ORIGINAL ARTICLES

Duration of Untreated Illness; Year of Onset Early/Late and Gender Differences, Symptoms in Patients with Major Depressive Disorder: An Eighteen-Month, Cross-Sectional, Clinical Study in Southwest China

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Background: *Previous studies have reported differences between adolescent-depression and adult- onset depression with respect to demographic and clinical symptoms. However, it remains unclear whether these sex and age of onset differences can be detected in regular scales based on symptom traits. The comparition of symptoms between early-onset (male/female) and late-onset (male/female) Chinese MDD patients was performed in the present study.*

Methods: *The present cross-sectional study was conducted in the psychiatric department of the sixth affiliated hospital at Kunming Medical University from Sep 2020 to Mar 2022. We recruited 229 outpatients with a first diagnosis of MDD. Two groups differed on seven-dimensional symptoms on the Hamilton Depression Rating Scale (HAMD-24) in addition, correlations between seven-dimensional symptoms were compared across two groups. Principal components analysis (PCA) was conducted to assess sex, SAS and SDS differences between two groups.*

Results: *1.Early-onset cases have a high score in Hopelessness score (p=0.049), whereas females have a higher score in Anxiety somatization score (p=0.005) and sleep disturbances（p=0.007）, There was no significant symptom difference in symptoms between the groups and other symptoms.2.female($p<0.01$) and early-onset（$p<0.05$）are risk factors for hopelessness in MDD, female（$p<0.05$）is a risk factor of sleep disturbances in late-onset MDD, early-onset（$p<0.05$）is a risk factor of cognitive impairment restrict in female in MDD. 3.we found no significant goodness of fit and predictive power in 4 groups categorized by year of onset.*

Conclusion: *larger samples sizes in different regions and time periods with targeted cognitive questionnaire are warranted to redress the new nosology in early-onset MDD based on DUI in additional studies2.Late-onset female patients show less cognitive impairment and more sleep disorder.3.the female and early onset year are risk factors in the hopelessness score in cases of MDD.*

Background

Major depressive disorder (MDD) is a complex, common and heterogeneous disorder charactered by functional impairment and high suicide rate1 in US the prevalence of 12-month and lifetime rate were 10.4% and 20.6% respectively[2,3] and 6% in the 12-month 4and 15-18% in lifetime2 across countries. Cognitive, physiological changes make

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adolescents more susceptible to MDD.5 Depressive episodes in adolescence always persist into adulthood and are associated with an increasing risk of hospitalization for other psychiatric disorders.[6] A recent global meta-analysis showed that the peak age of onset of depression was 15.5 years old, and more importantly, the first diagnosis was made at 19.5.[7] Which is associated with attrition in college from pre-matriculation.[8]Further study focused on the prognosis showing that depression in childhood had a better outcome than depression in adolescence[9] the age of implicit onset as an important indicator in the MDD diagnosis and treatment of early-onset of MDD.

Early- /Late-onset difference and onset age of MDD

Comparing with other mental disorders in episode onset year, MDD has a later AOO about mid-20, Physical symptoms basically including Gastritis, Migraines and stomach ulcers were reported highly prevalent and associated with developing MDD.in Chinese undergraduates.[10]Severe illness has been reported widely associated with early age at onset of major depression. And genetics of AAO-MD contribute to disease including schizophrenia, autism spectrum disorder, bipolar [11]increased Density of specific diseases comorbidity like: Axis I were also found associated with EOD,[12]potential gene-gene interaction, combined rs768705 (TMEM161B) and rs35936514 (LHPP) may modulate the risk of MDD, has been reported in incident MDD cases.[13]In disease prognosis, earlier remission was associated with improved quality of remission in the early phase. While QOL score and the adult social function were unaffected by the time to remission.[14] Despite there overall similarities between the groups in terms of LOD (late-onset depression) and EOD (early-onset depression). There are still enough notable differences in symptoms across groups. Comparing with LOD, EOD was related to longer episodes, recurrent suicidality, and higher lifetime suicidally. Rate of suicide and Hypersomnia, EOD was accompanied by generalized anxiety disorder, whereas MDD onset higher year of MDD onset was associated with dysthymic. while LOD was associated with anhedonia.[15]slower response in antidepressant therapy[16] LOD showed less frequent occurrence of some clinical features of depression compared to EOD including, depressive episodes personal history, childhood event, family history of depression, and elevated neuroticism[17]higher levels in both the unmarried and unemployment rate bipolar trait with lifetime and less manic episode[18,19] a Random Forest regression test also supported the finding that patterns of neurovegetative symptoms and cognitive-behavioral symptom profiles were associated with AOO.[20]

Sex Difference

Sex differences have been extensively reported in prior studies.[21] Women were more than twice as likely as men to have a positive family history of affective disorder. Accompanied by an early age of onset of MDD. And implicating the MDD.[22]in symptom level, broad pathways including externalizing symptoms, internalizing symptoms and psychosocial adversity have been reported in a developmental model in MDD risk among women.[23] Female were found to be at greater risk for MDD onset, longer duration of the episode .[24]Recent study found cytokines change in plasma (eg:IL-4) also associated with the difference in female MDD symptoms and may implicate in the pathophysiology of MDD sex difference.[25]

Object

In previous studies, AOO has been associated with neurovegetative symptoms in patients with MDD. Thus, the purpose of this study was to compare the symptoms of Early vs later onset symptoms in patients with MDD in HAMA-24 according to the sex difference.so there is an urgent need to assess the comparative difference in Early vs. Late onset for patients with MDD on a regular scale.

METHODOLOGY

Study protocol

The study was an observational clinical trial conducted at Clinical Psychology (The Sixth Affiliated Hospital of Kunming Medical

University) from September 2020 to March 2022.The ethics review board passed the protocol for the study. The guidelines for this pathway are in accordance with the Declaration of Helsinki and good clinical practice. Enrolled by Kunming Medical University united fund (202001AY070001-259), all participants completed the written informed consent at the same time as their baseline information. Patients were informed that they had the right to withdraw free from the research free of charge when clustering.

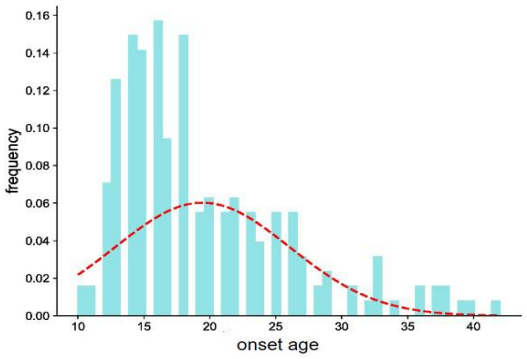
Participants

Eligible patients were Out-patients with an ages range of 14 to 60 years and meeting the DSM-V (Diagnostic and statistical manual of Mental Disorders-V) criteria for major depressive disorder with no history of psychotropic medication use. First-episode status and age of onset were self-reported. MDD should be diagnosed for the first time with a total HAMA-24 score ≥8. Exclusion criteria included 1) those who currently diagnosed with or had a history of a psychiatric illness listed in DSM-V-TR such as psychotic depression, bipolar disorder, schizophrenia, bulimia or anorexia, obsessive-compulsive disorder or other Axis I psychotic disorders, organic mental disorders of the brain; disorders of mental retardation, alcohol and other substances abuse disorder.2) serious clinical illness including HBP; diabetes; renal, liver, endocrinological illness.3) with a history of psychiatric medication use are excluded from the research.[26]

Age of onset of MDD

During the course of the research, the age of onset for each patient's first major depressive episode (MDE) was recorded during research by the physicians and clinical research coordinators (CRCs) who were responsible for and describing MDD and asked them to recall the age of the first MDE. Persistent anhedonia, low mood and other symptoms are defined by DSM-V of MDE. The duration of symptoms had to be last more than2 weeks, functional impairment or distress had to be accompanied by symptoms. The distribution of participants is shown in Figure 2.

Figure 2: "Frequency of Age of Onset and fitting curve. (original see S Table 1)"



Statistical analyses

Chi-square ($\chi 2$) or Fisher's exact test was used for comparison of means for categorical variables. Whereas t-tests or'Kruskal-Wallis'tests were used to compare the means for continuous variables. analysis of variance ANOVA was used to compare the means across multiple groups, frequencies (percentages) were used to describe Categorical variables and Mean ± Standard Deviation(X±SD) were used to describe continuous variables. SPSS software verson26(IBM, Armonk, NY, USA).in which all tests were two-sided and '**' and '*' represent statistically significant respectively when p less than 0.01 and 0.05 levels.

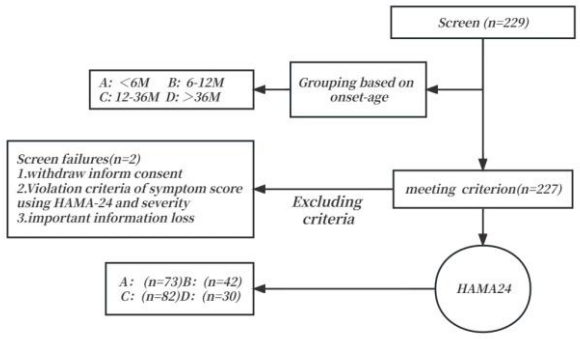
RESULTS

Cases

The patient flowchart is shown in Figure1. A total of 229 patients were enrolled; 2 participants failed screening, with 227 cases meeting the criteria continuing to complete the questionnaires. Traits including the socio-demographic and clinical characteristics of the cases are collected and baseline information is shown in Table 1 of these,227(73 on group A,42 on B,82 on C and30 on D) correctly completed the HAMA-24 correctly in the quality control review. 4/73(5.5%) cases in the A group;6/42(14.3%) in the B group;13/82(15.9%) in the C group and 2/30(6.7%). Eager cases and and vacancy completing the questionaries are the

main reasons for dropping out.

Figure 1: 'patient flowchart'



Socio-demographic and key clinical characteristics of the sample are summarized in Table 1. The total N is 229, while the groups B and D are less than 50.

In this research. there are 227 cases in this research with onset-data for patients with first-diagnosed major depressive disorder (MDD) patients. Like most clinical research samples in MDD, most people were female (74%), and the racial consist of Han (75.74%), Yi (16.33%) and other (7.92%). Majors of patients were employed (81.09%) but had low-income (0-3,000/month 71.96%) .Comparing of the data supplied by Yunnan Provincial Provincial Bureau of Statistics'stats.yn.gov.cn' in year 2021（N=25799762）, patients (university and junior:21.2% VS 32.88%, senior high 18.9% VS 44.59%, middle 53.5% VS 22.52%) are found to have a higher correlation of the level of tertiary education. The mean age of onset of MDD was 19 years (range:10-42 years). about 67% of patients had an onset of MDD in pre-adult, with a 12.4 year mean of onset in the early-onset group.

Table 1: "Baseline characteristics of first-diagnosed major depressive disorder patients in 4 groups (original see S Table 1)"

Characteristics	**n**	**%**		**n**	**%**
Race	202		gender	227	
Han	153	75.74%	male	59	25.99%
Yi	33	16.33%	Education	222	
La Hu	1	0.49%	middle	50	22.52%
Ha Ni	6	2.97%	Senior high	99	44.59%
Hui	3	1.49%	junior	21	9.46%
Dai	6	2.97%	university	52	23.42%
Marital status	227		Income(yuan/month)	189	
unmarried	183	80.61%	0-3,000	136	71.96%
married	35	15.42%	3,000-5,000	28	14.81%
divorced	4	1.76%	5,000-10,000	13	6.88%
widowed	1	0.44%	＞10,000	12	6.35%
else	4	1.76%	Drinking history	228	
Occupation	226			29	12.70%
Employed	181	81.09%	Smoking history	226	
Unemployed	45	19.91%		38	16.81%
	Mean (S.D)			**Median (observed range)**	
Age（n=228）		22.68±6.67		20（14-49）	
Age of onset of first MDE(n=199)		19.44±6.63		18（10-42）	
Duration of illness (in years) (n=217)		14.82±17.70		9（0-96）	
HAMA-24（n=227）		33.93±6.39		34（16-52）	
SAS（n=202）		45.14±7.23		45（30-67）	
SDS（n=202）		60.15±7.68		60.5（4-78）	

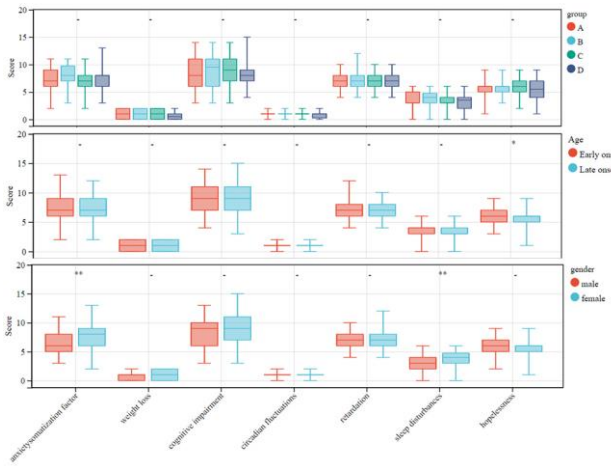
The age frequency distribution of MDD onset is shown in Figure 2. The duration of MDD was longer in early-onset cases (mean disease years 26.7 years, S.D.=7.6 vs. 20.4 years, SD=25.9; P<0.01), but with no difference in age.

Table 2 lists other crucial sociodemographic and clinical variables association. age, gender, mental and physical history do not differ significantly. HAMA, SAS, SDS overall.

Table 2:"the continuous sociodemographic and clin ical variables associated with groups with P-value"

Characteristics based on group	A (n=73)	B (n=42)	C (n=82)	D (n=30)	P-value
Age(years), `X±SD	21.46±6.77	20.42±5.94	19.35±6.26	21.90±7.84	0.22
Male, n (%)	13 (22.8)	7 (12.3)	26 (45.6)	11 (19.3)	0.053
mental disease history n (%)	5 (6.8)	2 (7.1)	2 (2.4)	3 (10.0)	0.517
physical disease history n (%)	8 (10.9)	1 (2.4)	12 (14.6)	9 (13.3)	0.216
HAMA-24, `X±SD	33.3288±6.32687	35.2619±6.34019	33.9268±6.32608	33.5667±6.82634	0.933

Figure 3: "Difference in symptoms factors between duration of untreated disease, sex and age of onset"



Early-onset cases show a high score in Hopelessness (MD=5.9483, SD=1.49176 VS MD=5.4911, SD=1.59657, p=0.049), Whereas females show a higher score in both Anxiety somatization (MD=7.5824, SD=1.88634 VS MD=6.6491, SD=2.1588 p=0.005) and sleep disturbances (MD=3.5824,SD=1.35731 VS MD=2.9825,SD=1.62009 p=0.007）, No significant difference were found in the groups and other symptoms (see Figure 3 and S Table 2)

MDD has different symptoms depending on its onset [early(male/female) vs. late(male/female)]

We were inspired by the enlightening result in Figure 3 on the cross-group analysis of sex and onset-year, our result indicate that female($p < 0.01$) and early-onset($p < 0.05$) are risk factors for hopelessness in MDD, female($p < 0.05$) is a risk factor of sleep disturbances in late-onset MDD, early-onset($p < 0.05$) is a risk factor of cognitive impairment restrict in female in MDD. (see Figure 4 and Table 3)

Figure 4: "symptom scores differ with MDD [early (male/female) vs. late (male/female)]" (original data see S Figure 2 and S Table 3)

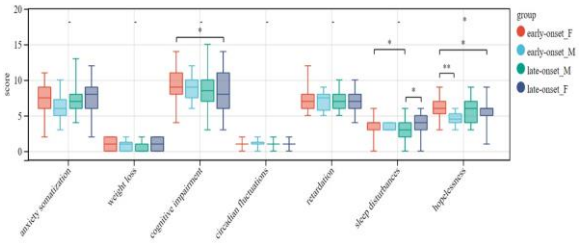


Table 3: symptom scores differ with MDD [early (male/female) vs late (male/female)]

HAMA items	Early-onset (<18)		Late-onset (≥18)		P-value
	N=58(25.6%)		N = 169(74.4%)		
	Male N=8(3.5%)	Female N=50(22.0%)	Male N=50(22.0%)	Female N=119(52.4%)	
	% (present)				
Anxiety somatization	7.9223±1.68225	6.2500±2.11345	7.6930±2.12567	8.0045±1.80051	0.17
Weight loss	0.9196±0.87619	0.8750±0.80623	8.8704±2.59728	0.9303±0.87695	0.88
Cognitive impairment	9.5469±2.66621	8.7500±1.98326	0.8141±0.82635	8.6697±2.71456	0.23
Circadian fluctuations	1.0751±0.62626	1.1250±0.61914	0.9662±0.59088	0.9494±0.56791	0.6
Retardation	7.3941±1.52141	7.0000±0.61914	7.3662±1.38433	6.9663±1.39459	0.35
Sleep disturbances	3.6810±1.49285	3.3750±0.50000	3.1887±1.63503	3.6618±1.34206	0.13
Hopelessness	6.2574±1.43992	4.6200±0.98747	5.7380±1.66098	5.5281±1.55289	0.02*

Correlations between the different symptoms in the HAMA-24

Pearson's correlation analysis was performed across participants to assess the relationship between levels of symptom dimensionality levels by HAMA-24 score in a questionnaire form. Which contains the following items: Anxiety somatization, Weight loss, Cognitive Impairment, Circadian Fluctuations, Retardation, Sleep disturbances and Hopelessness. Statistical threshold was set at a P value < 0.05 with family-wise error correction. Correlation analysis (see Figure 5 and S Table 4) revealed that anxiety/somatization was positively correlated with weight status, cognitive impairment, retardation, sleep disturbance and hopelessness. There was a positive correlation between weight loss and cognitive impairment, retardation and sleep disturbances. There was a positive correlation between cognitive impairment and circadian Fluctuation, retardation, Hopelessness. Circadian fluctuation were positively correlated with sleep disturbances and hopelessness was positively correlated with retardation and sleep disturbance.

Figure 5: "The association of 7 factors in HAMA-24 in first-diagnosed depression"

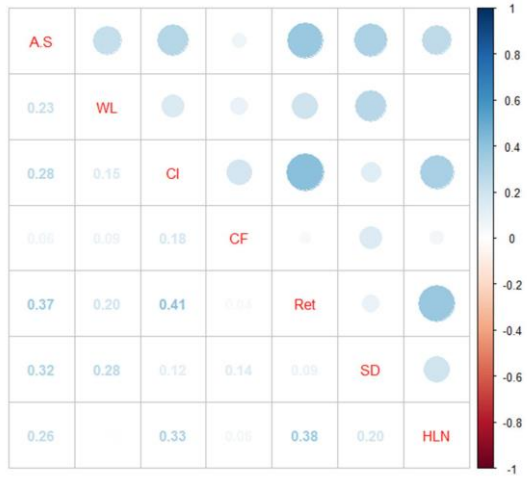


Figure 5 "The association of 7 factors in HAMA-24 in first-diagnosed depression"

(a)AS=anxiety/somatization factor; WL=weight loss; CI=cognitive impairment; CF=circadian fluctuations; Ret=retardation; SD= sleep disturbances; HLN=hopelessness.)
(b). The figure on the bottom left and the size of the circle on the top right represent the cross relevance of two factors in the X and Y axes, with the color corresponding to the color gradation value on the right.
(c). Original data see (S Table 4)

Discrimination between MDD symptoms levels and age-of-onset groups

The influence of onset-age on symptoms in HAMA, SAS, SDS was evaluated by using correlation between the symptom levels and onset-age. A PCA score plot was plotted to examine the grouping characteristics of the symptom differences (Figure 6a) and the loading plot was used to illustrate the contribution of the respective metabolites to the discrimination (Figure 6b).

Figure 6a and 6b: "loading plot of four groups"

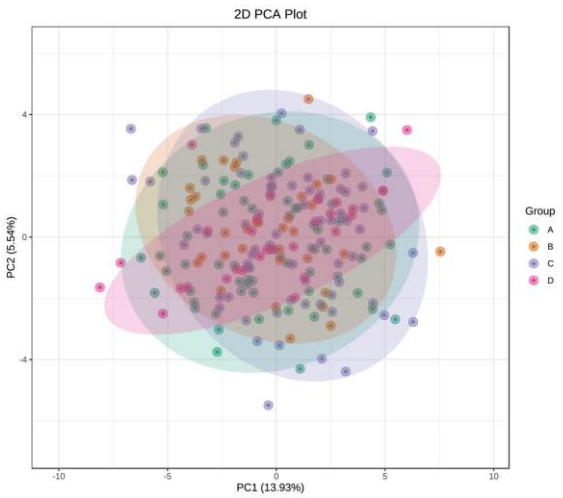


Figure 6a "PCA score plot in four groups"

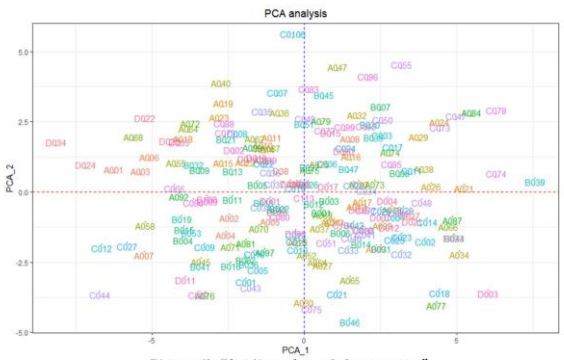


Figure 6b "loading plot of four groups"

(a.) A factor map of the PCA performed on 202 Cases.4 clusters was identified corresponding to the age of onset for the A(green), B(orange), C (purple), D(carmine), (Factor map is composed of 64 factors including: HAMA-24(24), SAS (20), SDS (20))

(b.) load plot of 4 extracted groups with the difference in duration of untreated disease duratio<6M,6-12M,12-36M, ＞36M.（M：month）

(c.) original data see S Figure 3 and S Table 5a and S Table 5b

The PCA score plots demonstrated the total variance of two major principal components (19.47%), with 13.93% accountable for principal component one (PC1) and 5.54% accountable for principal component two (PC2). As indicated by the score plot, MDD patients with different age-of-onset histories fell into four clusters with no distinct bound.PC1 relatively well between group A and group B while suggesting that extracts from groups A and D extracts shared similarities and thus were tightly clustered. PC2 discriminated relatively well between group C and group D while suggesting that extracts from groups A and B extracts shared similarities and thus were tightly clustered. This separation of the duration of the onset year prior to diagnosis was highlighted by their appearance in different regions of the loading plot: which indicates that the model shows no significant goodness of fit and predictive strength.

DISCUSSION

Key findings

In this cross-sectional study. we assessed comparative differences in early vs. late onset for patients with MDD. The result, evaluated by HAMA-24, SAS and SDS, the result suggested that: 1: patients with first-diagnosed MDD patients shows difference based on the Early/Late-onset age, not the duration of untreated illness .2: Late-onset female patients show less cognitive impairment and more sleep disorder. 3.female gender and younger age of onset are risk factors for hopelessness core in MDD patients.The findings suggested that symptoms differ from age of (Early or Late-onset) but were not significant found in duration of untreated disease in four groups. Women and early-onset are risk factors for first-episode symptom behavior in patients with MDD.

Epidemiological findings

Fifty-eight of 227 (25.6%) participants reported an early age of onset MDD(＜18 year), which is lower than the 37% onset of major depressive disorder prior to adulthood reported by a similar study.[12,27]Women were significantly more likely (22.0%) than men (3.5%) to have early-onset MDD. Although most patients are employed (81.09%) , underemployment is also a contributing factor to a higher risk of depression.[28]Supporting most low-income (0-3,000/month 71.96%) reported among patients. When compared to data by local provincial, shows a less educated state (college and junior:21.2% VS 32.88%; elderly high 18.9% VS 44.59%; middle 53.5% VS 22.52%) [29] and not married (80.61%)[30] were linked with an increased rate of MDD incidence. It is interesting to note that despite some previous studies reporting the opposite, high levels of education were associated with depress[30], particularly at the secondary level[31]which implied that the economic problems of the low-educated people and the academic or employment pressure of the high-educated may be considered independent risk factors in their respective categories.

Mean age

The average age of first diagnosed MDD was 19 years (range:10-42 years), which is fairly similar to the 19.5 years reported in the peak age in the early-onset groups by the global meta-analysis.[32] Despite their younger age, reported a longer duration (from first MDE to enrolled) of disease in the mean years of disease (26.7% years vs 20.4% years) in early-onset patients, compared to the overall group. Because of the mean age of onset (12.4 years) is younger in the early-onset group in the present study than the late-onset group (32.4 years) previously reported[33] the difference tended to be based on the early/late-onset age, not the duration of untreated disease.

Early-onset depression risk factor

Family history

Prior studies have sought to identify risk factors for early onset depression. A family history of depression is so commonly cited as a risk for depression and symptoms understanding.[34-37] Family psychiatric history, as reported in juvenile-onset MDD patients[38], has the potential to be considered as a risk factor for predicting severe behavioral such as disinhibition, reveling potential target treatment strategies based on specific etiological mechanisms of comorbidity and subtypes differences. But we found no association of elevated family burden to be relayed to early onset in 4 groups. With a mean history of mental illness of 5.3% (groups vary from 2.4% to 10.0%). Family history may be a restrictive risk factor for depression and may not be as strongly related to age of onset, other findings reported early parental age at MDD onset may be considered as a possible risk factor. Which could be explained by the evidence between juvenile-onset MDD and parental MDD. [39] while one study did report early-onset MDD, compared with late-onset MDD, was associated with both parental depression and maternal alcoholism. while the role of family history of depression as a risk factor has not to be definite.[40] Comparing with a diagnostic criterion for MDD in a semi-structured diagnostic interview, a family history of depression had worse outcomes than the symptom criteria of the DSM-IV. But performed better when a lifetime diagnosis was considered than a current diagnosis. The implication a family history may implicate the pathological processes of MDD. accompanied by other factors.[41]Among adolescents, these potential risk factors may include: early life stress[42-45]

Gender

We found that sex was the only risk factor that differentiated early- from late-onset MDD. An earlier study had found evidence of sex differences evidence in prevalence, symptoms, and treatment dimensionality in MDD patients[46] in prevalence level[47,48] with sex differences attributed to sociocultural, biological[49], economic[50] and other factors.[51]Other research focuses on the connection between sex-difference and the microbiota-gut-brain axis; the HPA axis, blood-brain barrier (BBB) difference and differential expression in brain areas. At the sex- microbiota-brain level, clusters

of altered gut microbiota clusters were found in female patients. as like bacteroideae operational taxons (OTUs). Gut microbiota can interact with sex-related features (including sex differences in the brain and sex hormones), which further affect the brain.[52] In the HPA axis, repeated exposure to stress impairs the responsivity of the HPA axis [53]and dampens allopregnanolone levels. Participating in the etiopathology of MDD.[54] those social stress also contribute to the blood-brain barrier(BBB)[55] and neurovascular pathology that associated with depressive symptoms with a gender difference.[46] resting state fMRI studies also showed the occipital lobe, calcarine, DLPFC, and DCG were the main different brain regions between male and female MDD patients.[56] accompanied by amplitude of low-frequency fluctuation (ALFF) change.[57] that help to understand the difference in prevalence rate of higher MDD prevalence rates. Rare studies have reported the mechanism of specific early-onset MDD based on gender differences.

Age of onset of MDD

Most study viewed 18-year as a boundary to classify MDD patients into early- /later-onset MDD. early-onset patients show specific brain structure change.[58-60]MultiOmics study on early- and adult-onset MDD patients also revels the different influence between metabolites and SNVs.[61] Because of lacking uniform standardization in the define. early-onset MDD also is called 'child-onset'[60] /'Juvenile onset'[62]/'pre-adult onset' in some studies. early-onset are used to compare with geriatric major depressives (also called Late-onset /later-onset MDD) the cut-off point was delayed to 55[63,64]or 60[65,66]future study should focus on a national recognition criterion to unify standard for easy integrate symptom and other information based on early-onset MDD to be distinguish juvenile MDD and geriatric major depressives separately.

Duration of untreated disease

Prior studies have shown that meeting the 2-week duration criterion is not a must in order to have symptoms similar to those that meet all DSM-IV criteria in preschoolers.[67] those MDD patients with a DUI ＞12 months are often charactered with females; longer duration of disease; and a higher rate of recurrence.[68] which implicating for a new nosology based on DUI. Therefore, we provisionally divided MDD patients into 4 groups according to DUI (A:<6month、B:6-12 month、C:12-36month、D:＞36 month),Unfortunately, we did not find significant association between 4 groups in symptoms according to the normal questionnaire. While this is similar to the view that most research does not consider DUI as a factor for new nosology. However, some studies do report that DUI was associated with change in year of onset, symptoms correction, therapeutic response. Since reported patients with a longer DUIs showed an earlier age of onset,[69] in another study suggested that longer DUI was negatively associated with clinical correlates of MDD. comparing with a shorter DUI[70] such as cognitive impairment.[71]a short duration of an untreated episode (DUE) showed greater improvement in depression and somatic symptoms to the therapeutic response level[72,73] untreated duration may be considered as a factor in predicting the severity of their follow-up.[74] what is of interest is that there was even a significant decrease in DUI in the major depressive disorder groups whose onset occurred prior to the last century vs, as reported in an Italy study.[75] larger samples in different regions and time periods with targeted cognitive questionnaire and are warranted to confirm these results in DUI in further studies

Outcome-based prediction of the high-risk group

Early-onset cases show a high score on Hopelessness ($p=0.049$), This is in line with previous results[76] the Child-Adolescent Suicidal Potential Index (CASPI) also found to be positively correlated with hopelessness in a high survey.[77] female is another independent risk factor for hopeless. ($p<0.01$) that is broadly consistent with the cardiac SWAN study[78] even after adjusting for income, site, race and cardiovascular disease status. Thus, female groups with early onset MDD should provoke our great attention from psychiatrists.

For us, what is exciting is that early-onset is a risk factor for restrictive cognitive impairment in female in MDD($p < 0.05$) whereas this gap could not be discovered in neither gender and early-/late-onset difference (see Figure 3), which is uncommonly reported in previous study. Future studies can address the mechanism of the combined sex-specific biology gap and the age character of MDD patients.It is worth mentioning that females tend to self-report higher symptoms levels than males in an equally severe type.[48] This may confuse physicians and lead to an uneven diagnosis.

Clinical implication

Patients with early-onset MDE have more symptoms of hopelessness. involving mental support is vital and important to alleviate the feeling of hopeless when using antidepressants. In onset-MDD patient Female shows more score in anxiety somatization and sleep disturbance. Particularly in cases of adult females. On the basis of anxious somatization, sleep disturbance and hopelessness show a significant correlation (in Figure 4) implicating that we can treat them based on sleep disturbance. With the age increasing, Hopelessness and cognitive impairment decrease with age. but sleep disruption increases. Implicating that we should offer more assistance to the pre-adult patients though psychological therapy, while ensuring the quality of sleep-in adult patients.

Strengths and limitations

This was an eighteen-month, cross-sectional study in southwest China and it was ultimately adequately powered to test the hypothesis; however, some limitations remain. Firstly, we did not measure baseline HAMA levels in healthy controls. It should be measured in future studies. which may help differentiate between anxiety and depression symptoms in patients. And offer a novel sight into understanding Early-onset MDD on symptoms. Secondly, this is a single- center trail in southwest of China in general hospital .it shows good representation in areas of low-income employment areas in China. A greater number of onset-patients in inpatient, psychiatric, other regions and national settings should be measured by questionnaire to confirm or supplement the result. Third, the drug's influence on the onset of relief-MDD symptoms should be tested in follow-up studies. Fourth, the dropout rate was somewhat high in this study prior to group enrollment. Dring the COVID-19 epidemic, it was inconvenient to see a doctor, which made cases difficult to complete the questionnaire patient and carefully. even worsen their original symptoms such as anxiety and depression. Fifth, the self-report onset year and duration of symptoms is a subjective index, and could be accompanied by recall bias. Research on the duration of untreated illness and symptoms prior to diagnosed awaits the establishment of a standard criterion or questionnaire.

Abbreviations

OA: onset-age; CI: Confidence interval; DSM-V: Diagnostic and Statistical Manual of Mental Disorders-V; HAMA-24:24-item Hamilton Depression Rating Scale; MDD: Major depressive disorder; SD: standard deviation. AOO: age of onset; LOD: late-onset depression; EOD: early-onset depression DUI : duration of untreated illness (DUI)

DECLARATIONS

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Sixth Affiliated Hospital of Kunming Medical University and was carried out according to the Declaration of Helsinki and the guidelines for good clinical practice. Prior to the start of the study, the trial was registered (Medical ethics in Yuxi province【2019】23) on Sep 4, 2019, All participants provided written informed consent prior to the commencement of any study procedures. Subjects were informed that they were free to withdraw from the study at any time. (The patient's name has been blinded)

Consent for publication

Not applicable

Availability of data and materials

Core data available within its supplementary materials (S Table 1) and original data available on request from the authors.

Competing interests

Dr. Yong Zeng received research support in Sixth Affiliated Hospital of Kunming Medical University, and finished it in second Affiliated Hospital of Kunming Medical University, Kunming. The other authors report no competing interests.

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Authors contributions

XC, ZL, YD contributed equally to this work and should be considered co-first authors. XH, YZ, YZ contributed equally in the writing of guidance articles and data collection to this and should be considered co-corresponding authors.
ZL and YZ: conceptualization and methodology, CX: data curation, visualization and writing original preparation. XZ, YL and XY: software YD and QZ: investigation. JW, ZG, FQ: supervision. XH and YZ: validation. XW and FT: writing-reviewing and editing
All authors contributed to the article and approved the submitted version

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