



Early-onset late-life depression: Association with body mass index, obesity, and treatment response

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ARTICLE INFO

Keywords:

Depressive disorder
Late-life depression
Chart review
Obesity
Treatment outcome

ABSTRACT

Early-onset (EOD) and late-onset (LOD) late-life depression might differ in etiology, clinical features, and treatment response. While EOD is more frequently associated with a family history of affective disorders and personality aspects, LOD is thought to be more strongly driven by acquired cerebrovascular risk factors associated with vascular pathology, executive dysfunction, and poor treatment response. However, in a systematic review, EOD and LOD only differed in the frequency of affective disorders in the family history. We compared EOD versus LOD using medical records. In this retrospective chart review, elderly depressed patients (N = 108; mean age: 69.0 ± 7.2 years) were characterized by sociodemographic, psychiatric, and somatic variables and divided according to age-at-onset (cut-off: 60 years): EOD (N = 67, mean age-at-onset: 40.2 ± 13.6 years) and LOD (N = 41, 67.5 ± 6.3 years). A family history of affective disorders was more common in EOD than LOD patients (49.2% vs. 19.5%). EOD patients had a higher body mass index (mean: 27.0 kg/m² vs. 23.1 kg/m²) and were more often obese compared with LOD patients (20% vs. 0%). There were fewer treatment responders in the EOD group than in the LOD group on trend level significance (46.3% vs. 63.4%). Higher frequency of affective disorders in the family history is compatible with a greater genetic risk of EOD. The larger metabolic burden of EOD might stem from the longer duration of depressive illness.

1. Introduction

In the elderly, major depressive disorder is linked to increased disability, healthcare utilization, and cardiovascular and all-cause mortality [1,2]. Depression in the elderly can be classified according to the age at onset as either a) recurrent disease with previous episodes earlier in life (early-onset depression [EOD]) or b) first episode in old age (late-onset depression [LOD]). However no consensus exists on the age cut-off differentiating between EOD and LOD in late-life depression [3]. Several authors have argued that there are distinct differences in the pathogenesis of EOD and LOD. While EOD is more frequently associated with a family history of affective disorders and personality aspects, LOD is thought to be more strongly driven by acquired cerebrovascular risk

factors associated with vascular pathology, executive dysfunction, and poor response to antidepressants according to the vascular depression hypothesis [4]. However, even individuals with EOD may be at risk of transitioning to vascular depression with aging since studies have demonstrated a bidirectional link between depression and metabolic syndrome, the concurrence of obesity-associated cardiovascular risk factors [5]. In fact, the risk of metabolic syndrome may even be higher for EOD than LOD because of the effects of poor health risk-related behaviors (such as smoking, unhealthy diet, and physical inactivity) associated with depression, and the longer exposure to drugs used to treat depression [6,7]. Importantly, cardiovascular diseases have been associated with worse treatment outcome and higher premature mortality in depression [8,9]. However, no differences have been found in

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<https://doi.org/10.1016/j.cpnec.2021.100096>

Received 16 August 2021; Received in revised form 19 October 2021; Accepted 22 October 2021

Available online 23 October 2021

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cardiovascular risk factors and treatment outcome between EOD and LOD in a systematic review, while the only clinical feature that differed was a higher frequency of affective disorders in the family history of EOD patients [10].

We conducted a retrospective chart review and compared socio-demographic, psychiatric, and somatic variables, and treatment outcome in EOD and LOD using medical records. While we expected both groups to be similar in their clinical presentation of depression, we expected a higher frequency of affective disorders in the family history of EOD patients and more cardiovascular risk factors in LOD patients. Because cerebrovascular lesions and reduced hippocampal volume have been associated with worse treatment outcome in late-life depression (LLD) [11–13], we visually assessed MRI scans in a subgroup of patients for white matter hyperintensities (WMH) and medial temporal lobe atrophy (MTA) in an exploratory manner.

2. Methods

2.1. Sample

For this retrospective study, we included medical chart data from 108 consecutive elderly depressed patients (≥ 60 years old) treated on a specialized psychiatry inpatient unit for affective disorders at Charité University Berlin, Dept. of Psychiatry, Campus Benjamin Franklin, between January 2014 and December 2016. The study was a sub-sample of a previous report on predictors of treatment outcome in depressed patients and consisted of all patients ≥ 60 years old [14]. There were no standardized criteria used for admission except for the clinical judgment of the attending psychiatrist that the patient is primarily suffering from an affective disorder and requires inpatient treatment. Further details regarding sampling can be found in Chae et al. [14]. The primary analyses were conducted using all patients ≥ 60 years old ($n = 108$; EOD: $n = 67$; LOD: $n = 41$). In a sensitivity analysis, we controlled for age and sex effects by matching patients in the EOD group ($n = 41$) as closely as possible with patients in the LOD group ($n = 41$) using the “optmatch” package (version 0.9.3) in R (version 3.1.3; <http://www.r-project.org>). In a second sensitivity analysis, we excluded patients with bipolar depression ($n = 10$). Results of both sensitivity analyses are reported in the supplementary information. This study was reviewed by the local ethics review committee. Written informed consent was not required for this review of routine clinical records.

To be included, patients had to meet International Classification of Diseases, 10th revision (ICD-10) diagnostic criteria for one of the following affective disorders: bipolar affective disorder; current episode of mild, moderate, or severe depression (F31.3x-5x); depressive episode (F32); or recurrent depressive disorder (F33). Exclusion criteria were schizoaffective disorder, schizophrenia, and bipolar affective disorder with a mixed current episode.

Following Grayson and Thomas [10], 60 years was the cut-off age for the first depressive episode to differentiate EOD (< 60 years) and LOD (≥ 60 years). Depression severity was assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) at admission.

2.2. Clinical measures

Variables were categorized into three domains. The first domain comprised *sociodemographic variables* including age, sex, number of years of education, employment status, and relationship status. The second domain consisted of *psychiatric variables* including symptom severity at admission, family history of affective disorders, family history of suicide or suicide attempts, psychotic symptoms in current episode, history of suicide attempts, number of psychiatric comorbidities and psychotropic medications, duration of current episode, chronic depression (defined as persistent depressive disorder diagnosis), and electroconvulsive therapy during hospital stay. The third domain contained *somatic variables* such as the number of somatic comorbidities and

medications, and the Charlson comorbidity index [15]. Cardiovascular and metabolic risk were assessed by the following variables: smoking status, body mass index (BMI), hypertension, diabetes, and hyperlipidemia as defined in Table 1. Obesity was defined as a BMI of 30 or higher and overweight as a BMI of 25.0–29.9. Unless stated otherwise, all measures were assessed at admission and laboratory measures were obtained in the fasting state to reduce variability associated with eating food.

2.3. MRI assessments

MRI examinations were conducted in a subgroup of patients during their hospital stay according to clinical considerations. Therefore, imaging variables were analyzed only in those patients (EOD: $n = 31$; LOD: $n = 25$) who received an MRI scan in an exploratory manner. A specialist (MFC) who was blinded to the clinical details visually rated WMH and MTA. WMH were scored using Fazekas scale [16] and MTA were scored using Scheltens scale [17] according to standardized procedures.

2.4. Treatment outcome

Treatment outcome was assessed using the MADRS at discharge. In 12 cases this was not available and treatment outcome was determined according to the hospital discharge report. Response to treatment was defined as a $\geq 50\%$ decrease in the MADRS score from baseline. Remission was defined as a MADRS score of < 10 at discharge.

2.5. Statistical analysis

Bivariate analyses were conducted to examine differences between EOD and LOD, responders and non-responders as well as patients with MRI and without MRI using Pearson’s chi-square test for categorical variables and *t*-tests for independent samples for continuous variables. Group differences in Fazekas and Scheltens scores between EOD and LOD were analyzed using the chi-square test after dichotomizing the ordinal scales into normal or abnormal scores of WMH (normal: 0–1; abnormal: 2–4) and MTA. Since MTA is age-dependent, we considered a normal score to be 0–1 in patients ≤ 70 years old, ≤ 2 in patients 70–80 years old, and ≤ 3 in patients > 80 years old [18]. MADRS scores at admission and discharge were analyzed using 2×2 ANOVA with repeated measures (between-subject factor: EOD vs. LOD; within-subject factor: admission vs. discharge). A *p*-value $< .05$ was considered to indicate statistical significance. All statistical analyses were performed using IBM SPSS Statistics 25.0.

3. Results

Table 1 presents sociodemographic and clinical characteristics, treatment outcome, and exploratory MRI findings for the whole group and for EOD and LOD separately.

3.1. Sociodemographic variables

Patients’ age ranged from 60 to 91 years (mean age: 71 ± 6.9 years) and differed ($p < .001$) between EOD (age range: 60–84 years; mean age: 66.7 ± 6.0 years) and LOD (age range: 60–91 years; mean age: 72.6 ± 7.7 years).

3.2. Psychiatric variables

EOD patients had a higher number of previous depressive episodes ($p < .001$) and previous hospitalizations ($p < .001$) than LOD patients. EOD patients had a higher frequency of affective disorders in their family history ($p = .002$) than LOD patients.

Table 1Comparison of sociodemographic and clinical characteristics, MRI findings, and treatment outcome between early-onset and late-onset depression.^a

Variables, unit	n	All patients (n = 108)		LOD (n = 41)		EOD (n = 67)		Statistics		
		Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	t/ χ^2	df	p
Sociodemographic variables										
Age, years	108	69.0	7.2	72.6	7.7	66.7	6.0	-4.482	106	< .001
Female, %	108	67	62.0	24	58.5	43	64.2	.344	1	.558
With partner, %	103	58	56.3	21	53.8	37	57.8	.155	1	.694
Length of education, years	96	10.9	1.6	10.9	1.6	10.9	1.6	.035	94	.972
Employed, %	100	14	14.0	4	10.8	10	15.9	.496	1	.481
Psychiatric variables										
Age at onset, years	108	50.6	17.5	67.5	6.3	40.2	13.6	-14.157	100.338	< .001
Family history of affective disorders, %	106	40	37.7	8	19.5	32	49.2	9.451	1	.002
Family history of suicide or suicide attempts, %	107	21	19.6	7	17.1	14	21.2	.275	1	.600
Number of psychiatric comorbidities	108	0.6	0.8	0.5	0.6	0.7	1.0	1.072	106	.286
Number of psychotropic medications	108	1.9	1.4	1.7	1.4	2.0	1.4	1.610	99	.111
Psychotic depression, %	108	18	16.7	9	22.0	9	13.4	1.329	1	.249
Bipolar depression, %	108	10	9.3	1	2.4	9	13.4	3.659	1	.056
History of suicide attempt, %	105	30	28.6	9	22.5	21	32.3	1.167	1	.280
Chronic depression, %	104	26	25.0	10	25.6	16	24.6	.014	1	.907
Duration of current episode, weeks	104	126.5	253.5	82.4	102.5	153.0	308.7	1.696	84.866	.093
Number of previous depressive episodes	96	4.0	5.0	1.7	1.0	5.6	6.0	4.801	59.387	< .001
Number of previous hospitalizations	103	3.5	2.8	2.5	1.4	4.2	3.2	3.665	90.729	< .001
ECT, %	108	34	31.5	13	31.7	21	31.3	.002	1	.968
MADRS score at admission	96	26.6	7.5	25.7	8.2	27.2	7.0	.967	94	.336
Somatic variables										
Number of somatic comorbidities	108	4.4	3.3	4.5	3.6	4.3	3.2	-.321	106	.749
Number of somatic medications	108	2.7	2.6	2.9	2.4	3.0	2.6	-.146	95	.885
Current smokers, %	107	37	34.6	10	25.0	27	40.3	2.591	1	.107
BMI at admission	99	25.5	4.5	23.1	3.5	27.0	4.4	4.676	97	< .001
Overweight (BMI 25.0–29.9), %	99	40	40.4	13	31.7	27	45.0	1.336	1	.248
Obese (BMI \geq 30), %	99	12	12.1	0	0.0	12	20.0	8.876	1	.003
Hypertension; antihypertensive therapy, %	108	76	70.4	29	70.7	47	70.1	.004	1	.949
Diabetes; HbA1c \geq 48 mmol/mol; antidiabetic therapy, %	108	8	7.4	1	2.4	7	10.4	2.379	1	.123
Hyperlipidemia; LDL-c > 130 mg/dl; triglycerides > 200 mg/dl; statin therapy, %	108	50	46.3	19	46.3	31	46.3	<.001	1	.994
Total leukocytes, /nl	105	6.8	1.9	6.4	1.6	7.0	2.0	1.484	103	.141
Charlson comorbidity index	108	3.2	1.5	3.6	1.7	3.0	1.3	-1.851	106	.067
Visual assessments of MRI scans										
Fazekas score, (normal/abnormal) ^b	56	45/11		18/7		27/4		1.998	1	.157
Scheltens score (R), (normal/abnormal) ^b	56	49/7		24/1		25/6		2.983	1	.084
Scheltens score (L), (normal/abnormal) ^b	56	50/6		22/3		28/3		.078	1	.780
Treatment outcome										
MADRS score at discharge	96	12.3	7.8	9.3	5.2	13.9	8.5	3.295	93.581	.001
Response (\geq 50% decrease in MADRS score from baseline), %	108	57	52.8	26	63.4	31	46.3	3.000	1	.083
Remission (MADRS score < 10 at discharge), %	108	38	35.2	16	39.0	22	32.8	.427	1	.513

ECT, electroconvulsive therapy; MADRS, Montgomery-Åsberg Depression Rating Scale; BMI, body mass index; HbA1c, glycated hemoglobin; LDL-c, low density lipoprotein cholesterol; MRI, magnetic resonance imaging. Variables with a p-value < .05 are depicted in bold.

^a For some variables there are missing data and n does not equal the total number of patients. Percentage calculations are based on available data.

^b Values are presented as number of patients.

3.3. Somatic variables

EOD patients had a higher BMI ($p < .001$) and were more frequently obese ($p = .003$) than LOD patients. There were no group differences regarding other sociodemographic, psychiatric, or somatic variables.

3.4. Treatment outcome

The MADRS total score significantly decreased in both groups (main effect time: $F(1, 90) = 272.66, p < .001, \eta_p^2 = 0.752$) and there was a significant main effect of group ($F(1, 90) = 4.57, p = .035, \eta_p^2 = 0.048$) indicating higher MADRS scores in EOD independent of time (Fig. 1a). While there was no significant time \times group interaction effect ($p = .196$) on continuous MADRS scores, there were fewer treatment responders in the EOD group than in the LOD group on trend level significance ($p = .083$; Fig. 1b). Because EOD patients also had a higher BMI and were more often obese than LOD patients, we explored whether responders and non-responders differed with respect to BMI/obesity. Non-responders (mean: 26.54; SD: 4.34) had a higher BMI than responders (mean: 24.65; SD: 4.45; $t(97) = 2.13; p = .036$), whereas the proportion of obese patients did not differ significantly between groups, although

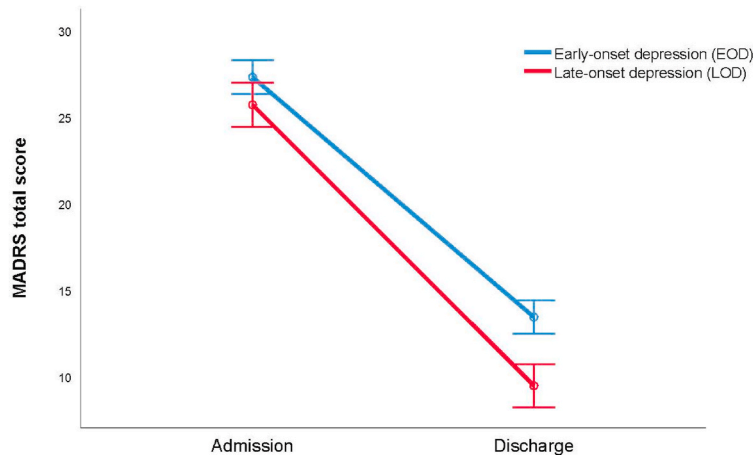
the number of obese patients was almost twice as high in non-responders versus responders (16.3% vs. 8.9%). The number of psychotropic medications, the number of previous depressive episodes, and the duration of current episode did not differ between responders and non-responders.

We conducted sensitivity analyses in sub-samples to a) match for age and sex as closely as possible and b) exclude bipolar patients and examine only unipolar patients. These results supported the findings of the whole sample and are reported in detail in the supplement.

3.5. Exploratory MRI findings

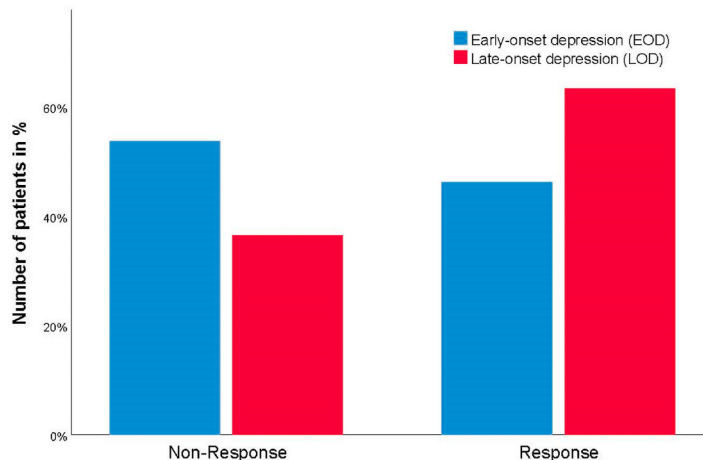
The median (IQR) Fazekas score was 1.0 (0) and the median (IQR) Scheltens scores for the right and left hemisphere were both 1.0 (1). These scores indicate that WMH and MTA were compatible with normal aging. The number of patients with normal and abnormal WMH and MTA scores are presented in Table 1. EOD and LOD did not differ in the severity of WMH and MTA. When patients that received an MRI were compared with those that did not, the only sociodemographic and clinical characteristic that differed between the groups was the relationship status. The percentage of patients with partner was higher in the group with MRI compared to the group without MRI (66.7% vs.

a)



The MADRS score decreased from admission to discharge in both groups (main effect time), and EOD had higher MADRS scores than LOD independent of time (main effect group). There was no time × group interaction effect. Values are means and error bars represent ± SE.

b)



There were fewer responders in the EOD group than in the LOD group on trend level significance. Values represent the relative number of patients.

46.2%; $\chi^2(1) = 4.4, p = .036$.

4. Discussion

In this retrospective chart review, we found a higher frequency of affective disorders in the family history of EOD patients. EOD patients also had a higher BMI and were more often obese compared with LOD patients. There were fewer treatment responders in the EOD group than in the LOD group on trend level significance. In exploratory analyses, the groups did not differ in the severity of WMH and MTA.

Our findings are consistent with a systematic review that also found affective disorders to be more common in the family history of EOD patients than that of LOD patients [10]. In addition, EOD patients had a higher BMI and were more often obese than LOD patients. These results indicate that a longer duration of depressive illness might put the patient at higher risk for excessive weight gain. Our results may contradict the vascular depression hypothesis that associates LOD with cerebrovascular risk factors such as obesity [4]. However, early onset of depression

Fig. 1. Change in MADRS total score from admission to discharge a) and treatment response b) in EOD and LOD.

a) The MADRS score decreased from admission to discharge in both groups (main effect time), and EOD had higher MADRS scores than LOD independent of time (main effect group). There was no time × group interaction effect. Values are means and error bars represent ± SE.

b) There were fewer responders in the EOD group than in the LOD group on trend level significance.

Values represent the relative number of patients.

patients. Our results suggest that the actual presence of metabolic risk factors may be a better predictor for treatment response than the late-onset of depression in the elderly. Similarly, younger age at onset and more chronic diseases were associated with chronic course of depression in elderly depressed patients [22]. Previous studies have demonstrated greater symptom severity, greater chronicity, and poorer treatment response in middle-aged and elderly depressed patients with comorbid obesity/metabolic syndrome [23–25]. However, because we assessed BMI only at admission, we did not perform formal mediation analyses. Longitudinal studies should investigate whether reducing metabolic risk in depressed patients at an earlier age improves treatment outcome in LLD.

In exploratory analyses, we did not find group differences in WMH contrasting a large body of evidence supporting increased lesion load in LOD than in EOD consistent with the vascular depression hypothesis [26]. We believe that the higher percentage of obesity in our EOD group might have contributed to the lack of group differences since cardiovascular risk factors including obesity have been associated with WMH [27,28]. Importantly, we evaluated MRI scans in only a subgroup of patients that had received the examination according to clinical considerations. In our sample, the participants that received an MRI did not differ from those that did regarding sociodemographic and clinical characteristics except for relationship status. Nevertheless, it is likely that participants that received an MRI differed from those that did not, for example in cognitive function, which limits the conclusions that can be drawn from the MRI findings. Furthermore, we used a rather rough but clinically established estimation of WHM: the categorical Fazekas score [16]. Although there was no significant difference in effect size between volumetric outcomes and visual rating scales in a meta-analysis, volumetric measurements of WMH might be more sensitive when studying differences between EOD and LOD [26]. Finally, our limited sample size likely contributed to our null Fazekas score results. Indeed, seven out of 25 LOD patients had an abnormal Fazekas score in contrast to only four out of 31 EOD patients. This is a limitation of the retrospective chart review and its low sample size.

In two different meta-analyses, hippocampal atrophy has been suggested to correlate with either EOD [29] or LOD [30]. In our study, we visually rated MTA using the Scheltens scale and found that MTA severity did not differ between EOD and LOD. Again, this lack of difference is likely explained by power problems because we found a trend for more abnormal MTA scores in EOD patients than LOD patients in the right (but not left) medial temporal lobe (see Table 1).

Our study has several limitations. First, this study took place at a single inpatient ward that specializes in difficult-to-treat depression. Therefore, generalizability cannot be assumed. Second, cognitive function was not assessed. Pronounced executive deficits were associated with increased cerebrovascular burden and poor treatment outcome in LOD [31]. Third, EOD patients were younger than LOD patients. Age is known to be associated with an increase in cardiovascular and metabolic risk factors [32]. However, in our study, EOD patients had a larger BMI and were more often obese even though they were younger. Also, sensitivity analyses confirmed our primary results. Fourth, for 12 patients (six EOD patients and six LOD patients) the MADRS score at discharge was not available, and treatment outcome was based on the hospital discharge report. In all these cases, treatment outcome was documented as non-response and non-remission. Because these cases with missing MADRS scores at discharge were evenly distributed in the groups, it is unlikely that this biased our results. Fifth, the clinical diagnosis of depression was solely based on medical chart information. Furthermore, recall bias might have influenced our findings. Elderly patients may not have remembered previous episodes and therefore got misclassified as LOD. Lastly, selection bias might have occurred as EOD patients with severe depression might have died through illness or suicide before reaching old age. This might have lessened the comorbidity burden and lack of treatment response found in EOD patients. This means that any selection bias would have worked in the opposite

direction of our findings.

5. Conclusions

Despite these limitations, many of which are inevitable in a retrospective study, our findings point to an increased obesity risk in EOD along with poorer treatment outcome. From the clinical point of view, this evidence emphasizes the need to prevent and reduce metabolic risk in depressed patients.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SMG reports personal fees from Almirall S.A., Celgene, and Mylan. CO reports personal fees from Allergan, Ferring, Fortbildungskolleg, Limes Kliniken, MedOnline, Medical Tribune, Neuraxpharm, Sage Therapeutics, and Stillachhaus. All other authors declare that they have no conflicts of interest.

Acknowledgements

none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnc.2021.100096>.

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