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Severe sleep disturbance is associated with executive function impairment in patients with first-episode, treatment-naïve major depressive disorders

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Abstract

Background: Sleep disturbance and executive function impairment are common in patients with major depressive disorder (MDD), though the relationship between the two remains unclear. We investigated this association in first-episode, treatment-naïve patients with MDD.

Methods: We analyzed data from 242 patients with MDD. We divided the patients into 2 groups based on sleep disturbance severity and compared the executive function odds ratios between the groups.

Results: A total of 121 pairs of patients were matched (age 39.4 ± 10.1, 70.2% female). After propensity score matching, the odds ratios for cognitive impairment in patients with MDD and severe sleep disturbance were 1.922 (1.068–3.459, $P = 0.029$, $q = 0.044$) in executive functioning; 2.023 (1.211–3.379, $P = 0.007$, $q = 0.021$) in executive shifting.

Conclusions: Sleep disturbance is associated with executive functioning impairment in first-episode, treatment-naïve patients with MDD. Severe sleep disturbance can be a marker and aid in recognizing executive function impairment in patients with first-episode treatment-naïve MDD. Severe sleep disturbance can be a potential modifiable factor to improve executive function in MDD, as well as an effective measurement to improve cognition for sleep symptom management that should be enforced at initial treatment of first-episode MDD. Further study is required to confirm our results.

Trial registration: ClinicalTrials.gov: NCT02023567; registration date: December 2013.

Keywords: Major depressive disorder, Cognitive functioning, Sleep disturbance, Executive functioning

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Cui *et al. BMC Psychiatry*   (2021) 21:198

Page 2 of 11

Background

Major depressive disorder (MDD) is a disabling disease with significant social and economic consequences, including decreased work productivity and poor psychosocial outcomes [1, 2]. MDD has been associated with cognitive impairment in several domains, including attention, memory, executive functioning, and information processing speed [3], and approximately 90% of patients with MDD complain about impaired cognition [4].

Patients with first-episode MDD can suffer from impaired cognition [5]. Cognitive dysfunction especially executive function impairment is associated with a high risk of relapse and a low rate of remission [6, 7], increasing the risk of treatment-resistant MDD, so it is imperative to intervene early during the course of the first episode of MDD. Executive impairment has 3 dimensions including inhibition (defined as suppressing or avoiding an automatic response), shifting (defined as switching between task sets and response rules), and work memory (defined as actively maintaining or manipulating information across a short delay, which can be further divided into verbal and visuospatial components) [8], and has been identified as one of the main impaired cognitive domains in patients with MDD [8]. Deficits in executive functioning have been associated with pathophysiology in the prefrontal cortex-subcortical brain circuitry in MDD patients [9].

Sleep disturbances are common complaints in patients who are depressed [9], and they, in turn, increase the risk of developing a depressive disorder [10–12]. Sleep disturbances are manifest in different ways, including difficulty falling asleep, frequent nocturnal awakenings, and waking early in the morning, unable to go back to sleep, resulting in sleep fragmentation and poor sleep efficiency. Studies about sleep electroencephalograms in MDD patients have found disinhibition of rapid eye movement (REM) sleep- a decrease in REM sleep latency and an increase in REM sleep duration [13]. The prefrontal cortex (PFC) is deactivated and decoupled from posterior associative regions during REM sleep [14].

Therefore, potential complex relationships are existed among sleep disturbance, depressive disorder, and executive function impairment. Executive function impairment has been reported in old insomnia patients [15]. Functional alterations in the prefrontal cortex, cingulate gyrus, and subcortical regions, combined with deficits in executive functioning, have been observed in patients with sleep disorders [16]. A recent meta-analysis concluded that insomnia has a profound effect on a wide range of cognitive domains, including manipulation in working memory, problem-solving, and perceptual functions [17]. Insomnia has been reported to relate to impairment in executive function and visual-motor processing speed in MDD patients [18]. However, the result is the opposite in the individuals with chronic fatigue syndrome, and the sleep symptoms are not related to impaired cognitive function [19]. The previous studies mainly selected health individuals as the control group with small sample sizes.

Researchers have found several risk factors for executive impairment in patients with MDD, including age [20], age of onset [21], depression severity and duration, comorbid physical disease, episode frequency [1], childhood trauma [22, 23], and MDD subtype [24]. Most studies have focused on recurrent depressive disorders or cognitive impairment in late-onset depression [25]. Some risk factors are unmodifiable, such as age, and others are potentially modifiable, such as MDD severity. Though previous studies have explored the negative consequences of sleep disturbances in patients with MDD or executive function impairment [11, 26, 27], it is still not known about the role, if any, of sleep disturbances play in executive function impairment in patients with MDD.

Previous studies have included patients with both first-episode and recurrent depressive disorders, and the influence of antidepressants has not been clarified. So, we hypothesize that severe sleep disturbance is associated with poorer executive function and its dimensions in MDD patients than the patients with normal or up to moderate sleep disturbance. If so, then treating sleep disturbances may be an option in reducing executive function impairment in a clinical setting. Here we report on the relationship between sleep disturbances and executive function impairment in the setting of a clinical trial.

Methods

Participants

Between December 2013 and December 2016, researchers recruited Chinese adults to participate in the multicenter, multistage, prospective study Objective Diagnostic Indicators and Individualized Drug Intervention of Major Depressive Disorder (OIMDD), project No. 2013CB531305. We conducted a secondary, cross-sectional analysis using the baseline data from OIMDD for participants diagnosed with MDD. Nine hospitals in China participated in the study. All participants provided written consent, and the study protocol was approved by the research ethics board of the institution where it was performed.

Study participants included patients between the ages of 18 and 65 years who had been diagnosed with their first episode of MDD, did not receive any antidepressant treatment in the acute phase of the disease, and had a total score of ≥14 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) [28]. Patients were excluded if they had severe somatic diseases, such as severe heart disease, malignant

tumors, or a history of epilepsy. Pregnant or lactating women were also excluded [29].

Depression diagnosis and clinical assessment

Using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), psychiatrists made a diagnosis of MDD and then conducted structured clinical interviews with the prospective participants using the Mini-International Neuropsychiatric Interview (MINI), Chinese Version 5.0.0 [30]. After the interviews, HAMD-17 was used to assess depressive symptoms, evaluating functioning in 5 subscales: cognitive impairment, retardation, anxiety or somatization, sleep disturbance, and weight change [31]. Sleep disturbance severity was assessed by evaluating the following metrics on the HAMD-17 scale: item 4, difficulty falling asleep; item 5, waking in the middle of the night for any reason except to void; and item 6, waking early in the morning and unable to go back to sleep. Each item could be rated from 0 (no difficulty) to 2 (nightly difficulty), with a total possible score of 6. A sleep subscale score > 4 was defined as a severe sleep disturbance, and patients in this category were assigned into Group 1; the remainder, were assigned into Group 2. The Hamilton Anxiety Rating Scale (HAMA) was used to assess 2 areas of somatic anxiety: muscular (pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, and increased muscular tone) and sensory (tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, and pricking sensation) [31, 32].

Executive function tests

A battery of cognitive tests was performed to evaluate executive functions including dimensions of executive inhibition that was assessed by the Stroop Color Word Test (SCWT), and executive-shifting that was assessed by color line II. We selected the cognitive test battery in our study from the MCCB (MATRICS Consensus Cognitive Battery) of the MATRICS (the Measurement and Treatment Research to Improve Cognition in Schizophrenia) study. The MCCB has been widely used to evaluate the cognitive function of patients with mental disorders. The test scores for each domain were transferred into global deficit scores (GDS), which were adjusted for age, sex, and education level. A global deficit score ≥ 0.5 was defined as cognitive impairment [33, 34].

Confounding covariables

In addition to gathering basic demographic data—marital status, living situation (whether the subject lives alone or with others), religious affiliation, work status, the type of work (whether it requires mental labor, physical labor, or both), independence (degree to which the subject depends on someone else for life's basics), and body mass index (BMI), we obtained information on potential confounding covariables that could alter a person's risk for cognitive impairment. Some comorbid conditions are known to increase the risk of cognitive impairment, including cardiovascular disease and diabetes. Other suspected risk factors include duration of disorder, severity of depression and/or anxiety, family history of psychiatric disorders, history of alcohol abuse, smoking history, and childhood trauma [1].

We collected previous disease history at baseline, including hyperlipidemia, hypertension, and diabetes. Diabetes was defined as a fasting blood glucose (FBG) level ≥ 126 mg/dL (7.0 mmol/L), oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L), HbA1c ≥ 48 mmol/L (6.5%), or a history of diabetes mellitus. Hyperlipidemia was defined as having total cholesterol (TC) ≥ 5.17 mmol/L, triglycerides (TG) ≥ 1.7 mmol/L, low-density lipoprotein (LDL) cholesterol ≥ 3.37 mmol/L, or a history of hyperlipidemia. Social demographic variables were assessed using questionnaires that asked about age, sex, marital status, occupation, alcohol use, and smoking status. Body mass index was calculated as weight in kilograms divided by squared height in meters (kg/m^2). BMI was divided into low weight (BMI < 18.5), normal weight (BMI ≥ 18.5 to < 24), overweight (BMI > 24 to ≤ 28), and obesity (BMI > 28).

Childhood trauma was assessed using the childhood trauma questionnaire (CTQ), which evaluates the subject's experience of abuse and/or neglect before the age of 18 years. The CTQ includes domains of emotional, physical, and sexual abuse, as well as of emotional and physical neglect. Items are rated from 1 ("never true") to 5 ("very often true") according to the frequency with which each event occurred in childhood. We considered the history of trauma as a dichotomic variable (yes/no) if the person rated items as moderate or severe according to the subscale cutoff criteria in at least one type of trauma [1, 35].

Statistical analyses

Summary statistics were presented as mean ± standard deviation for variables that conformed to a normal distribution, as medians and quartile for data did not conform to a normal distribution, and as percentages for categorical variables. To make the 2 groups more comparable, we performed propensity score matching. Propensity scores were estimated using a logistic regression model that contained known or suspected covariates that were unbalanced between the 2 groups. To perform the propensity score matching,

we included the type of work, marital status, religion, alcohol use, and HAMD-17 weight subscale. Because the independent-variable global deficit scores are functions converted from standard scores corrected by age, sex, and education, we did not include these variables in the propensity score matching. Subjects were matched 1:1 without replacement, using a 0.00 caliper width. Effect size was calculated to estimate the balance of the baseline data between the 2 groups. Cohen d was calculated using a t test and φ(phi) or φc (Cramer's phi) was calculated using the chi-square test. Effect size > 0.20 was considered to be an imbalance between the 2 groups. For multiple hypothesis tests with same data settings, to reduce false positive, correction was analyzed with the method of Benjamini and Hochberg, and corrected p value (q value) was calculated.

Statistical analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA) and version R 3.3.3 (Foundation for Statistical Computing, Vienna, Austria). The R package of MatchIt was used for the propensity score analysis. Logistic regression analysis was used to estimate the odds ratios for the global deficit scores for each cognitive domain and their corresponding 95% confidence intervals (CIs).

Results
Of the 296 patients included in our analysis, 121 had symptoms of severe sleep disturbance. Chi-square analysis and nonparametric test of the demographic and clinical characteristics between the 2 groups revealed significant differences in the groups' social demographics (see Table 1), including type of work (10.924, P = 0.004), marital status (17.072, P < 0.001), living situation (19.919, P < 0.001), religion (4.457, P = 0.035), alcohol use (14.284, P = 0.001), and HAMD weight subscale (P = 0.001). Because the 2 groups were so heterogeneous, we performed propensity score matching and the variables above were included into matching, after which the baseline characteristics of the 2 groups were highly comparable and we were able to successfully match 121 pairs of participants (average age 39.42 ± 10.07, 70.2% female). No differences in the other variables were observed between the 2 groups, with the exception of age (Table 2).

Before matching, compared with the patients in Group 2 (no severe sleep disturbance), chi-square analysis revealed that patients in Group 1 (severe sleep disturbance) had more impairment in executive functioning (32.2% vs 20.6%; P = 0.024, q = 0.036), and executive shifting (55.4% vs 40.0%; P = 0.009, q = 0.027), and executive inhibition (35.5% vs 23.4%, P = 0.036), respectively. After propensity score matching, for Group 1, the odds ratio for having a greater degree of cognitive

impairment in executive function was 1.922 (95% CI: 1.068, 3.459, P = 0.029, q = 0.044), and that for executive shifting was 2.023 (95% CI: 1.211, 3.379, P = 0.007, q = 0.021) (Tables 3 and 4).

Subgroup and sensitivity analyses
We analyzed the effects of severe sleep disturbance stratified by age, sex, and depression severity on executive function domain.

We evaluated the effects of severe sleep disturbance on executive function in different age group. (Table S1–3). In patients aged < 30 years, sleep disturbance had influence on executive shifting (OR = 13.714, 95% CI: 2.739, 68.678, p = 0.001, q = 0.003). In patients aged ≥30 and < 45, effect was observed on executive function (OR = 3.450, 95%CI: 1.367, 8.704, p = 0.009, q = 0.027). Such an effect was not obvious after correction of multiple tests in executive inhibition (OR = 2.568, 95% CI: 1.039, 6.344, p = 0.041, q = 0.061). The effects of sleep disturbance on executive function were not observed in patients aged> 45.

We performed subgroup analyses of the effects of severe sleep disturbance on sex.(Table S4–5). For male, the effect was not observed on executive function. In women, the effect was obvious on executive shifting (OR = 2.358, 95% CI: 1.274, 4.365, p = 0.006, q = 0.018), which was not obvious in executive function after correcting of multiple tests (OR = 2.135, 95% CI: 1.031, 4.420, p = 0.041, q = 0.061).

Since the severe sleep disturbance was associated with a more serious MDD, we assessed the effect on different MDD severity groups by HAMD-17 scores after the sleep-subscale score was removed. The MDD severity was split into two degrees according to the median score (17) of the remained HAMD score. Executive shifting (OR = 2.777, 95% CI: 1.386,5.564, P = 0.004, q = 0.006) and inhibition (OR = 3.556, 95% CI: 1.507,8.386, P = 0.003, q = 0.009) were obviously influenced in patients with HAMD≥17, while the effect was not observed in patients with HAMD < 17.

Discussion
In this study, we evaluated the effects of severe sleep disturbance on cognitive functioning in treatment-naïve patients with first-episode MDD and found a link between severe sleep disturbance and impaired executive functioning. We found significant differences in stratification by sex, age, and depression severity between Groups 1 and 2.

The baseline characteristics of the 2 groups had significant heterogeneity, so we performed propensity score matching to reduce bias, which reduced the sample size to 242 participants and enabled us to perform between-group comparisons, though the statistical power was

Table 1 Demographic and clinical characteristics of study participants before matching

	Group 1 (121)	Group 2 (175)	Effect Size	t, z, or Chi-square	P value
Age	41.8 ± 9.2	35.1 ± 10.6	0.675	−5.600 [a]	< 0.001
Education years (year)	11.9 ± 4.0	13.1 ± 3.7	0.311	2.588 [a]	0.010
Sex (male) (%)	39 (32.2)	52 (29.7)	0.027	0.213 [b]	0.645
Occupation (%)					
Full-time or part-time	83 (68.6)	127 (72.6)			
Unemployed or retired	38 (31.4)	48 (27.4)	0.043	0.549 [b]	0.459
Nature of work (%)					
Mental talents labor	58 (47.9)	117 (66.9)			
Physical labor	39 (32.2)	33 (18.9)			
Both	24 (19.9)	25 (14.3)	0.192	10.924 [b]	0.004
Marital status (%)					
Married or remarried	101 (83.5)	107 (61.1)			
Divorced or widowed or single	20 (16.5)	68 (38.9)	0.240	17.072 [b]	< 0.001
Living situation (%)					
Living alone	12 (9.9)	15 (8.6)			
With parents or spouse	31 (25.6)	66 (37.7)			
With spouse and child	9 (7.4)	35 (20.0)			
Other	69 (57.1)	59 (33.7)	0.259	19.919 [b]	< 0.001
Independence (%)					
Independent	115 (95.0)	156 (89.1)			
Need assistance	6 (5.0)	19 (10.9)	0.104	3.219 [b]	0.073
Childhood trauma (%)					
Yes	39 (32.2)	71 (40.6)	0.085	2.131 [b]	0.144
Religion (%)					
No	117 (96.7)	158 (90.3)	0.123	4.457 [b]	0.035
Smoking history (%)					
Never	89 (73.6)	136 (77.7)			
Quit smoking	11 (9.0)	7 (4.0)			
Smoking now	21 (17.4)	32 (18.3)	0.105	3.246 [b]	0.197
Alcohol use (%)					
Never	89 (73.6)	106 (60.6)			
Quit drinking	10 (8.3)	5 (2.8)			
Drinking now	22 (18.1)	64 (36.6)	0.220	14.284 [c]	0.001
Hypertension (%)					
Yes	14 (11.6)	10 (5.7)	0.105	3.293 [b]	0.070
Diabetes (%)					
Yes	7 (5.8)	4 (2.3)	0.091	2.448 [c]	0.131
Hyperlipidemia (%)					
Yes	9 (7.4)	18 (10.3)	0.049	0.700 [b]	0.403
First degree relatives (%)					
Yes	20 (16.5)	33 (18.9)	0.030	0.264 [b]	0.608
Duration of MDD (months)	6.0 (2.0, 12.0)	6.0 (3.0, 21.0)		−1.513 [d]	0.130
BMI (%)			0.144	6.157 [b]	0.104
Low weight	11 (9.1)	18 (10.3)			

Table 1 Demographic and clinical characteristics of study participants before matching *(Continued)*

	Group 1 (121)	Group 2 (175)	Effect Size	t, z, or Chi-square	P value
Normal	59 (48.8)	107 (61.1)			
Overweight	41 (33.8)	42 (24.0)			
Obesity	10 (8.3)	8 (4.6)			
HAMD anxiety subscale	5.8 ± 2.2	6.1 ± 1.8	0.149	0.972 [a]	0.332
HAMD weight subscale	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)		−3.422 [d]	0.001
HAMD cognition subscale	3.0 ± 1.9	3.1 ± 1.6	0.057	0.493 [a]	0.623
HAMD retard subscale	6.8 ± 1.7	6.5 ± 1.8	0.171	− 1.534 [a]	0.126
HAMA somatic anxiety	13.4 ± 4.1	13.2 ± 3.7	0.051	− 0.544 [a]	0.687
HAMA psychological anxiety	6.9 ± 4.3	7.5 ± 4.2	0.141	1.182 [a]	0.238

G1 Group 1, patients with severe sleep disturbance, *G2* Group 2, patients without severe sleep disturbance
[a] Independent sample t-test; [b] chi-square test; [c] Fisher's exact test; [d] nonparametric test

decreased because the sample was somewhat smaller. There was a difference in the effect size of age between the 2 groups, though we had already considered the effect of age when we calculated the global deficit scores.

In our study, severe sleep disturbance was related to impaired executive function and executive shifting in patients with MDD, while such an effect was not obvious on executive inhibition. The result was in line with a previous study that MDD patients with poorer sleep quality contribute to impaired executive function [18]. Though no statistically significant difference in executive inhibition was observed between severe sleep disturbance group and no severe sleep disturbance group, statistical significance was observed through subgroup analysis among patients with more serious depression.

We extended the previous research on relationship between insomnia and impaired executive function in adult by assessing different dimensions of executive function in MDD patients [17]. The different effects of severe sleep disturbance on executive dimensions suggested distinct responsible brain region and organization in different tasks, though the dimensions of executive inhibition and shifting were co-related with each other [36, 37]. Few study explored the mechanism of which sleep disturbance is associated with a poor executive function in MDD patients. However, functional magnetic resonance (fMRI) studies about executive inhibition in unmedicated first-episode MDD patients revealed decreased prefrontal function and disrupted functional connectivity of prefrontal cortex and the left cerebellum at the rest state [38], which supported our hypothesis that sleep disturbance in MDD is related to a deactivated prefrontal cortex and less connection of corti-subcorti. Moreover, patients with insomnia showed less functional connective variability between the anterior salience network and the executive-inhibition network, rather than less network functional connectivity

strength [39]. The impaired executive function in MDD was related to not only distinct alteration of brain regions, but also the functional network. The alteration of fMRI of sleep disturbance on executive inhibition in MDD was differed from that on insomnia, which can explain the insignificant result found on executive inhibition. Moreover, further study of distinct alteration of sleep in MDD is essential for a better understanding of how executive impairment is developed.

We stratified study participants by age, sex, and severity of MDD and analyzed the effects of sleep disturbances in executive function. Our results showed that patients who fell into discrete categories of age, sex, and depression severity were more impaired by severe sleep disturbance. Specifically, patients younger than 30 years were more likely to experience cognitive impairment in executive shifting. Several analyses did not reveal the effect of age on executive function in MDD patients [8], while the executive flexibility matured at early adulthood and decreased along with age [40]. Therefore, sleep disturbances were related to executive flexibility more in younger MDD patients due to the delayed development during the key period of executive flexibility. Furthermore, executive inhibition matured at the age of adolescence, so it was less impacted by sleep disturbances at adulthood. We found that patients between the ages of 30 and 45 were more likely to have deficits in executive functioning. The general executive function peaked at the third decade of life span, and disturbed sleep seemed to influence such a process [41].

We did observe a difference by sex. Severe sleep disturbance were more likely to affect women in executive shifting. Sex difference existed in cognitive processes and females were more influenced by sleep disturbance on cognitive function, which has been reported by several previous studies [42, 43]. Orexin may modulate

Table 2 Demographic and clinical characteristics after matching

	Group 1 (121)	Group 2 (121)	Effect Size	t, z, or Chi-square	P Value
Age	41.8 ± 9.2	37.1 ± 10.4	0.478	−3.699 [a]	< 0.001
Education years	11.9 ± 4.0	12.7 ± 3.8	0.205	1.588 [a]	0.114
Sex (male) (%)	39 (32.2)	33 (27.3)	0.054	0.712 [b]	0.399
Occupation (%)					
Full-time or part-time	83 (68.6)	86 (71.1)			
Unemployed or retired	38 (31.4)	35 (28.9)	0.027	0.177 [b]	0.674
Nature of work (%)					
Mental talents labor	58 (48.0)	75 (62.0)			
Physical labor	39 (32.2)	28 (23.1)			
Both	24 (19.8)	18 (14.9)	0.141	4.836 [b]	0.089
Marital status (%)					
Married or remarried	101 (83.5)	89 (73.6)			
Divorced, widowed, or single	20 (16.5)	32 (26.4)	0.121	3.527 [b]	0.060
Living situation (%)					
Living alone	12 (9.9)	9 (7.4)			
With parents or spouse	31 (25.6)	42 (34.7)			
With spouse and child	9 (7.4)	17 (14.1)			
Other	69 (57.1)	53 (43.8)	0.166	6.646 [b]	0.084
Independence (%)					
Independent	115 (95.0)	112 (92.6)			
Need assistance	6 (5.0)	9 (7.4)	0.051	0.640 [b]	0.424
Childhood trauma (%)					
Yes	39 (32.2)	46 (38.0)	0.061	0.889 [b]	0.346
Religion (%)					
No	117 (96.7)	114 (94.2)	0.061	0.857 [b]	0.355
Smoking (%)					
Never	89 (73.6)	96 (79.3)			
Quit smoking	11 (9.0)	5 (4.1)			
Smoking now	21 (17.4)	20 (16.5)	0.102	2.539 [c]	0.281
Alcohol use (%)					
Never	89 (73.6)	84 (69.4)			
Quit drinking	10 (8.2)	4 (3.3)			
Drinking now	22 (18.2)	33 (27.3)	0.143	4.916 [c]	0.086
Hypertension (%)					
Yes	14 (11.6)	9 (7.4)	0.105	1.201 [b]	0.381
Diabetes (%)					
Yes	7 (5.8)	3 (2.5)	0.091	1.669 [c]	0.333
Hyperlipidemia (%)					
Yes	9 (7.4)	13 (10.7)	0.049	0.800 [b]	0.371
First degree of relatives (%)					
Yes	20 (16.5)	20 (16.5)	0.030	0.000 [b]	1.000
Duration of MDD (months)	6.0 (2.0, 12.0)	6.0 (3.0, 12.5)		0.198 [d]	0.843
BMI (%)			0.139	4.709 [b]	0.194
Low weight	11 (9.1)	13 (10.7)			

Table 2 Demographic and clinical characteristics after matching *(Continued)*

	Group 1 (121)	Group 2 (121)	Effect Size	t, z, or Chi-square	P Value
Normal	59 (48.8)	73 (60.3)			
Overweight	41 (33.8)	29 (24.0)			
Obesity	10 (8.3)	6 (5.0)			
HAMD anxiety subscale	5.8 ± 2.2	5.8 ± 1.8	0.000	−0.129 [a]	0.897
HAMD weight subscale	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)		−1.757 [d]	0.080
HAMD cognition subscale	3.0 ± 1.9	3.0 ± 1.6	0.000	−0.073 [a]	0.942
HAMD retard subscale	6.8 ± 1.7	6.7 ± 1.7	0.059	−0.675 [a]	0.500
HAMA somatic anxiety	13.4 ± 4.1	13.3 ± 3.6	0.026	− 0.133 [a]	0.894
HAMA psychological anxiety	6.9 ± 4.3	7.2 ± 3.8	0.066	0.615 [a]	0.539

G1 Group 1, patients with severe sleep disturbance, *G2* Group 2, without severe sleep disturbance
[a] Independent sample t-test; [b] chi-square test; [c] Fisher's exact test; [d] nonparametric test

executive shifting and sleep in female mice, which can explain the sex difference found in our study [44]. A recent meta-analysis found an insignificant influence of sex difference on executive inhibition, which is in line with our founding [45]. As PFC was affected by oestrogen and susceptible to fluctuations across endogenous hormone cycle [46], the effects of hormone level on distinct executive dimensions cannot be ruled out.

Cognitive impairment has also been reported to be related to MDD severity. Patients with severe depression are more likely to show impairment in executive inhibition and executive shifting. The severe sleep disturbance was related to a more serious depression, which could be "double hit" on brain function and related to poorer executive shifting and inhibition. However, executive impairment was considered as a trait-like feature that is not secondary to MDD severity and often persisted after clinical remission [6]. Therefore, the proportion of general executive function impairment was stable in patients with different level of MDD severity. Here we evaluated executive function impairment in a more strict way and calculated GDS according to stroop color word test and color line II; the rate of executive impairment is lower than that of executive-inhibition and executive-shift in different MDD severity categories.

Our study had some limitations. The cross-sectional study data we accessed had a weak cause-and-effect relationship. Future longitudinal studies will be essential in evaluating the link between sleep disturbance remission and cognitive impairment in MDD patients. Moreover, further neurobiological mechanism study is necessary to explore the underlining association between sleep disturbance and executive function in MDD patients. Our sample population was restricted to Chinese adults aged 18 to 65 years, so our results may not be generalizable to other populations. Also, the ages of the participants in our study varied so widely that a between-group imbalance in age ranges remained after propensity score matching. Meanwhile, we did not include work memory assessment in this study. Finally, we used the HAMD sleep subscale to estimate severe sleep disturbance rather than objective measurement such as polysomnography. More specific measurement tools will be necessary to evaluate the effects of the stages of sleep in patients with MDD.

Conclusions

We explored the link between symptoms of sleep disturbance and executive function impairment in first-episode, treatment naïve patients with MDD, and stratified the effect of sleep disturbance symptoms by age, sex, and depression severity in different domains. To evaluate the presence and degree of cognitive impairment, we used a battery of comprehensive, cognitive measurement tests, which have proved sensitive in identifying impaired cognition in mental disorders.

Table 3 Cognitive impairment in patients before matching

Cognitive domains	G1 (n, %)	G2 (n, %)	Chi-square	OR	95%CI	P	q
Executive function	39 (32.2)	36 (20.6)	5.141	1.836	1.082, 3.116	0.024	0.036
Executive shifting	67 (55.4)	70 (40.0)	6.799	1.816	1.164, 2.975	0.009	0.027
Executive inhibition	43 (35.5)	41 (23.4)	5.160	1.802	1.081, 3.003	0.024	0.036

G1 Group 1, patients with severe sleep disturbance (HAMD-17 sleep score > 4), *G2* Group 2, patients without severe sleep disturbance (HAMD-17 sleep score ≤ 4)

Cui *et al. BMC Psychiatry*   (2021) 21:198

Page 9 of 11

Table 4 Cognitive impairment in patients after matching

Cognitive domains	G1 (n, %)	G2 (n, %)	Chi-square	OR	95%CI	P	q
Executive function	39 (32.2)	23 (19.0)	5.551	1.922	1.068, 3.459	0.029	0.044
Executive shifting	67 (55.4)	48 (39.7)	5.982	2.023	1.211, 3.379	0.007	0.021
Executive inhibition	43 (35.5)	27 (22.3)	5.146	1.749	1.000, 3.060	0.050	0.050

G1 Group 1, patients with severe sleep disturbance (HAMD-17 sleep score > 4), *G2* Group 2, patients without severe sleep disturbance (HAMD-17 sleep score ≤ 4)

Our results indicate that severe sleep disturbance is associated with impaired executive functioning in first-episode, treatment-naïve patients with MDD. Certain patients, including women,age < 45, with severe depression, may be more likely to exhibit the symptoms of executive impairment. Severe sleep disturbance can be a marker of executive function impairment and can aid in recognizing executive impairment in patients with MDD. Moreover, severe sleep disturbance can be a potential modifiable factor to improve executive function, as well as an effective measurement to improve cognition for sleep symptoms management that should be enforced at initial treatment of first-episode MDD.

Abbreviations
MDD: Major depressive disorder; MINI: Mini-International Neuropsychiatric Interview; HAMD-17: 17-item Hamilton Rating Scale for Depression; HAMA: Hamilton Anxiety Rating Scale; CTT: Color Trial Test; SCWT: Stroop Color Word Test; MATRICS: The Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB: MATRICS Consensus Cognitive Battery; GDS: Global deficit score; BMI: Body mass index; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; LDL: Low-density lipoprotein; CTQ: Childhood trauma questionnaire

Supplementary Information
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Additional file 1.

Authors' contributions
First author FC compiled the database, analyzed the data, wrote the manuscript, and made revisions as suggested by the reviewers. QL, the corresponding author, was the study's principal investigator and directed most of the research. RL contributed to the statistical analysis. XL, HT, JW, KZ, GZ, QC, GW, XW, and NZ were the principal investigators at the individual participating research centers and were responsible for directing and overseeing the research at their individual centers and ensuring the integrity of the results. YH designed the database for this study. TS and XY designed the study and registered the project, and had oversight over all research activities as the principal investigators of this multicenter study. All authors approved the final version to be published. All persons who have made substantial contributions to the work reported in this manuscript, including those who provided editing and writing assistance but who are not authors, are named in the acknowledgement section of the manuscript and have given their permission to be named.

Availability of data and materials
The dataset analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from all eligible participants. The study was approved by the research ethics board of the each institution including Peking University Sixth Hospital, Peking University Institute of Mental Health; Nankai University Affiliated Anding Hospital, Tianjin Mental Health Center; Peking Union Medical College Hospital; First Hospital of Shanxi Medical University; The First Affiliated Hospital of China Medical University; Dalian Seventh People's Hospital; Beijing Anding Hospital, Capital Medical University; The First Hospital of Hebei Medical University; and Tianjin Medical University General Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Cui *et al. BMC Psychiatry*   (2021) 21:198

Page 10 of 11

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Cui *et al. BMC Psychiatry*   (2021) 21:198

Page 11 of 11

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