater family loading of affective disorder among patients with early onset. There may be several reasons for these discrepancies between our findings and findings from other studies. Firstly, treatment outcome and suicidal ideations assessed in previous studies relate to the index episode and not exclusively to the first episode as in the present study. Secondly, it seems that these characteristics are general terms of illness severity, which are probably associated with a higher risk of recurrence of chronicity. Thus, previous findings might be a consequence of selection bias (individuals with early onset have a higher probability of being enrolled in studies performed many years later, if they have a chronic course or many recurrences). Thirdly, the results might be confounded by current age and the history of depression among participants (the clinical appearance of the depressive episodes might chance during the course of repeated episodes or with increasing age [34]. This explanation is further supported by a large study of age differences, in which objective severity scale scores increased with *current* age, whereas severity was not influenced by age-of-onset [6]. Otherwise our results were consistent with previous studies regarding co-morbid PD, anxiety, atypical features, and gender. The prevalence of SLE has been investigated in one study by means of self-report questionnaires (cut-off age 25 years), finding no difference between patients with early and late onset depression [29]. Besides using questionnaires instead of interviews, patients with melancholic depression were excluded, which might also have influenced the prevalence of SLE among the participants. No other study has evaluated SLE in age groups comparable to the present study, but assessment of SLE in late-life depression as compared to depression with earlier onset have provided divergent results [8, 35].

CONCLUSION

Patients with onset of depression in the early adult age (18-30 years) were characterised by a higher level of neuroticism and a higher prevalence of co-morbid PD and they had less often experienced SLE prior to onset compared to individuals experiencing the first depression at a later age (31-70 years). The results point to aetiological divergences not only between the extreme age groups such as childhood and geriatric depressions (genetic susceptibility *versus* vascular brain pathology), but also between early adult and late adult onset depressions (personality factors versus environmental factors).

ABBREVIATIONS

ATHF	=	Antidepressant Treatment History Form
B	=	Correlation Coefficient
BDI 21	=	Beck Depression Inventory (21 item)
CI	=	Confidence Interval
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EAD	=	Early Adult Depression
EPQ	=	Eysenck Personality Questionnaire
Ham-D 17	=	Hamilton Rating Scale of Depression (17 item)
ICD-10	=	The International Classification of Diseases, 10th Revision
IRLE	=	Interview of Recent Life Events
LAD	=	Late Adult Depression
OR	=	Odds Ratio
PD	=	Personality Disorder

SCAN = Schedules for Clinical Assessment in Neuropsychiatry

SCID II = Structured Clinical Interview for DSM-IV axis II personality disorders

SD = Standard Deviation

SLE = Stressful Life Event

SPSS = Statistical Package for the Social Sciences

WHO = World Health Organization

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DISCLOSURE

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