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ORIGINAL RESEARCH

Dynamic Impact of the Sleep Disorder, Depression and Anxiety on the Cognitive Function in the First-Episode Depressive Patients

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Background: Sleep disorder is closely related to depressive and anxious status as well as cognitive symptoms.

Materials and Methods: A total of 173 cases with the first-episode major depressive disorder (MDD) were involved in this study. The Hamilton Depression Scale (HAMD-17), Hamilton Anxiety Scale (HAMA), Pittsburgh Sleep Quality Index (PSQI), and Repeatable battery for the Assessment of Neuropsychological Status (RBANS) were used to assess the patients. Three visits were set at baseline at the 4th and the 8th weeks. Latent Growth Curve Models (LGCM) were used to analyze the changing tendency and correlation between sleep disorder, depression, anxiety status, and cognitive function in patients with MDD.

Results: Baseline sleep status in patients with MDD could predict cognitive function (p=0.043) and changes in cognitive function (p=0.016), and changes in depressive symptoms could negatively predict cognitive function (p=0.021). Changes in depressive status negatively predictability of its cognitive function (p=0.005). Changes in sleep status negatively predict cognitive function (p=0.099). Sex, age, educational duration, and nature of work were included in the LGCM. The comparison among the subgroups in the LGCM indicated that these four dimensions showed consistency in dynamic tendency, demonstrating that cognitive function changes with sleep status.

Conclusion: The more severe the sleep disorder in patients with first-episode MDD, the more obvious was the damage to cognition. The dynamic impact of sleep quality on cognitive function is positively correlated, and over time, there is an association between the remission speed of depressive or anxiety symptoms and improving the speed of cognitive function in patients with MDD.

Keywords: major depressive disorder, sleep disorder, cognitive function, dynamic tracking, correlation, Latent Growth Curve Model

Backgrounds

Major depressive disorder (MDD) is a persistent condition. Its clinical manifestation includes loss of pleasure, decreased interest, disrupted sleep rhythm and recurrent thoughts of death, etc.[1] Clinically, a patient with the above symptoms with a total Hamilton Depression Scale (HAMD-17) score of more than 24 points could be diagnosed with MDD.[1] As one of the mental disorders with the greatest impact on public health, MDD is characterized by high morbidity, high recurrent rate, low cure rate and high disability rate.[1,2]

A previous study showed that sleep disorder increased the risk of depression.[3] Another study found that the irregularity of the circadian rhythm and sleep schedule was frequently observed in patients with MDD, not only in the acute attack stage but also in the prodromal and remission stages.[4,5] An 18-year follow-up study showed that in patients with MDD and a wide range of anxiety levels, the more severe the anxiety they have at the time of onset, the higher the level of depression and lower the quality of sleep.[6] Conversely, 9 years later, the level of anxiety and depression become higher in the patients with lower quality of sleep; 18 years later, the level of anxiety become more serious in the patients with lower quality of sleep.[6] Normalization of sleep is an important measure to improve the anxiety and depression and the quality of life among patients with MDD.[7,8]

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A wide range of cognitive function disorders are commonly seen in patients with MDD, mainly including executive dysfunction, attention deficit, and memory impairment.[1] The patients with MDD, combined with the onset of sleep disorder, have multiple aspects of cognitive function. The depression-related symptoms (eg: sleep changes, cognitive disorder, blockage), age or marital status might be the risk factors of the cognitive function impairment in MDD patients with sleep disorder.[9] Based on the study of Jian et al, more serious depression will lead to poorer quality of sleep and more impairment on the cognitive function in MDD patients.[10] In addition, partial cognitive impairment will still exist after the remission of the depressive symptom despite the improvement of the cognitive function. Sleep disorder also tend to relapse easily, affecting the quality of life of patients.[11,12]

Based on the existing literatures,[3–12] we assume that the dynamic changes in sleep quality in patients with MDD may be closely associated with the level of depression and anxiety and interact with each other, jointly affecting the cognitive function of the patients. However, it remains unclear how the relationships between these variables change over time. Therefore, this study used a longitudinal follow-up design. The dynamic correlations among sleep disorder, anxiety, depressive status, and cognitive function were explored based on the objectively evaluated data.

Methods and Materials

Subject of the Study

This was a longitudinal non-interventional follow-up study based on the data of patients with first-episode MDD recruited from the outpatient department of Tianjin Anding Hospital between January 2019 and January 2023. The study was approved by the Ethics Committee of Tianjin Anding Hospital (No.2019–18). All patients and their families signed written informed consent forms for this clinical research.

The diagnostic criteria of "MDD" in DSM-5 must be met[13] for the included patients, and the Hamilton Depression Scale (HAMD-17) score should be more than 24 points; the included patients should be aged 18–55 years, males or females with a primary school level or above, and at the first episode of MDD, with the course within one year and no unconsciousness disorder or depressive stupor symptoms at the time of visiting the hospital; they should have no systemic treatment with psychotropic substances (without enough courses of treatment),[12] without the history of use of benzodiazepines, and without long-term (more than 2 months) regular use of benzodiazepines as hypnotic medical treatment.[14] The following patients should be excluded: those patients with physical diseases, such as severe cardiovascular and cerebrovascular diseases, severe respiratory system diseases, severe liver diseases, severe kidney diseases, malignant tumors, or poor control of chronic physical diseases; and those patients with alcohol and other psychoactive substance abusers; and those who are unwilling to participate in research and treatment combined with other antipsychotic drugs.

After signing the informed consent form based on voluntary and unified medication and disease health knowledge training, the enrolled patients were evaluated using the relevant scales in this study. The researchers will fill in the <General Information Questionnaire> according to the situation of the patients and track the changes of the treating course at the baseline, the 4th week and the 8th week.

Investigating Tools

The researchers did consistency training, the researchers completed the following questionnaire/investigation scales by asking the participants one item by one item.

Self-Made General Information Questionnaire

The social demographic data of the patients were collected, including name, sex, age, nationality, occupation, education, marital status, basic family situation, exercise situation, physical illness, use of dependent substances, and medication situation.

The Hamilton Depression Scale

HAMD is the most commonly used scale to evaluate depression. The version with 24 items was adopted in this study. The HAMD scale rating was independently performed by two well-trained evaluators on the patients before and after the communication between the evaluators and the patients, as well as during the observation of the patients. The total score

consisted of 24 items. Major depression was considered when the score was above 35 points; mild or moderate depression was considered when the score was above 20 points; and no depressive symptoms were considered if the patients scored lower than 8. Effectiveness might be considered if the total score reduction value of the HAMD is ≥50% compared to the baseline data in the clinical effectiveness evaluation. The evaluators achieved a considerably high level of consistency after training. The reliability coefficient r of the total score evaluation is between 0.88 and 0.99 (P<0.01). Validity: The total HAMD score is a good indicator of disease severity, and the coefficient r related to the GAS is greater than 0.84.[15]

The Hamilton Anxiety Scale

Hamilton Anxiety Scale (HAMA) is a 14-items tool used to evaluate anxiety disorders. Normally, HAMA shall be jointly examined by two well-trained evaluators through the way of dialogue with the patients and observation and then graded independently before and after the examination.[16] This was also the procedure followed in the current study. Major anxiety may be considered then the HAMA scores ≥29; obvious anxiety must be considered if it scores ≥21; the patient must have anxiety if the HAMA scores ≥14; the anxiety may be considered if the scores are more than 7; if it gets lower than 7, then no anxious symptom is considered.

Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index (PSQI)[17] is set up to evaluate the subjects' sleep quality over the past month. This scale applies to the evaluation of sleep quality in patients with sleep and mental disorders and is also applicable to the evaluation of sleep quality in general individuals.

The PSQI consists of 19 self-evaluated items and 5 evaluated items. The 19th self-evaluated item and the other five evaluated items were excluded from the total score. Only 18 self-evaluated items that participated in the score rating were included in the study. The 18 items consisted of 7 components, each rated on 0–3 scale. The accumulated scores from each component were the total scores of the PSQI in the range of 0–21. Higher scores indicate poorer sleep quality. The completion time for the participants was 5–10 minutes.

Repeatable Battery For the Assessment of Neuropsychological Status

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was developed by Randolph C in 1998, consisting of 12 testing tasks and covered by 5 areas of neuropsychological function.[18] Instant memory: two tasks including vocabulary memory and story memory; visual spatial structure: two tasks including graphic description and line angle; language: two tasks include image naming and language fluency; notice: two tasks include number width and encoding; delayed memory: four tasks include vocabulary recall, vocabulary re-recognition, story recall, and graphic recall. The reliability and validity of the Chinese version of RBANS were studied and verified by Zhang et al, and the results showed that except for speech function and visual breadth, the internal consistency reliability of the summary table and other component tables was above 0.7 with 0.90 of the retested reliability in the summary table.[19]

Quality Control

A tertiary Grade A hospital was selected for the study. All participating licensed physicians were members of the same working team, with the tiles of attending physician or above and more than eight years of clinical experience. The scale consistency training and assessment must be completed by all scale-evaluated participants.

The examiners were asked to read out the question item by item according to unified guidance to the patients with clear and fluent language and to inform the patients about the meaning of the questions in a neutral manner without any hint or bias. The results of each question on the scales were recorded, and relevant values were calculated. After each investigator completed the questionnaire, a comprehensive examination was conducted on all filled-in contents to ensure omission and mistake correction. A third person will be responsible for reviewing and calculating after all the data are obtained.

Statistical Analysis

Based on the enrolled first-episode MDD patients, the changing tendencies of the different scale results, including HAMD, HAMA, PSQI, and RBANS, from the patients at baseline, the 4th week, the 8th week were examined through the

established linear unconditional latent variable growth model, the changing tendency of the depressive and anxious symptoms, sleep situation, and cognitive function, as well as the premise of a good fit between the data and model determined by confirmatory factor analysis. The changing value on the RBANS scales will serve as the dependent variable to identify the developing tendency of depressive symptoms to change with anxiety symptoms and to finally confirm whether the trend of its changes with PSQI, meaning that sleep disorder will have significant predictability. (Statistically significant at ***$p<0.001$, **$p<0.01$, *$p<0.05$)

Subsequently, the data were divided into 5 dimensions, including sex (male and female), age (above, equal or below 35 years old at the time of onset), education duration (above, equal or below 12 years), type of work (mental or physical work regularly), 8-week deduction rate of HAMD (above, equal or below 50%), the inter-group difference is observed by *t*-test then the Latent Growth Curve Model (LGCM) is constructed. The intercept and gradient of the calibration curve for sleep problems were used to predict the gradient of the RBANS, whereas the intercept of the calibration curve for sleep problems was used to predict the intercept of the RBANS. x2 Test on LGCM will be used to examine whether there is a difference in the dynamic impact of sleep disorder on cognitive function in patients from different subgroups.

Results

General Information

Based on the inclusion criteria, 300 cases were screened, 127 questionnaires were excluded due to insufficiency, distortion, and loss to follow-up, and 173 questionnaires from the patients were eventually included. The distributions are listed in Table 1. In this study, the number of female patients was significantly greater than the number of male patients. Less than 15% of the patients had a positive family history of MDD (see Table 1).

Table 1 Demographics and General Information of the Patients With Major Depressive Disorder at Baseline

General Data		Distribution Situation
Sex	Male	50(28.90%)
	Female	123(71.10%)
Ethnicity	Han	94.79%
	Non-Han Nationality	5.21%
Age (Years old)		29.7±9.34
Education Duration (Years)		14.3±2.95
Marital Status	Married	43.42%
	Unmarried	56.38%
Occupation	Mental Work	89(51.44%)
	Physical Work	35(20.23%)
Living Situation	Solitary	12.68%
	Non-Solitary	87.32%
Physical Illness	Hypertension	2.63%
	Diabetes	2.63%
	Craniocerebral Injury History	1.32%
Combined Medicine	Anti-Depressant Drugs	3(1.73%)
	Benzodiazepines	9(5.20%)
Participated Leisure Sports	Low-Intensity	10.98%
	Moderate-Intensity	13.29%
	High-Intensity	23.12%
Positive Family History		13.87%

The Situation of Sleep and Cognition at Different Time of the Evaluation

The scale values for all the patients at different stages are presented in Table 2. All patients had severe depressive symptoms with anxiety and sleep disorder at the beginning of the evaluation according to the baseline data on every scale. The mean value of depressive symptoms improved to moderate depressive or low depressive at the 8th week, and anxiety, sleep disorder and the value of the RBANS also showed significant improvement.

The Correlation of the Scores Between Depressive Symptom and Neurological Impairment

Four dimensions, including sex, age, education level, and the nature of occupation, of patients with MDD were further divided into two subgroups based on the different principles of classification. Sex, education duration, and the nature of occupation were the only factors with statistical differences based on the RBANS scores at baseline and the 8-week incremental rate when different scales were compared (P=0.006, P<0.01, P=0.027). No significant differences were found between the different subgroups based on the scores of the other three scales (HAMD, HAMA, and PSQI) (P>0.05, Table 3).

According to the incremental rate of the value at baseline and the 8th week on both the HAMD and RBANS scales in patients with MDD, it was found that depressive symptoms and cognitive function disorders had no significant correlation at baseline, the decremental rate (HAMD), or the incremental rate (RBANS) at the end of the 8th week. (See Table 4).

Table 2 Scores on the Scales at Different Stages of the Evaluation in Patients With Major Depressive Disorder

	Baseline	The 4th Week	The 8th Week
HAMD	23.73±6.08	16.81±6.87	10.82±6.47
HAMA	21.54±7.25	14.92±6.89	9.17±5.87
PSQI	17.95±6.71	14.71±6.50	12.32±6.70
RBANS	223.12±29.47	251.93±26.09	275.61±31.60

Abbreviations: HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 3 Change in Value From Different Scales in MDD Patients at Baseline and the 8th Week

Baseline		HAMD	HAMA	PSQI	RBANS
Sex	Male	23.12±5.70	20.46±6.79	17.04±7.50	225.38±29.57
	Female	23.98±6.23	21.98±7.41	18.32±6.36	222.20±29.50
	P value	0.403	0.211	0.258	0.522
Age	≤35 years old	24.14±5.94	21.83±7.34	17.68±6.11	226.69±28.32
	>35 years old	22.52±6.37	20.70±7.01	18.73±8.27	212.66±30.60
	P value	0.128	0.376	0.445	0.006*
Education Level	≤12Years	23.31±5.66	20.72±7.00	17.17±6.91	209.48±29.23
	>12Years	23.79±6.25	21.97±7.41	18.22±6.60	229.34±27.75
	P value	0.301	0.637	0.340	<0.001*
Working	Mental Work Activity	23.09±5.43	21.71±7.24	18.49±6.73	228.36±25.34
	Physical Work Activity	23.14±6.43	21.80±7.48	17.83±6.90	214.69±31.70
	P value	0.950	0.963	0.623	0.027*

(*Continued*)

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Table 3 (Continued).

Baseline		HAMD	HAMA	PSQI	RBANS
The 8th week-Baseline		Decremental Rate %	Decremental Rate%	Decremental Rate%	Incremental Rate%
Sex	Male	53.89±25.00	55.43±33.23	30.79±34.39	22.48±16.05
	Female	55.86±22.67	56.65±24.90	27.49±55.20	25.88±16.63
	P value	0.616	0.792	0.695	0.221
Age	≤35 years old	54.82±23.63	54.96±28.07	27.77±54.97	23.51±15.65
	>35 years old	56.69±22.53	60.22±25.53	30.39±31.69	28.96±18.32
	P value	0.274	0.647	0.765	0.058
Education Level	≤12Years	57.38±19.32	59.29±20.29	20.76±77.91	29.28±18.46
	>12Years	54.99±24.53	55.72±29.51	31.95±29.91	22.97±15.30
The 8th week-Baseline		HAMD	HAMA	PSQI	RBANS
		Decremental Rate %	Decremental Rate%	Decremental Rate%	Incremental Rate%
	P value	0.360	0.529	0.177	0.031*
	Mental Work Activity	61.93±20.73	63.79±22.31	31.66±29.21	24.54±15.29
	Physical Work Activity	63.28±11.45	64.86±17.23	33.16±25.64	30.15±18.01
	P value	0.798	0.648	0.791	0.083

Note: * $p<0.05$.
Abbreviations: MDD, major depressive disorder; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Table 4 Correlation Analysis of the Changing Rate at Baseline and the 8th Week on HAMD and RBANS Scales

	RBANS Baseline		RBANS 8-Week Incremental Rate	
	R Value	P value	R Value	P value
HAMD Baseline	0.132	0.85		
HAMD8-week Decremental Rate			0.124	0.105
Intra-Group Decremental Rate≥50%			−0.036	0.699
Intra-Group Decremental Rate<50%			−0.129	0.358

Abbreviations: HAMD, Hamilton Depression Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Development Trajectory of the Depressive Symptom, Anxious Symptom, Sleep Situation and Cognitive Function

The linear unconditional latent variable growth model, as shown in Figure 1, for patients with MDD was established to examine the changing tendency of depressive and anxious symptoms, sleep situations, and cognitive function. According to the fit indicators in Table 5, the unconditional model showed a good fit with the data.

The specific parameter estimation results for the model were shown in Table 6. Table 6 suggests that depression decreased linearly during the three measurements (Gradient=−6.505, SE=0.222, $p<0.001$). Furthermore, the change in the intercept was significantly greater than 0 (σ^2=33.434, SE=5.858, $p<0.001$), indicating a significant difference in depression at baseline among individuals with MDD patients. However, no significant difference was observed between the change in gradient and 0 (σ^2=4.493, SE=2.316, p=0.052), suggesting that depressive symptoms that changed over time were not significantly different among individuals with MDD patients. Finally, the intercept was negatively associated with the gradient (r=−0.478, $p<0.001$), indicating that in patients with MDD, the higher the baseline depressive symptoms, the faster the depression level decreased during the three measurements.

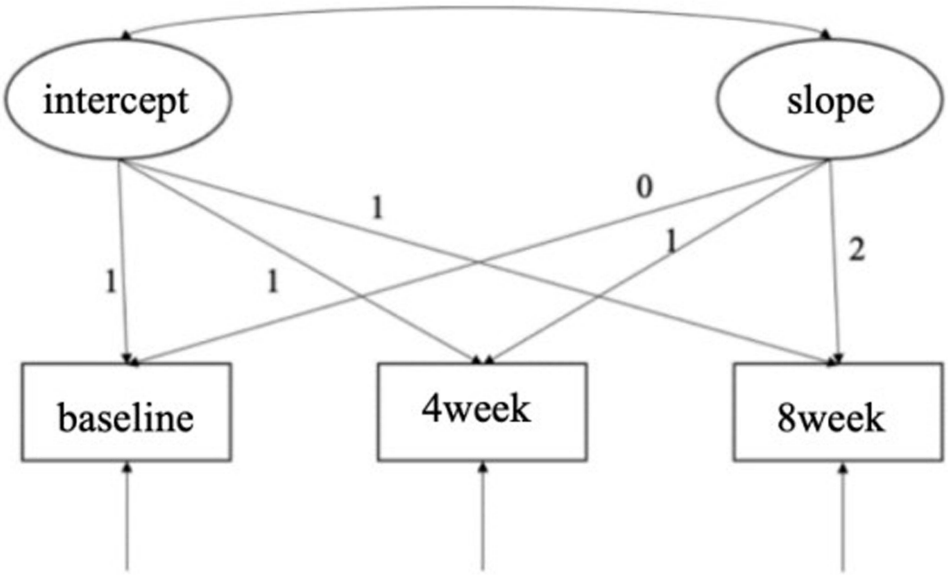

Figure 1 The linear infinite latent variable growth model established by the linear unconditional latent variable growth model of depressive symptom/anxious symptom/sleep situation/cognitive function.

Anxiety symptoms presented a linear decrease during the three measurements (gradient =−6.229, SE=0.263, p<0.001). Furthermore, the change in the intercept was above 0 significantly (σ2=49.617, SE=7.554, p<0.001), indicating a significant difference in anxiety symptoms at the baseline level among different individuals with MDD patients. The change in the gradient was significantly greater than 0 (σ^2=8.383, *SE*=2.509, *p*=0.001), suggesting that anxiety symptoms

Table 5 The Fit Indicators of the Linear Unconditional Latent Variable Growth Model

Model	χ^{2}/df	CFI	TLI	RMSEA	SRMR
Depression	1.482	0.997	0.992	0.053	0.019
Anxiety	1.387	0.998	0.993	0.047	0.018
Sleep Problem	2.206	0.996	0.989	0.083	0.018
Cognitive Function	9.168	0.976	0.929	0.217	0.026

Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

Table 6 The Specific Parameter Estimation Results of the Linear Unconditional Latent Variable Growth Model

Model	Coefficient		Variation		Intercept Gradient
	Intercept	Gradient	Intercept	Gradient	
Depression	23.698*	−6.505*	33.434*	4.493	−0.478*
Anxiety	21.519*	−6.229*	49.617*	8.383**	−0.748*
Sleep Situation	17.724*	−2.738*	29.870*	1.821	0.083
Cognitive Function	224.738*	26.000*	703.850*	173.319*	−0.373*

Note:*p<0.001, **p<0.01.

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that changed over time were significantly different among individuals with MDD patients. Lastly, the intercept was negatively associated with the gradient (r=−0.748, p<0.001), indicating that in patients with MDD, the higher the levels of baseline anxiety symptoms, the faster the anxiety level decreased during the three measurements.

Sleep disorder presented a linear decrease during the three measurements (−2.738, SE=0.194, p<0.001). In addition, the change in the intercept was above significance (σ2=29.870, E=4.882, p<0.001), indicating a significant difference in sleep disorder at the baseline level among different individuals with MDD patients. However, no significant difference was observed between the change in gradient and 0(σ2=1.821, SE=1.961, p=0.353), suggesting that sleep disorder changes over time were not significantly different among individuals with MDD patients. (r=0.083, p=0.795)

Cognitive function presented a linear decrease during the measurements (gradient=26.000, SE=1.217, p<0.001). Furthermore, the change in the intercept was significantly greater than 0 (σ2=703.850, SE=90.497, p<0.001), indicating a significant difference in cognitive function at baseline among the different individuals with MDD patients. The change in the gradient was significantly greater than 0 (σ2=173.319, SE=35.585, p<0.001), suggesting that cognitive function changes over time were significantly different among individuals with MDD patients. Finally, the intercept was negatively associated with the gradient (r=−0.373, p<0.001), indicating that in patients with MDD, the higher the baseline cognitive function, the lower the cognitive function increased during the three measurements.

The Impact of the Variation of Depression/Anxiety/Sleep Disorder on the Variation of the Cognitive Function

The LGCM was established to investigate the impact of the variation of depression/anxiety/sleep disorder on the variation of the cognitive function (Table 6).

To investigate the association between depressive symptoms and cognitive function, the intercept and gradient of depression were used to predict the gradient of cognitive function, whereas the intercept of depression was used to predict the intercept of cognitive function. The model showed a good fit with the data (χ^2/df=5.478, CFI=0.936, TLI=0.880, RMSEA=0.161, SRMR=0.056), and the specific results are shown in Figure 2. Specifically, there was no significant prediction of the depressive level at baseline on the baseline cognitive function in MDD patients (β=−0.142, SE=0.087, p=0.103), and the depression level at baseline was not an outstanding predictor of the variation in cognitive function (β=0.075, SE=0.112, p=0.501). The variation in depression in MDD patients could significantly negatively predict their variation in cognitive function (*β*=−0.328, *SE*=0.142, *p*=0.021), which means that the faster the depression decreased over time, the faster the cognitive function increased in MDD patients.

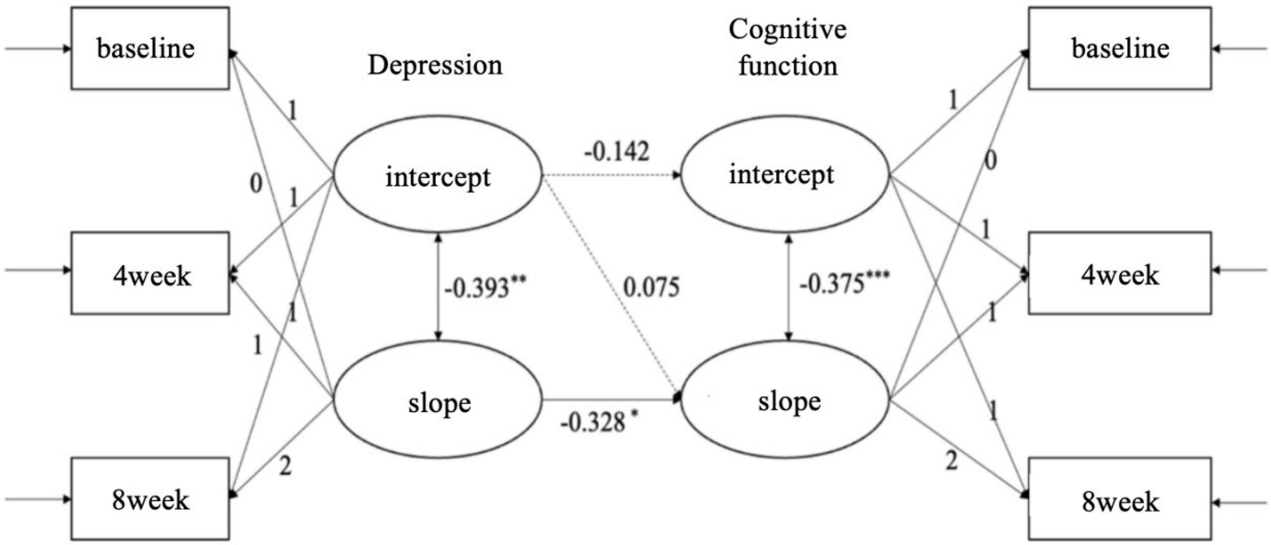

Figure 2 The parameter estimation results of the Latent Growth Curve Model of depressive symptom and cognitive function.
Note:***p<0.001, **p<0.01, *p<0.05.

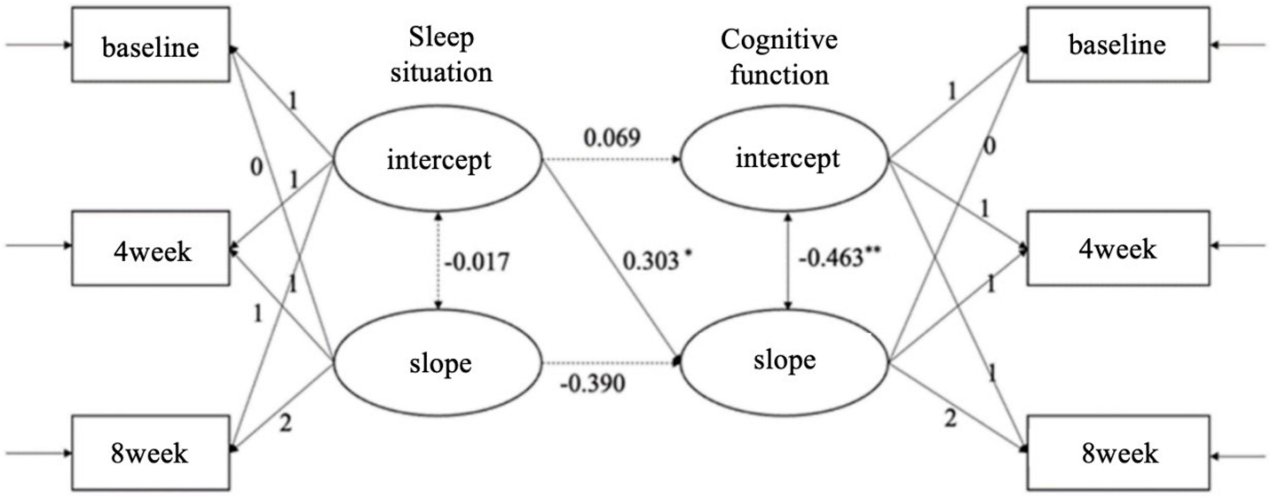

Figure 3 The parameter estimation results of the Latent Growth Curve Model of sleep situation and cognitive function.
Note:*p<0.05, **p<0.001.

The LGCM of anxiety, sleep situations, and cognitive function was established in the same manner. The model showed a good fit to the data (χ^2/df=4.124, CFI=0.954, TLI=0.913, RMSEA=0.134, SRMR=0.050). Specifically, there was no significant prediction of the anxiety level at baseline on the baseline cognitive function in MDD patients (β=−0.104, SE=0.085, p=0.222), and the anxiety level at baseline was not an outstanding predictor of the variation in cognitive function (β=−0.118, SE=0.135, p=0.383). The variation in anxiety in MDD patients could significantly negatively predict their variation in cognitive function (β=−0.408, SE=0.147, p=0.005), which means that the faster the anxiety decreased over time, the faster the cognitive function increased in MDD patients.

The LGCM of the sleep situation showed a good fit with the data (χ^2/df=2.626, CFI=0.981, TLI=0.964, RMSEA=0.097, and SRMR=0.025). The results are shown in Figure 3. Moreover, no significant changes occurred in the results when the depressive symptoms of the patients were added to the model as the corrective situation, indicating that there was a significant prediction of the sleep situation at baseline on the baseline cognitive function in MDD patients (β=0.069, SE=0.089, p=0.043), and the variation of the sleep situation in MDD patients could significantly positively predict their variation in cognitive function (β=0.303, SE=0.126, p=0.016), indicating that the more serious the sleep problem MDD patients have at baseline, the faster the cognitive function increased over time in MDD patients. Meanwhile, the variation in the sleep situation in MDD patients could significantly negatively predict their variation in cognitive function, which means that the faster the sleep situation improved, the faster the cognitive function increased over time in MDD patients (β=−0.390, SE=0.237, p=0.099).

Study the Relevant Factors of the Dynamic Impact of the Sleep Disorder on the Cognitive Function in MDD Patients

LGCM has been established in both male and female patients. According to the model fit indicators, χ^2/df=1.215, CFI=0.992, TLI=0.985, RMSEA=0.066, SRMR=0.055 in male patients with MDD, and χ^2/df=2.180, CFI=0.980, TLI=0.962, RMSEA=0.098, SRMR=0.033 in female patients with MDD. The model fit the data well. Therefore, sex variation was added to the model, based on the model expressing the relationship between sleep conditions and cognitive function. The intergroup comparative method was used to examine whether differences in the cognitive function of patients with MDD changing with sleep existed in both sexes. The results are presented in Table 7. The difference was not significant in the chi-square test between the free estimation model (M1) and restricted path model (M2)($\Delta\chi^2$=3.962, Δdf=3, p=0.266>0.05). This result indicated that there was no significant difference in the model expressing the relationship between sleep status and cognitive function between the sexes.

Table 7 Comparison of the Variations on the Model Expressing the Variation Relationship Between the Sleep Situation and the Cognitive Function of Both Sexes in MDD Patients

Model	χ^2	df	CFI	TLI	RMSEA	SRMR	$\Delta\chi^2$	Δdf
M_1	28.954	16	0.981	0.964	0.097	0.060	——	——
M_2	32.916	19	0.980	0.968	0.083	0.070	3.962	3

Note: M1 is an unrestricted model that allows male and female patients to estimate the coefficients of each pathway freely. M2 is a restricted model that allows male and female patients to have fixed and equal path coefficients in the model only. MDD, major depressive disorder.

Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

According to the fit indicators of the model, $2\chi^{2/}$df=2.292, CFI=0.980, TLI=0.963, RMSEA=0.100, and SRMR=0.031 in MDD patients aged ≤35 years and $\chi^{2/}$df=1.188, CFI=0.991, TLI=0.983, RMSEA=0.066, and SRMR=0.074 in MDD patients aged >35 years. The model fits the data well. Therefore, age variation was added to the model based on the model expressing the relationship between sleep disorder and cognitive function. The inter-group comparative method was used to examine whether differences in the variation of cognitive function in patients with MDD changing with sleep existed at different ages. The results of Table 8. The difference was not significant in the chi-square test between the free estimation model (M3) and restricted path model (M4) ($\Delta\chi^2$=5.151, Δdf=3, p=0.161>0.05). This result indicated that there was no significant difference in the model expressing the relationship between sleep problems and cognitive function at both ages.

LGCM was established for patients with different educational durations. According to the fit indicators of the model, $\chi^{2/}$df=1.612, CFI=0.990, TLI=0.976, RMSEA=0.093, and SRMR=0.046 in patients with an education of 12 years or less and $\chi^{2/}$df=2.721, CFI=0.984, TLI=0.976, RMSEA=0.093, and SRMR=0.059 in patients with an education of more than 12 years. The model fits the data well. Therefore, education duration was added to the model, based on a model that expresses the relationship between sleep problems and cognitive function. The intergroup comparative method was used to examine whether the difference in the relationship between the variation of the sleep problem and the variation of cognitive function existed for different education durations. The results of Table 9. The difference was not significant in the chi-square test between the free estimation model (M5) and restricted path model (M6) ($\Delta\chi^2$=4.876, Δdf=3, p=0.166>0.05). This result indicated that there was no significant difference in the model expressing the variation of sleep problems and the variation of cognitive function in patients with different education durations.

LGCM was established for patients engaged in mental and physical work. According to the fit indicators of the model, $\chi^{2/}$df=2.292, CFI=0.980, TLI=0.963, RMSEA=0.100, and SRMR=0.031 in patients engaged in mental work and $\chi^{2/}df$=1.188, CFI=0.991, TLI=0.983, RMSEA=0.066, and SRMR=0.074 in patients engaged in physical work. The model fit the data well. Therefore, differences in occupation were added to the model based on the model expressing the

Table 8 Comparison of the Variations on the Model Expressing the Variation Relationship Between the Sleep Problem and the Cognitive Function of Patients With Major Depressive Disorder Above or Below 35 Years Old

Model	χ^2	df	CFI	TLI	RMSEA	SRMR	$\Delta\chi^2$	Δdf
M_3	27.644	16	0.983	0.968	0.092	0.044	——	——
M_4	32.795	19	0.980	0.968	0.092	0.057	5.151	3

Note: M3 is an unrestricted model that allows patients aged above or below 35 years to freely estimate the coefficients of each pathway in the model. M4 is a restricted model that allows patients aged above or below 35 years to have fixed and equal path coefficients in the model only.

Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

Table 9 Comparison of the Variations on the Model Expressing the Variation Relationship Between the Sleep Problem and the Cognitive Function in the Patients With the Education of 12 Years or Below

Model	χ^2	df	CFI	TLI	RMSEA	SRMR	$\Delta\chi^2$	Δdf
M_5	27.990	16	0.990	0.976	0.093	0.046	——	——
M_6	32.866	19	0.984	0.976	0.093	0.059	4.876	3

Note: M5 is an unrestricted model that allows patients with an education level of 12 years or less to freely estimate the coefficients of each pathway. M6 is a restricted model that allows patients with an education of 12 years or less to have fixed and equal path coefficients in the model only.

Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

relationship between sleep problems and cognitive function. The intergroup comparative method was used to examine whether the difference in the relationship between the variation in sleep problems and the variation in cognitive function existed in patients with different occupations. The results of Table 10. The difference was not significant in the chi-square test between the free estimation model (M7) and restricted path model (M8) ($\Delta\chi^2$=5.083, Δdf=3, p=0.217>0.05). This result indicated that there was no significant difference in the model expressing the variation of sleep problems and the variation of cognitive function in patients engaged in mental and physical work.

LGCM was established for patients with an 8-week decremental rate of HAMD of <50% or ≥50%. According to the fit indicators of the model, χ^2/df=1.772, CFI=0.982, TLI=0.978, RMSEA=0.101, and SRMR=0.056 in patients with an 8-week decremental rate of HAMD < 50%, and χ^2/df=1.621, CFI=0.990, TLI=0.981, RMSEA=0.066, and SRMR=0.069 in patients with an 8-week decremental rate of HAMD ≥50%. The model fits the data well. Therefore, improvement was added to the model based on the model expressing the relationship between sleep problems and cognitive function. The inter-group comparative method was used to examine whether a difference in the relationship between the variation in sleep problems and the variation in cognitive function existed in patients with different levels of depression improvement. The results of Table 11. The difference was not significant in the chi-square test between the free estimation model (M9) and restricted path model (M10) ($\Delta\chi^2$=4.445, Δdf=3, p=0.187>0.05). This result indicated that there was no significant difference in the model expressing the variation of the sleep problem and the variation of the cognitive function in patients with an 8-week decremental rate of HAMD < 50% and ≥50%, which showed consistency in the trend of cognitive function changes with sleep status in patients with MDD with different levels of depression improvement.

Table 10 Comparison of the Variations on the Model Expressing the Variation Relationship Between the Sleep Problem and the Cognitive Function in the Patients Engaged in Mental and Physical Work

Model	χ^2	df	CFI	TLI	RMSEA	SRMR	$\Delta\chi^2$	Δdf
M_7	27.828	16	0.981	0.972	0.095	0.062	——	——
M_8	32.911	19	0.980	0.972	0.088	0.072	5.083	3

Note: M7 is an unrestricted model that allows patients to engage in mental and physical work to estimate the coefficients of each pathway freely. M8 is a restricted model that allows patients engaged in mental and physical work to have fixed and equal path coefficients only in the model.

Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

Table 11 Comparison of the Variations on the Model Expressing the Variation Relationship Between the Sleep Problem and the Cognitive Function in the Patients With 8-Week Decremental Rate of HAMD <50%–≥50%

Model	χ^2	df	CFI	TLI	RMSEA	SRMR	$\Delta\chi^2$	Δdf
M_9	28.362	16	0.982	0.980	0.095	0.062	——	——
M_{10}	30.812	19	0.990	0.980	0.083	0.072	4.445	3

Note: M9 is an unrestricted model that allows patients with an 8-week decremental rate of HAMD < 50% and ≥50% to freely estimate the coefficients of each pathway in the model. M10 is a restricted model that allows patients with an 8-week decremental rate of HAMD < 50% and ≥50% to have fixed and equal path coefficients in the model only.
Abbreviations: CFI, Comparative Fit Index; TLI, Test of Logical Interpretation; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized root mean square residual.

Discussion

The current study presented that the more severe the sleep disorder in patients with first-episode MDD, the more obvious was the damage to cognition. The LGCM indicated that the dynamic impact of sleep quality on cognitive function is positively correlated, and over time, there is an association between the remission speed of depressive or anxiety symptoms and improving speed of cognitive function in patients with MDD.

The Correlation Between the Pre and Post Treatment Changing Characteristics and the Sleep Disorder in MDD Patients

According to the PSQI at baseline, almost all patients with MDD had sleep disorder including sleep difficulty, early awakening, and decreased sleep quality. Female sex, older age at the time of onset, higher education level, marital status, and mental work were risk factors for patients with more severe sleep disorder, which was consistent with a previous study, bringing enormous pain to the patient's life.[6,7,20] Based on LGCM, a significant difference in sleep problems at baseline was found between individuals, and the difference also existed in the tendency of sleep problems to change over time between individuals. However, the sleep situation did not present a significantly consistent level of dynamic change over time, nor did it perform the same as the changing tendency on the improvement of depressive symptoms. This study shared the same results as another study that analyzed the influencing factors of sleep disorder using a multilevel linear regression method based on the theoretical framework of the Dahlgren-Whitehead model.[21] As the general information showed that patients who had exercise habits (mainly focused on medium- and high-intensity sports) had benefits on the baseline scores of the sleep disorder and the tendency to change over time. These results are consistent with those of the previous research.[22]

The Changes of the Cognitive Function Before and After Treatment as well as Its Related Factors in MDD Patients

Previous study suggested that the depressive patients had severe impairment of the cognitive function before and after treatment, which is also the risk factors of the recurrence of depressive symptom.[3–5] As the biggest risk factor on the prognosis of the depressive patients,[23] its impairment not only leaves an impact on the efficacy and curability of the anti-depressant drug[24] but also increases the risk of Alzheimer disease, leading to irreversible damage.[25] In this study, a significant decrease occurred in the areas such as memory, language ability, abstract thinking ability and executive function in most of the MDD patients, and there is significant difference between individuals, which had the same results with the study of Greden et al.[26] The patients with lower scores on RBANS scales yielded higher scores among the items related to sleep, blockage symptoms and psychological anxiety. The LGCM showed significant differences in cognitive function at baseline in different individuals, and this significant difference in the changes in cognitive function over time also existed in different individuals. Patients with severe depressive symptoms show slower improvements in cognitive function over time. Improvement in depressive symptoms led to a significant increase in cognitive function. These results

show a small discrepancy with those of the previous studies. In a previous study, more severe depression was found to lead to poorer sleep disorder and more severe impairment of cognitive functions. Cognitive function impairment still exists, even after improvements in depression and sleep.[10,11]

Comparative analysis of the RBANS baseline values and decremental rate from the samples of patients with different characteristics showed the following results: 1. Older patients had greater improvements in their planning and control abilities. 2. Patients with a longer education duration had a greater speed of improvement in memory function and a stronger ability to control attention bias. 3. Patients engaging in mental work have a more significant decrease in areas such as memory and language ability but have a greater speed of recovery compared to physical work workers. 4. According to the baseline data of the HAMD, HAMA, and RBANS, more severe depressive symptoms lead to more severe memory impairment in patients with MDD. 5. Patients with more severe depressive symptoms have more severe impairments in execution ability and fluency of language. 6. Patients with a more event-slow mentality will have a lower surgical accuracy. 7. Patients with more obvious depressive sleep disorder will experience more significant damage to areas such as attention-controlling and memory-maintaining functions. All of these results demonstrate that close concern regarding cognitive function should still be maintained even after the improvement of symptoms in patients with MDD.

Dynamic Influence of the Sleep Disorder on the Cognitive Function in MDD Patients

According to the *t*-test and LGCMs, this study found that the tendency of cognitive function disorder to change with sleep was not affected by the improvement of depressive symptoms based on the groups of patients with different levels of improvement of depressive symptoms. Additionally, the more severe the sleep problems at baseline, the more severe the cognitive function impairment. Moreover, patients with more severe sleep problems at baseline will have a greater speed of improvement in cognitive function with the advancement of treatment, and the changes in cognitive function will have a positive correlation with the tendency of sleep changes. It is noticeable that the severity of sleep disorder has a huge impact on the changes in cognitive function, which shared the same results as the previous study.[27] After further analysis on the scales, the patients who scored higher in the areas such as the increased frequency of early awakening and awakening, breathing difficulty, and nightmares on PSQI scales had more severe damage to the functional items including memory, language fluency, attention, etc. On RBANS scales. Furthermore, MDD patients with relatively good sleep situation scores of less than 10 (45 cases) on the PSQI scales had little influence on their language fluency, which is similar to the results of a previous study.[28]

Previous reports found that sleep disorder accounted for a larger proportion of the chief complaints in first-episode depressive patients.[28] In the clinical treatment process, the improvement of sleep problems often occurs sooner than the improvement of depressive symptoms. In this study, 89% of the patients used sleep-related medicine as their primary drug. Given the fact that the significant difference may have on the symptoms of sleep disorder in MDD patients at the time of presentation and some patients have received sleep-related medicine as treatment, their baseline data could not predict improvement in cognitive function impairment and sleep disorder. However, sleep problems achieved obvious remission ahead of the improvement of depressive and anxious emotions after systemic treatment in patients with MDD. Their cognitive function gradually changed faster, which means more improvement in sleep disorder and a shorter time for improvement. Cognitive function impairment can improve faster. This study is the first to draw such a conclusion, which is slightly different from previous past.[28]

Multiple Factors That Influence the Cognitive Function Changing Dynamically With the Sleep Disorder

Previous studies have shown that age, sex, education level, social support, nature of occupation, marital status, etc, are independent risk factors for cognitive function impairment in patients with depression.[1,3,28] This study strictly controlled certain variables that might have had an impact on the study results, and four aspects including sex, age, education level, and mental and physical work were analyzed. No statistical significance was found for any of the four influencing factors. Even in the subgroup comparison, the trend of cognitive function disorder changing with sleep disorder was not affected

by other influencing factors, possibly validating the fact that sleep disorder may play an independent role in affecting cognitive function impairment[29] instead of varying in different groups, which is consistent with a previous study.[30]

Female patients with MDD have more severe sleep disorder than male patients with MDD. Cognitive function impairment at baseline was lower than that in male patients. However, with improvement in sleep disorder, there was no significant difference in the variation tendencies of these two factors. This result indicated that the severity of the primary sleep disorder had no effect on the dynamic variation tendency of cognitive function improvement. Regarding the influencing factor of age, cognitive function will gradually decrease in the population aged >35 years according to a previous study.[31] Patients aged >35 years at the time of onset had more serious manifestations of sleep disorder, and their primary level of cognitive function was relatively low; therefore, physiological factors could not be ruled out. However, further verification is needed since no significant difference was found in the tendency of cognitive function impairment as a result of sleep disorder. Regarding the influencing factors of education level and the nature of occupation, sleep disorder had no significant difference in the initial scores and in the subsequent tendency of cognitive function changing by sleep. Thus, the following conclusions were drawn: the normal level of cognitive function in patients can neither predict the severity of sleep at the primary stage of the disease nor have any impact on the dynamic tendency of their cognitive function to change with the sleep situation after receiving subsequent treatment.

The Innovation of This Study

Patients with MDD without regular administration were included in this study, and a statistical analysis based on LGCMs was performed on depressive and anxious symptoms, sleep situation, and cognitive function. The dynamic impact of sleep disorder on cognitive function in patients as well as related factors was analyzed. The conclusions drawn from this study provide evidence of the mechanism of cognitive function impairment in patients with depressive disorders.

Weakness of This Study

This study found that most patients with MDD had individual differences in the data at baseline. However, no significant variation was observed in the changes over time. More rapidly, depression would improve within 8 weeks in patients with more severe depressive symptoms. The main reasons for this are as follows: 1. The sample size was small and the study lasted for only eight weeks. 2. All subjects had first-episode MDD with relatively high medical compliance and sensitivity.[32] 3. To minimize errors caused by other related factors, a restriction was set up for the inclusion criteria, including age, physical illness, medication history, etc.[28] 4. More obvious improvement was observed in the patients with more severe initial depressive symptoms. All the scales were covered by the subjects' feelings during the interview, which might have led to the discrepancy of such results caused by subjective factors.

As the disease with the highest rate of comorbidity in depressive patients, anxiety symptoms were measured independently, and the results showed that the difference in anxiety level at baseline existed in different individuals. There was also a significant difference in the tendency of anxiety symptoms to change over time among the different individuals. The higher the anxiety level at baseline the MDD patients had, the faster it decreased during the 8-week course of treatment. Thus, the change in anxiety symptoms is independent of the general process of improvement in patients with MDD, which is not completely related to the improvement of depressive symptoms, although anxiety symptoms are one of the common symptoms in patients with MDD. To explain the above reasons, the family background, environmental support, and life events, or perhaps the individual differences including the illness and physical situation, individualized medication therapy for depression (some antidepressants have the effect of improving anxiety) may be related factors.[33] Because this study mainly targeted MDD patients, no information on anxiety was collected separately based on these factors.

Limitation of This Study

This study has a few limitations for this study: 1. This was a single-center study and the general statistical elements lacked comprehensiveness. Further investigation based on larger samples, more evaluation items (eg, family support and physical illness), and prolonged observation in the future are required. 2. No other options are available for evaluating sleep quality. In addition to the PSQI (the only indicator for sleep disorder evaluation in this study), PSG monitoring

equipment should be included as an objective tool for the evaluation of sleep quality. 3. Multiple factors can influence cognitive function. Although potential influencing factors, including sex, age, and education, were collected as much as possible in this study, some confounding factors were not controlled, such as the deficiency of objective testing on substance addiction in the patients. Lastly, study medication had a relatively strong impact on changes in symptoms. As this was a non-interventional observational study, no controlling procedure was conducted for the treatment strategy of the patients. Therefore, the design limitations should be considered when explaining the results of this study.

Conclusion

Patients with MDD have obvious anxiety symptoms, sleep disorder, and cognitive impairment. LGCM indicated that the levels of depression and anxiety in patients with more severe depressive symptoms have improved faster with the advancement of treatment. During the treatment process, patients with MDD experienced remission of sleep disorder earlier than depressive and anxious emotions, and their cognitive function gradually improved faster. Among the common factors influencing the improvement of cognitive function in patients with MDD, four factors, including sex, age, education duration, and nature of occupation, did not affect the tendency of cognitive function impairment to change with sleep disorder.

Abbreviations

MDD, major depressive disorder; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; LGCM, Latent Growth Curve Model.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Tianjin Anding Hospital (No.2019-18). All patients and their families signed a written informed consent form for clinical research. This study complies with the Declaration of Helsinki.

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The authors declare that they have no competing interests in this work.

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