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The prevalence of depression in isolated/idiopathic rapid eye movement sleep behavior disorder: A systematic review and meta-analysis

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YS and FM equally contributed to this study.

YS and FM designed the study, collected and screened the articles, analyzed the data, performed the statistical analysis, and wrote the first draft of the manuscript.

YO and HK critically reviewed the data and manuscript. All authors approved the final version of the manuscript.

Ethic approval and consent to participate:

As the online databases used in our analysis are publicly available, this study was exempt from review by an institutional review board.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Summary

This systematic review and meta-analysis aimed to investigate depression prevalence and depression-related symptoms among patients with isolated/idiopathic rapid eye movement sleep behavior disorder (iRBD). We systematically searched online databases (PubMed and Scopus), performed meta-analyses of psychiatric symptoms prevalence using a random-effects model, and calculated 95% prediction intervals (PIs) and I^2 values to evaluate the degree of heterogeneity. We conducted a meta-regression analysis to assess the relationship between psychiatric symptom severity, age at diagnosis, and disease duration from onset of iRBD. We analyzed 31 studies which included 3,576 patients (2,871 men, 80.3%; mean age, 66.6 ± 8.6 years). The pooled depression prevalence was 28.8% (95% CI 23.1–35.2, 95% PI 8.1–65.1, and I^2 = 83.9%). We found a significantly negative correlation between depression-scale scores and disease duration in iRBD ($p = 0.012$, $\beta = -0.36$, R^2 analog = 0.33). Pooled prevalence of apathy and anxiety was 38.4% (95% CI 27.7–50.4, 95% PI 0.02–99.9, and I^2 = 57.8%) and 21.3% (95% CI 15.5–28.5, 95% PI 4.2–62.6, and I^2 = 47.1%), respectively. Few articles on alexithymia were available for meta-analysis. This study confirmed high prevalence of depression, apathy, and anxiety in patients with iRBD.

Keywords:

REM sleep behavior disorder, depression, systematic review, meta-analysis, apathy, anxiety, alexithymia

Glossary of Terms:

Alexithymia

Isolated/idiopathic RBD (iRBD)

Synuclein

Synucleinopathies

Abbreviations:

BDI: Beck depression inventory

CI: confidence interval

DAT: dopamine transporter

DEB: dream enactment behavior

DLB: dementia with Lewy bodies

DSM: Diagnostic and Statistical Manual of Mental Disorders

HADS: Hospital anxiety depression scale

ICSD: International Classification of Sleep Disorders

iRBD: isolated/idiopathic rapid eye movement sleep behavior disorder

OR: odds ratio

PD: Parkinson's disease

PSG: Polysomnography

PI: prediction interval

RBD: rapid eye movement sleep behavior disorder

REM: rapid eye movement

TAS-20: Toronto Alexithymia Scale

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is an REM parasomnia characterized by dream-enacting behaviors (DEBs) [1, 2]. Two studies have found the polysomnography (PSG)-confirmed community-based prevalence of RBD in middle-to-older age adults to be 1.06% and 1.23% [3, 4]. Risk factors for RBD include the following: constipation, olfactory and taste dysfunction, head injury, concurrent mood disorder, use of antidepressants, family history of parkinsonism or dementia, hyperlipidemia, smoking, use of alcoholic beverages, lower socioeconomic status, pesticide exposure, and prior carbon monoxide poisoning [5-8]. RBD is considered a harbinger of α-synucleinopathies (neurodegenerative diseases characterized in association with α-synuclein accumulation), such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy [9, 10]. RBD that manifests in isolation of any neurodegenerative disease or other causal conditions linked with it (e.g., tumors, stroke, or autoimmune diseases) [11] is termed isolated/idiopathic RBD (iRBD). Patients with iRBD frequently experience autonomic dysfunction signs such as constipation and orthostatic hypotension [12, 13], as well as hyposmia [14], minor hallucinations (including visual illusions, presence hallucinations, and passage hallucinations) [15], and other biomarkers of neurodegeneration [16].

Depression is a common complication of α-synucleinopathies. Depression and RBD are the prodromal symptoms of PD [17]. Moreover, depression is a risk factor for PD development [18]. Patients with PD often have comorbid depression, with a prevalence of 35% [19]. Neuropsychiatric symptoms in patients with PD can impair health-related quality of life [20]. According to systematic reviews, the prevalence of apathy and the point prevalence of anxiety disorders is 39.8% [21] and 31% [22] in PD, respectively. Alexithymia is defined as the difficulty

to identify and describe one's emotions or feelings [23]. The prevalence of alexithymia is approximately double in patients with PD, compared to that of controls [24].

RBD may be associated with depression owing to the neurodegenerative factors that are precursors to PD and DLB. iRBD is an intermediate stage of neurodegeneration [1] and may be prone to psychiatric complications. Furthermore, considering that the vast majority of middle-aged and older patients with iRBD subsequently progress to PD, those with PD and comorbid RBD may experience more severe non-motor symptoms, including depression and cognitive decline, than those without RBD [25]. Patients with RBD may have varying levels of stress, from mild to severe, because of specific conditions: worry about the high risk of accidental injury (32–65%) [26] or even lethal behavior [27] to themselves or their bed partners owing to DEBs and concerns about progression to neurodegenerative disorders (called phenoconversion) [28], i.e., the high proportion of future progression to phenoconversion (82.4% at 10.5-years follow-up) [29].

Researchers have yet to determine the prevalence of depression or depression-related symptoms in patients with iRBD. Several studies have discussed the comorbidity of depression in iRBD [30-32]; however, no systematic review on this topic has been conducted. In addition, the association between organic factors and depression in PD (i.e., dopaminergic denervation [33] or noradrenergic and serotonergic neural damage [19]) warrant a more thorough elucidation of the relationship between the progression of α-synucleinopathies and the severity of psychiatric symptoms in iRBD. Therefore, we conducted a systematic review and meta-analysis of depression and its related symptoms in patients with iRBD. To clarify the relationship between psychiatric symptoms and the development of α-synucleinopathies, we examined the relationship between the severity of these depressive symptoms, age at RBD onset, and disease duration of

RBD.

The primary aim of this systematic review was to examine the comorbidity of depression and iRBD. Moreover, we sought to investigate the relationship between the severity of depressive symptoms in iRBD, the age at diagnosis, and disease duration of RBD. In addition, we conducted a survey on depression-related symptoms in patients with iRBD.

Methods

Protocol and registration

Our study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Center for Reviews and Dissemination, University of York, York, United Kingdom) under CRD42021256149.

Search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [34]. We searched the PubMed and Scopus electronic databases on May 08, 2021, using terms related to RBD and depression. The two databases were searched by ("RBD" OR "rapid eye movement sleep behavior disorder" OR "REM sleep behavior disorder") AND ("depress*" OR "dysthymi*" OR "mood disorder*" OR "affective disorder" OR "affective symptoms" OR "apathy" OR "anxiety"). Two authors (Y.S. and F.M.) independently searched and assessed the eligibility of articles and further extracted the data.

Study selection

The inclusion criteria were as follows: 1) written in English; 2) observational study; 3) involved

patients diagnosed with idiopathic RBD; and 4) included the prevalence of depressive state and/or measured mood symptoms using scales, such as the Beck Depression Inventory (BDI) [35]. In contrast, the exclusion criteria were as follows: 1) review articles, 2) case reports, 3) case series, 4) conference proceedings, or 5) animal studies. Interventional studies were not excluded from our analysis.

Outcome measures

The outcome measures were as follows: 1) the prevalence of depression or depressive state and depression-related symptoms, including anxiety, apathy, and alexithymia, in patients with iRBD; or 2) scores related to the depressive state, such as BDI, BDI-II, HAMD, or the Hospital Anxiety and Depression Scale (HADS) [36]).

Quality assessment

Each study was assessed for its methodological quality and potential bias. We used the critical appraisal checklist developed by the Joanna Briggs Institute (JBI) for prevalence studies [37]. This list contains nine items that examine the quality of prevalence studies based on how they were designed, conducted, and reported (**Table S1**). Each item is answered with a "yes," "no," "unclear" (for no reported information), or "not applicable" (for a question that is not applicable to a certain study design). We calculated the quality score for each study based on the total number of positive items. For the third item on this list ("Was the sample size adequate?"), we used a formula ($n= Z^2 * P (1-P) / d^2$) recommended for calculating the minimum sample size in prevalence studies [37, 38]. Z means a level of confidence and is assigned 1.96, P means expected prevalence and is assigned 0.3, and d means precision is assigned 0.05 [39]. According

to this formula, we required a minimum sample size of 323 participants. Two authors (Y.S. and F.M.) independently performed the quality assessment. Disagreements were discussed until a consensus was reached.

Data extraction

Data relevant to the research purpose were extracted from each article as follows: 1) participant characteristics; 2) outcome measures, including the prevalence, means, and standard deviations; 3) diagnostic criteria of RBD, such as the International Classification of Sleep Disorders-Third Edition (ICSD-3); 4) confirmed PSG; 5) the duration of RBD from its estimated onset and/or RBD diagnosis; and 6) current medications, including antidepressant usage. Two authors (Y.S. and F.M.) independently extracted and cross-checked data. If the extracted data differed between the two authors, the original studies were referred to and consensus was reached. **Table 1** summarizes the results of this data-extraction process.

Statistical analysis

We used the Comprehensive Meta-analysis (www. meta-analysis. com) software (CMA) version 3 for data synthesis and graph plotting. A random-effects model was used for all analyses. We ran a series of meta-analyses to pool the prevalence in patients with iRBD, the prevalence odds ratio in patients with iRBD, and controls in patients without either iRBD or neurodegenerative disorders. We also analyzed the mean difference in scores related to depressive states when there were three or more eligible studies. The 95% prediction interval (PI) [40] was calculated for each outcome using the CMA program for PI (www.meta-analysis.com/pages/prediction.php). We used the I^2 statistic to assess the degree of heterogeneity across the included studies.

Heterogeneity > 80% and < 25% is considered high [41] and low [42], respectively. We evaluated potential publication bias using funnel plots, and the two-sided (two-sided) significance level was set at 0.05. We performed a meta-regression analysis to assess the relationship between the pooled effect size and the following moderators: age, the disease duration from RBD onset and its diagnosis, and the percentage of antidepressant consumption. CMA was also used for meta-regression analysis to calculate regression coefficient (β) and coefficient of determination for the meta-regression analysis (R^2 analog). This analysis was conducted for more than 10 eligible studies according to the guidelines described in the Cochrane Handbook for Systematic Reviews [43].

Results

Figure 1 outlines the selection process used in this systematic review. Our online search identified 775 articles, of which 31 met the eligibility criteria. **Table 1** summarizes the included studies with extracted data, such as the study population, investigated measures, and individual parameter value. A total of 3,576 patients (2,871 men, 80.3%) were included in the selected studies. The mean age of overall patients, except for two studies, was 66.6 ± 8.6; one study did not list standard deviation [44], and one study only showed median, not mean participant age [30]. Of the 31 studies, 19 had controls, with a total number of 1,307 (868 men, 66.4%). The mean age of overall controls, except in one study, was 66.2 ± 9.1; one study did not list the standard deviation [44]. Thirty, six, three, and fifteen studies reported on the prevalence or score of depression or depressive state [30-32, 44-70]; apathy [30, 53, 56, 64, 66, 67]; alexithymia [56, 60, 71]; and anxiety [30, 31, 45, 48, 49, 52, 56, 57, 62, 63, 65-68, 70], respectively. Regarding RBD diagnosis, 25 studies followed the ICSD-2 or ICSD-3 criteria [30-32, 46-50, 52-56, 59-69,

71]; in contrast, two studies [44, 70] provided detailed information, such as the American Academy of Sleep Medicine criteria; one study [51] used rapid eye movement sleep behavior disorder screening questionnaire scores as the criteria; and three studies [45, 57, 58] did not provide detailed descriptions of the RBD diagnosis. Twenty-six, three, and two studies conducted PSG [30-32, 44, 47, 49, 50, 52-67, 69-71], partially performed PSG [46, 51, 68], or did not describe PSG [45, 48], respectively. Information on the medications used was available in 19 studies [30, 31, 47-49, 52, 54, 55, 57-60, 62-66, 69, 71], whereas 12 studies provided unclear information on medication usage [32, 44-46, 50, 51, 53, 56, 61, 67, 68, 70].

The participants did not overlap among the extracted studies. **Table S1** summarizes the results of the quality assessment (e.g., risk of bias). **Figure S1** depicts the funnel plots.

Quality assessment of included studies

Table S1 outlines the quality and risk of bias assessments. Only one study (3.2%) had a sufficient sample size of 323, as indicated by the methods [70]. The majority of studies (93.5%) had a sample size < 200 patients with iRBD. Additionally, the majority of the included studies had JBI scores ≥ 3, whereas one study had a score of 1 [46] due to study-design concerns (e.g., unclear recruitment criteria, insufficient sample size, and unclear study settings). Nevertheless, this study provided a detailed research background on the motor symptoms, autonomic neuropathy, or cognitive functions related to iRBD, and was thus considered sufficient for its inclusion in the meta-analysis.

Depression or depressive state

Twelve studies reported on the prevalence of depression or depressive state in patients with

iRBD [30, 32, 47, 49, 55, 57, 59, 62-64, 69, 70], six of which compared the prevalence of depression or depressive state between patients with iRBD and controls [47, 59, 62-64, 69]. Twenty-four studies demonstrated depressive states scores, such as the BDI in patients with iRBD [31, 44-54, 56, 58-68], and 17 of those studies compared the scores of depressive states between patients with iRBD and controls [31, 44, 45, 47, 49, 52-54, 56, 59-65, 68].

Prevalence of depression or depressive state

The pooled prevalence of depression or depressive state among patients with iRBD was 28.8% (95% CI 23.1–35.2, 95% PI 8.1–65.1, and I^2 = 83.9%) (**Figure 2.**). The odds ratio in the pooled prevalence of depression or depressive state for patients with iRBD and controls was 2.57 (95% CI 1.74–3.78, 95% PI 0.59–11.1, and I^2 = 24.3%) (**Figure 3.**).

Scores of depressive state

Eleven studies [44, 46-48, 53, 56, 58, 60, 62, 63, 67] used the BDI to measure depressive-state scores, and nine studies [31, 49, 50, 52, 54, 59, 64-66] used BDI-II to measure depressive-state scores. The mean difference of the BDI and BDI-II scores between patients with iRBD and controls was 3.72 (95% CI 2.75–4.69, 95% PI 1.04–6.40, and I^2 = 50.1) (**Figure S2**). One study used the HADS [45], and no studies used the HAMD.

Meta regression analysis

We obtained insufficient data on the prevalence of depression or depressive state for the meta-regression analysis (< 10). Scores of depressive states assessed using the BDI or BDI-II and the age of patients revealed a tendency of association (β = -0.23, p = 0.052, R^2 analog = 0.35)

(**Figure 4. a) (upper left**). The scores of depressive states were significantly associated with the duration from RBD onset (β = -0.36, p = 0.012, R^2 analog = 0.33) (**Figure 4. b), upper right**). We had insufficient data on the duration from diagnosis to performing the meta-regression analysis. There were no associations between the depressive-state scores and the proportion of patients using antidepressants (β = -0.01, p = 0.806, R^2 analog = 0.00) (**Figure 4. c) (lower left**).

Depression-related symptoms

In addition to depression, researchers assessed apathy, alexithymia, and anxiety in several studies. Three studies included in our analysis reported on the prevalence of apathy [30, 64, 66], whereas five studies reported on the scores in patients with iRBD [53, 56, 64, 66, 67]. Of them, only one study compared its prevalence between patients and controls [64]. Three studies compared apathy-related scores between patients and controls [53, 56, 64]. Unfortunately, one study used the Hamilton Apathy Rating Scale [56], and two studies used the Lille Apathy Rating Scale [53, 64]; therefore, the scores could not be integrated.

Only two studies reported on the prevalence of alexithymia [60, 71], whereas three studies demonstrated the scores [56, 60, 71]. All studies on alexithymia compared the prevalence and scores between patient controls, and all studies reported on alexithymia scores assessed using the 20-Item Toronto Alexithymia Scale (TAS-20) [72].

Five studies [30, 49, 57, 62, 70] reported on the prevalence of anxiety, and 13 studies [30, 31, 45, 48, 49, 52, 56, 62, 63, 65-68] reported on anxiety scores. Of these, one study compared the prevalence between patients and controls [62], whereas nine studies compared the scores using items for anxiety, including the HADS [31, 45, 49, 52, 56, 62, 63, 65, 68].

Prevalence of apathy and anxiety

The pooled prevalence of apathy and anxiety among the patients with iRBD was 38.4% (95% CI 27.7–50.4, 95% PI 0.02–99.9, and I^2 = 57.8%) and 21.3% (95% CI 15.5–28.5, 95% PI 4.19–62.6, and I^2 = 47.1%), respectively (**Figure 5** and **Figure 6.**). The number of studies on alexithymia was insufficient for our meta-analysis. Furthermore, we could not calculate the OR in the pooled prevalence of anxiety and apathy because of there being fewer (less than three) such studies.

Alexithymia and anxiety scores

The mean difference of TAS-20 scores related to alexithymia between patients with iRBD and controls was 7.06 (95% CI 2.62–11.50, 95% PI -29.44–43.56, and I^2 = 63.1%) (**Figure S3)**. Similarly, the mean difference in HADS-A related to anxiety between patients with iRBD and controls was 1.71 (95% CI 0.35–3.07, 95% PI -13.22–16.63, and I^2 = 56.5%) (**Figure S4**). However, we could not calculate the mean difference in apathy between the iRBD and control groups because of there being fewer such studies.

Discussion

In this study, the prevalence of depression in patients with iRBD was 28.8% (95% CI: 23.1–35.2%), and the OR for depression was 2.57 (95% CI: 1.74–3.78), compared to those in controls. Contrary to our initial assumption, the level of depression was negatively correlated with RBD duration in patients with iRBD (**Figure 4. b)**), suggesting the need for monitoring psychiatric symptoms in patients who have recently been diagnosed with iRBD. The prevalence of apathy and anxiety was 38.4% (95% CI: 27.7–50.4%) and 21.3% (95% CI: 15.5–28.5%) in patients with iRBD, respectively. Considering the limited number of reports on the prevalence of alexithymia

in patients with iRBD (two articles), we could not perform a meta-analysis.

Depression

The general prevalence of unipolar major depression has been reported to be approximately 5% [73]. The 12-month prevalence of depressive states in the countries included in this review was 10% in US [74], 3% in Italy [75], 4.8% in Canada [76], 6% in France [73], 2% in Japan [73] and 4% [73] in Spain. With the exception of the Canadian data, diagnoses are based on Diagnostic and Statistical Manual of Mental Disorders version IV or 5 (DSM-IV or DSM-5) criteria using fully structured interviews. Based on these studies, the prevalence of depression associated with iRBD is higher than in the general population.

Similarly, the prevalence of depression in PD was 35% in a previous study [19], with an OR of 3.02 [77]. Our findings indicated a moderate association between iRBD and depression, compared to that with PD. According to the 12 primary studies, the prevalence of depression in patients with iRBD was approximately 15–45%. Zhou et al. [55] reported that depression was prevalent in 5.6% (10/179) patients, with BDI scores > 14 as the criterion for current depression; this finding suggested a small prevalence compared to that in other studies. However, these authors noted that the lifetime prevalence of depression was 20.1% in their study, thus supporting the possibility that iRBD is associated with depression.

Depression comorbidity in iRBD can be associated with a negative response to medication treatment in DEBs [32]. Therefore, identifying the comorbidity of depression in iRBD is essential to predicting treatment response in DEBs and considering treatment benefits and side effects.

Meta-regression of depression severity

We investigated the relationship between the depression scale scores and age, the disease duration of RBD, and the proportion of antidepressant use using meta-regression, thereby indicating the novelty of this study. Contrary to our expectations that the severity of depressive symptoms would be positively correlated with age and RBD duration, the depression scores were negatively correlated with duration from RBD onset and displayed a negative trend with age (**Figure 4**).

There are two possible explanations for the negative correlation between the severity of depression and the duration of RBD in patients with iRBD. First, a decrease in the severity of DEB over time may lessen concerns about injury. DEB poses considerable risk of injury to patients or their bed partners [78]; thus, its psychological impact and burden are severe. However, DEBs often improve with the use of clonazepam or other medications [79]. In addition, we previously found that the frequency of DEBs peaked 2–8 years following the onset of RBD and subsequently tended to decrease [80]. Hence, the associated psychological burden may decrease as treatment and the natural course of the disease alleviate DEBs that are initially severe at the onset of RBD, leading to fewer depressive symptoms as the disesase progresses. Second, patients may develop a psychological acceptance of their disease over its long term. Patients with iRBD exhibit a high rate of phenoconversion as the disease progresses [29], and experience considerable anxiety and distress when informed of their prognosis [81]. However, they may gradually accept their disease with explanations and counseling from doctors and psychologists. Phenoconversion often takes ≥ 5 years to develop [29], and not all patients progress to phenoconversion. Wing et al. reported that depression comorbid with iRBD was a risk factor for phenoconversion [82], whereas it was not a significant risk factor in a separate

multicenter study [70]. In any case, the complications of psychiatric disorders can impair patients' quality of life. Advancing research into the disease may alleviate distress and depression in some patients.

Apathy

The prevalence of apathy in patients with iRBD was similar to that in those with PD. Despite the inclusion of only three studies in the meta-analysis of apathy prevalence, the prevalence of apathy in patients with iRBD was 38.4% (95% CI: 27.7–50.4%), which is comparable to that of a previous systematic review and meta-analysis study of PD (apathy prevalence, 39.8%; 95% CI, 34.6–45.0%) [19].

Anxiety

In this study, the prevalence of anxiety in patients with iRBD was 21.3% (95% CI: 15.5–28.5%), which was marginally lower than that in those with PD in a previous systematic review and meta-analysis (anxiety prevalence, 31.0%; 95% CI: 24.5–46.7%) [22]. We included in the current analysis only five primary studies; nonetheless, the prevalence of anxiety in iRBD was not markedly different from that in PD, and the heterogeneity index was not excessive (I^2 = 47.1%, **Figure 4**).

Generalizability

The information provided to the patients with iRBD was adequate to generalize our findings. The diagnostic and assessment methods of RBD and the characteristics of the included population were consistent with those of the general population of patients with iRBD [1, 9]. Regarding

RBD diagnosis, 25 studies (80.6%) followed the ICSD-2 or ICSD-3 criteria, and only three studies did not describe the diagnostic criteria used. Video-PSG is required for diagnosing RBD [2], and cases of suspected RBD without video-PSG assessment are classified as "probable RBD." In this study, video-PSG was performed with all patients in 26 studies (83.9%) and with some patients in three studies; two studies did not contain a description of PSG. Detailed information on the diagnostic criteria for RBD and PSG administration would ensure consistency among the included patients.

The age, sex, and disease duration of the included patients were comparable to the standard RBD population [1, 9]. The patients in our analysis were primarily in their early sixties to early seventies, and a majority were men (2,871 men, 80.3%). The duration from RBD onset was 5–10 years in most cases, and that from the first visit or PSG administration was approximately 1–5 years. These data are consistent with RBD characteristics, in which the disease onset is more common in patients in men who are 50 or older [2].

In our analysis, the mean age and disease duration in each study indicated that younger-onset patients with RBD may either be excluded from analysis or present in fewer cases. In addition, we did not include studies on patients with specific conditions, such as psychiatric hospitalization. In contrast to patients with older-onset RBD, those with younger-onset RBD have increased comorbidity with narcolepsy or autoimmune disorders [83, 84]. Considering that our purpose was to investigate the characteristics of iRBD, which is a precursor for PD or DLB, the inclusion of patients with younger-onset RBD may lead to distorted results.

Relationship with antidepressants

We found no significant correlation between the percentage of antidepressant use and the degree

of depression (**Figure 3 c**). The use of antidepressants leads to complications in patients with RBD. It is reasonable and ethical to use antidepressants to treat comorbid psychiatric disorders (e.g., depression, apathy, alexithymia, and anxiety) in RBD. However, antidepressants prescribed for a psychiatric disorder that precedes RBD may contribute to the onset of RBD [47]. The similarity between antidepressant-induced and non-antidepressant-induced RBD is debatable [47, 83, 85]. While assessing comorbid depression in iRBD, clinicians must consider whether patients with iRBD are merely comorbid with depression or if they have developed RBD due to antidepressant use for preexisting depression (i.e., antidepressant-induced RBD). In some of the primary studies we included in this review, the authors excluded "drug-induced RBD" (i.e., RBD originating immediately following the initiation of antidepressants) [52]. However, it may be difficult to clearly determine if RBD following antidepressant use is antidepressant-induced, particularly considering that there is concurrent and persistent evidence that antidepressants increase REM sleep muscle tone [86, 87].

To address this complicated issue, we initially explored the proportion of antidepressant use in primary studies; in our analysis, 19 of 31 studies reported medication information, and the proportion of antidepressant use ranged from 0% to 32.2% (**Table 1**). We then considered the possibility that patients taking antidepressants may have antidepressant-induced RBD or that the depressive symptoms of non-antidepressant users may be less salient, and thus examined the relationship between the proportion of antidepressant use and psychiatric symptoms across all studies. The meta-regression results did not reveal a significant correlation between the two variables. Moreover, in the four studies with 0% antidepressant use [31, 58-60], the depressive symptom scores were not lower than those in other studies (**Figure 3 c**). In other words, most patients with iRBD do not use antidepressants. Moreover, despite including patients taking

antidepressants, the percentage of drug use was not significantly related to depressive symptom scores ($\beta = -0.01$, $p = 0.806$, R^2 analog = 0.33). To further study the relationship between antidepressants and RBD, it is essential to clarify the temporal relationship between RBD onset and depression. It may be necessary to distinguish between patients who have been prescribed antidepressants before and after RBD diagnosis.

We were unable to examine the relationship between apathy, alexithymia, anxiety, and antidepressant use because of the availability of fewer primary studies.

Strengths

The primary strength of this study was that we used meta-analytic methods to investigate the prevalence of various types of psychiatric symptoms among patients with iRBD. Despite numerous reports on depression and limited studies on apathy, alexithymia, and anxiety, this systematic review and meta-analysis is worthwhile because it summarizes current findings. iRBD is located in the prodromal phase of α-synucleinopathies; thus, clinicians should consider the degree of psychiatric symptoms in iRBD along with age and disease duration of RBD.

Another strength of our analysis was that we performed meta-regression using the age and disease duration as variables for comparison. Contrary to the assumption that depression worsens with increased duration of Lewy body diseases, the meta-regression between disease duration and depression scores revealed a significant inverse correlation. This discrepancy necessitates future research to investigate the validity of the influence of DEBs on symptom relief and patients' acceptance of their disease.

Our results are reliable when assessing the severity of psychiatric symptoms rather than the prevalence of such sypmtoms owing to the use of validated assessment tools (e.g., BDI [35]).

Moreover, we were able to generalize significant differences in depression, alexithymia, and anxiety scores between patients with iRBD and controls (**Figures S2–4**).

Limitations

This study had some limitations. We identified heterogeneity in the definition and measurement of symptoms among the primary studies. The definitions of depression, apathy, and anxiety differed across some studies. Despite using similar questionnaires, some studies used different cut-off values for these questionnaires (**Figure 2 and 3**). For example, we conducted a meta-analysis of 12 studies reporting on the prevalence of depression (**Figure 2**). However, the prevalence was defined differently in these studies; seven studies [28, 33, 40, 44, 46, 48, 50] defined depression based on depressive symptom scores, four studies [31, 42, 49, 55] relied on interviews or physicians' discretion, and one study used a combination of depressive symptom scores and interviews [56]. Furthermore, when defined by the depressive symptom scores, the criteria for depression varied across studies: the definition of depressive symptoms by the BDI-II score was ≥17 [44], >14 [40], ≥14 or >13 [33, 46], and ≥10 [48]. Vilas [49] and Fujishiro [42] used interviews and the DSM-IV or DSM-5 as the criteria [70]. Conversely, Frauscher [55] and Postuma [31] relied on physician discretion as the basis for disease diagnosis. For psychiatric symptoms, such as depression in patients with iRBD, patients patients may be more likely to visit physicians than psychiatrists. In addition, the questionnaires do not provide a diagnosis, as they are intended be used as adjunctive tools for diagnosis [70], and each questionnaire does not have a clear cut-off value for the diagnosis. Therefore, the definitions of depression inevitably differed in each study. The severity of psychiatric symptoms often varied between self-assessment and evaluation by medical staff; nonetheless, researchers have not investigated the

limitations of questionnaires and interviews for psychiatric symptom assessment in patients with iRBD. It appears unlikely that the prevalence would markedly differ depending on the method used, i.e., a questionnaire or interview; however, researchers should record differences between the questionnaires and interviews while considering the results of included studies (**Figure 2**). Another limitation was our inability to perform a subgroup analysis because of the limited number of primary studies. A subgroup analysis using the definition or evaluation methods for psychiatric symptoms could prove helpful in future studies.

Our meta-analysis results revealed a high degree of heterogeneity with $I^2 > 80\%$ in the prevalence of depression (86.4%) and moderate heterogeneity in the prevalence of apathy and anxiety, with $I^2 = 57.8\%$ and 47.1%, respectively. I^2 has the potential to be large and misleading for studies with precise confidence intervals, such as in prevalence reviews [88, 89]. According to a recent report, the median I^2 in a sample of 134 meta-analyses of prevalence was 96.9% (interquartile range 90.5–98.7) [90]. The I^2 values in the present analysis were not exceptionally high. Nevertheless, we calculated the PI [40], in addition to I^2, to address the issue of heterogeneity in the included studies.

Publication bias may have led to an underestimation or overestimation of the prevalence of psychiatric symptoms. Furthermore, the exclusion of articles written in languages other than English may have underestimated or overestimated the prevalence of psychiatric symptoms in patients from non-English-speaking countries.

Some patients included in the meta-analysis were taking antidepressants, which may have reduced their depressive symptoms. However, we addressed this issue by performing a meta-regression analysis on the percentage of antidepressant use. There was no significant decrease in depressive symptom scores with higher rates of antidepressant use (**Figure 4 c**).

Future research

Herein, we discuss issues for future research on the psychiatric symptoms associated with iRBD. To address the problem of inconsistent diagnostic criteria, it may be appropriate to conduct subgroup analyses according to the method used for disease diagnosis.

Factors associated with psychiatric symptom complications in iRBD warrant further investigation. Examining the relationship between psychiatric symptoms and clinical, psychological, genetic, and lifestyle factors will facilitate better understanding of the complications of psychiatric symptoms in iRBD [91-93].

In the present study, the psychiatric symptoms were assessed using general questionnaires (e.g., BDI and Geriatric Depression Scale [94]) and a questionnaire specifically developed for patients with PD (i.e., the Unified Parkinson's Disease Rating Scale Part I [95]). Patients with iRBD are at risk of future phenoconversion [29] and stress owing to DEBs [1, 26]. Therefore, it would be beneficial to develop an iRBD-specific tool that assesses psychiatric symptoms, including concerns about the psychological burden of DEBs and the future progression of iRBD to neurodegenerative diseases [28, 96].

Further studies exploring psychological or biological treatment options for the psychiatric symptoms are needed. The pathogenesis of depression, apathy, and anxiety in patients with iRBD remains unclear. Psychological factors, such as DEBs and pessimism about a grave prognosis, may affect patients' psychological state. Alternatively, organic changes may affect patients' mental state (e.g., dopaminergic degeneration reduces the function of the reward system), similar to that in PD [19, 33]. Interestingly, some studies have reported an association between serotonergic degeneration and apathy in patients with iRBD [66], and that patients with late-

onset depression exhibit reduced dopamine transporter (DAT) accumulation [97]. Future studies are required to determine appropriate prognostic counseling options and to select appropriate psychotropic medications according to organic factors. Apathy and anxiety may exacerbate DEBs [98], thus warranting the need to consider the risks and benefits of antidepressant use in patients with iRBD and depression-related symptoms.

Conclusions

In conclusion, this systematic review and meta-analysis demonstrated a high prevalence of psychiatric symptoms in iRBD, with approximately 30%, 40%, and 20% of patients presenting with depression, apathy, and anxiety, respectively. Unexpectedly, depressive symptoms were negatively correlated with age and disease duration of RBD. Our findings suggest the importance of psychiatric complications in patients with iRBD, particularly in those with shorter disease duration. Psychiatric symptoms should be routinely screened for in iRBD even among physicians and healthcare providers who do not specialize in psychiatry. Identifying psychiatric symptom complications in patients with iRBD may reduce psychiatric symptoms, improve these patients' quality of life, and decrease societal costs. Further studies are required for a subgroup analysis of methods for assessing psychiatric symptoms in patients with iRBD, and to investigate factors related to the prevalence of each symptom.

Practice Points

1. Patients with iRBD frequently experience comorbid depression, apathy, and anxiety.
2. Healthcare professionals are encouraged to screen psychiatric symptoms while examining patients with iRBD.

3. The severity of depressive symptoms was negatively correlated with duration from the onset of RBD. For patients with iRBD with short disease duration, psychological factors, such as the burden of DEBs and concerns about future phenoconversion, may be burdensome and lead to depressive symptoms.

Research Agenda

1. Psychiatric symptoms, including depression, were defined by questionnaire scores and interviews with physicians in different studies. The issue of inconsistent diagnostic criteria necessitates a subgroup analysis of the specific method used for assessing psychiatric symptoms.
2. Clinicians should consider the psychological context specific to iRBD (i.e., distress from DEBs and concerns about future neurodegenerative disease progression). Considering the influence of these factors on psychiatric symptoms, it would be beneficial to develop iRBD-specific psychiatric symptom assessment tools.
3. It is necessary to investigate the relationship between psychiatric symptoms in iRBD and the degree of neurodegenerative progression (e.g., reduced DAT single photon emission computed tomography accumulation).
4. Antidepressant-induced RBD may be included in iRBD. To avoid confusion between the two, researchers must clarify the onset of RBD, depression, and the beginning of antidepressant use, in addition to establishing a consensus on the duration of antidepressant use and RBD onset to be considered "not drug-induced."

1 **Table 1.** Characteristics of the included studies

Study Number	Author, year	Country		Study population (male/female)	Age (mean ± SD) (years)	Medication	Duration from RBD onset (mean ± SD, years)	Duration from first visit or PSG (mean ± SD, years)	Diagnostic criteria of RBD	PSG confirmed
1	Aguirre-Mardones et al., 2015 [62]	Spain	Patients	44 (35M/9F)	70.89 ± 6.12	8 (18.2%) antidepressants, 32 (72.7%) benzodiazepine, 28 (63.6%) clonazepam	9.64 ± 6.25	3.82 ± 3.21	ICSD-3	yes
			Controls	40 (29M/11F)	70.13 ± 6.08	4 (10.0%) antidepressants, 3 (7.5%) benzodiazepine, 0 (0.0%) clonazepam	-	-	-	-
2	Assogna et al., 2021 [56]	Italy	Patients	38 (31M/7F)	67.61 ± 6.99	unclear	5.08 ± 6.64	unclear	ICSD-3	yes
			Controls	38 (31M/7F)	67.47 ± 7.40	unclear	-	-	-	-
3	Barber et al., 2017 [65]	UK	Patients	171 (151M/20F)	64.7 ± 9.0	55 (32.2%) antidepressants	7.07 ± 6.30	unclear	ICSD-3	yes
			Controls	296 (145M/151F)	64.9 ± 10.2	34 (11.5%) antidepressants	-	-	-	-
4	Barber et al., 2018a [64]	UK	Patients	88 (83M/5F)	66.9 ± 7.62	40 (45.5%) clonazepam	8.5 ± 6.7	3.0 ± 2.5	ICSD-3	yes
			Controls	33 (15M/18F)	68.4 ± 8.94	unclear	-	-	-	-
5	Barber et al., 2018b [66]	UK	All patients	43 (42M/1F)	65.1 ± 7.57	8 (18.6%) antidepressants	8.7 ± 7.34	2.5 ± 2.27	ICSD-3	yes
			Non-apathetic	25 (24M/1F)	66.5 ± 6.92	3 (12.0%) antidepressants	unclear	unclear	ICSD-3	yes
			Apathetic	18 (18M/0F)	63.1 ± 8.18	5 (27.8%) antidepressants	unclear	unclear	ICSD-3	yes
6	Barber et al., 2020 [67]	UK	All patients	42 (41M/1F)	64.8 ± 8.03	unclear	unclear	2.5 ± 2.44	ICSD-3	yes
			with dorsal nigral hyperintensity	29 (unclear)	unclear	unclear	unclear	unclear	ICSD-3	yes
			without dorsal nigral hyperintensity	11 (unclear)	unclear	unclear	unclear	unclear	ICSD-3	yes
			Controls	30 (24M/6F)	69.1 ± 8.15	unclear	-	-	-	-

7	Beauchamp et al., 2020 [45]	Australia	Patients	14 (13M/1F)	63.5 ± 9.9	unclear	7.6 ± 4.7	unclear	unclear (clinical RBD diagnosis)	unclear
			Controls	16 (9M/7F)	72.9 ± 5.1	unclear	-	-	-	-
8	Bourgouin et al., 2019 [49]	Canada	All patients	46 (36M/10F)	66.19 ± 6.37	12 (26.1%) antidepressants, 15 (32.6%) anxiolytics	12.61 ± 12.49	1.23 ± 2.16	ICSD-3	yes
			with depression	17 (12M/5F)	67.35 ± 5.32	no antidepressants	15.98 ± 14.53	2.20 ± 3.05	ICSD-3	yes
			without depression	27 (22M/5F)	65.85 ± 6.25	unclear	10.54 ± 10.82	0.75 ± 1.41	ICSD-3	yes
			with anxiety	16 (12M/4F)	65.65 ± 6.61	2 (12.5%) anxiolytics	13.85 ± 13.48	1.15 ± 2.00	ICSD-3	yes
			without anxiety	30 (24M/6F)	66.48 ± 6.34	13 (43.3%) anxiolytics for other clinical symptoms (i.e., RBD symptoms)	11.95 ± 12.12	1.28 ± 2.27	ICSD-3	yes
			Controls	31 (21M/10F)	63.28 ± 8.35	unclear	-	-	-	-
9	Byun et al., 2021 [61]	Korea	Patients	50 (29M/21F)	66.5 ± 6.9	unclear	7.1 ± 4.6	unclear	ICSD-3	yes
			Controls	20 (11M/9F)	68.1 ± 3.4	unclear	-	-	-	-
10	Chahine et al., 2021 [68]	US	Patients	38 (32M/6F)	69.5 ± 5.5	unclear	10.1 ± 7.4	unclear	ICSD-2	yes (where available)
			Controls	92 (75M/17F)	68.4 ± 5.3	unclear	-	-	-	-
11	Chiu et al., 2021 [30]	Australia	Patients	49 (42M/7F)	68 (median)	2 (4.1%) antidepressants	6 (median)	unclear	ICSD-3	yes
12	Cock et al., 2020 [53]	France	Patients	21 (17M/4F)	68.7 ± 6.9	unclear	11.4 ± 11.2	unclear	ICSD-2	yes
			Controls	38 (31M/7F)	69.1 ± 7.2	unclear	-	-	-	-
13	Dušek et al., 2019 [52]	Czech Republic	Patients	74 (66M/8F)	67.5 ± 6.3	15 (20.3%) antidepressants	6.5 ± 5.8	unclear	ICSD-3	yes
			Controls	39 (32M/7F)	65.2 ± 8.2	1 (2.6%) antidepressants	-	-	-	-
14	Frauscher et al., 2014 [69]	Multi-country	Patients	318 (259M/49F)	67.3 ± 9.8	55 (17.3%) antidepressants	unclear	unclear	ICSD-2	yes
			Controls	318 (244M/74F)	66.2 ± 9.8	29 (9.1%) antidepressants	-	-	-	-
15	Fujishiro et al., 2019 [57]	Japan	Patients	9 (7M/2F)	71.8 ± 7.8	2 (22.2%) antidepressants, 4	unclear	unclear	unclear	yes

						(44.4%) benzodiazepine, 1 (11.1%) non-benzodiazepine hypnotics, 1 (11.1%) antipsychotics, 1 (11.1%) anticholinesterase inhibitor				
16	Godin et al., 2013 [71]	Canada	Patients	32 (23M/9F)	61.5 ± 11.12	6 (18.8%) antidepressants and anxiolytics, 4 (12.5%) anticonvulsants	unclear	unclear	ICSD-2	yes
			Controls	30 (19M/11F)	57.2 ± 14.47	none (free of any medications known to influence sleep, vigilance, or motor activity for ≥ 1 week before the PSG evaluation.)	-	-	-	-
17	Honeycutt et al.,2021 [31]	Canada	Patients	114 (88M/26F) *2	69.0 ± 9.1	no antidepressants	7.9 ± 7.0	unclear	ICSD-3	yes
			Controls	44 (31M/13F)	66.3 ± 9.8	unclear	-	-	-	-
18	Jun et al., 2020 [59]	Korea	Patients	94 (53M/41F)	67.6 ± 7.3	without any drug that can trigger RBD, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors; Twelve patients were taking clonazepam only, 50 were taking melatonin only, and 17 were taking both treatments.	5.9 ± 4.6	unclear	ICSD-3	yes
			Controls	50 (24M/26F)	65.4 ± 6.0	unclear	-	-	-	-
19	Kim et al., 2020 [60]	Korea	Patients	86 (59M/27F)	63.4 ± 6.2	no antidepressants	3.9 ± 5.6	unclear	ICSD-3	yes
			Controls	74 (45M/29F)	63.9 ± 4.7	unclear	-	-		
20	Postuma et al., 2006 [44]	Canada	Patients	25 (22M/3F)	69.2 ± unclear	unclear	10.5 ± unclear	unclear	*1	yes

			Controls	25 (22M/3F)	69.2 ± unclear	unclear	-	-	-	-
21	Postuma et al., 2009 [46]	Canada	Patients	17 (15M/2F)	73.2 ± 7.8	unclear	unclear	unclear	ICSD-2	partially
22	Postuma et al., 2013 [47]	Canada	All patients	100 (74M/26F)	66.8 ± 10.0	27 (27.0%) antidepressants	10.1 ± 10.4	unclear	ICSD-2	yes
			with antidepressants	27 (20M/7F)	64.1 ± 10.5	27 (100.0%) antidepressants	9.8 ± 11.1	unclear	ICSD-2	yes
			without antidepressants	73 (54M/19F)	67.8 ± 9.7	no antidepressants	10.2 ± 10.2	unclear	ICSD-2	yes
23	Postuma et al., 2015 [48]	Canada	Patients	89(65M/24F)	66.9 ± 9.3	26 (29.2%) antidepressants, 41 (46.1%) clonazepam, 13 (14.6%) melatonin	9.2 ± 9.3	unclear	ICSD-2	unclear
24	Postuma et al., 2019 [70]	Multi-country	Patients	1280 (1056M/224F) *3	66.3 ± 8.4	unclear	unclear	unclear	AASM criteria 2007	yes
25	Rahayel et al.,2021 [50]	Canada	Patients	48 (37M/11F)	65.8 ± 6.4	unclear	12.1 ± 12.2	unclear	ICSD-3	yes
26	Ryu et al., 2018 [58]	Korea	All patients	188 (122M/66F)	67.4 ± 7.3	no antidepressants, clonazepam	unclear	unclear	unclear	yes
			with disruptive behavioral symptom	160 (111M/49F)	66.8 ± 7.4	no antidepressants, clonazepam	unclear	unclear	unclear	yes
			without disruptive behavioral symptom	28 (11M/17F)	70.5 ± 6.0	no antidepressants, clonazepam	unclear	unclear	unclear	yes
27	Schrempf et al., 2016 [54]	Germany	Patients	18 (9M/9F)	53.7 ± 15.0	3 (16.7%) antidepressants, 3 (16.7%) clonazepam, 1 (5.6%) quetiapine	11.3 ± 11.9	unclear	ICSD-2 and RBDSQ score ≥ 5	yes
			Controls	22 (11M/11F)	59.8 ± 9.5	unclear	-	-	-	-
28	Sunwoo et al., 2020 [32]	Korea	All patients	123 (76M/47)	66.0 ± 7.7	unclear	4.1 ± 4.0	unclear	ICSD-3	yes
			No response	27 (15M/12F)	65.7 ± 8.5	unclear	4.4 ± 6.2	unclear	ICSD-3	yes
			Improved	96 (61M/35F)	66.1 ± 7.5	unclear	4.1 ± 3.2	unclear	ICSD-3	yes
29	Vilas et al., 2015 [63]	Spain	Patients	72 (53M/19F)	71.39 ± 6.68	49 (68.1%) clonazepam, 5 (6.9%) melatonin	10.2 ± 7.09	3.71 ± 3.41	ICSD-3	yes
			Controls	71 (49M/22F)	70.70 ± 6.10	unclear	-	-	-	-

30	Ye et al.,2020 [51]	China	All patients	56 (41M/15F)	66.0 ± 7.9	unclear	unclear	unclear	RBDSQ ≥ 5	confirmed in 22/56
			Patients developed disease	15 (10M/5F)	66.1 ± 5.3	unclear	unclear	unclear	RBDSQ ≥ 5	unclear
			Developed disease-free	41 (31M/10F)	66.0 ± 8.7	unclear	unclear	unclear	RBDSQ ≥ 5	unclear
31	Zhou et al., 2017 [55]	Hong Kong	Patients	179 (144M/35F)	66.3 ± 9.8	21 (11.7%) antidepressants, 52 (29.1%) hypnotic drugs, 4 (2.2%) antipsychotics	unclear	5.8 ± 4.3	ICSD-2	yes

Abbreviations:

AASM, American Academy of Sleep Medicine;

ICSD-2, International Classification of Sleep Disorders—Second Edition;

ICSD-3 International Classification of Sleep Disorders—Third Edition;

PSG, polysomnography;

RBD, rapid eye movement sleep behavior disorder;

RBDSQ, rapid eye movement sleep behavior disorder screening questionnaire.

*1 defined according to standard criteria: 1) history of elaborate motor activity during sleep associated with dream content; 2) increase of tonic chin electromyography activity during REM sleep (≥ 30% of REM sleep with tonic electromyographic activity, scored by a standardized method); 3) presence of behavioral manifestations occurring during REM sleep in at least one of two nights

of polysomnographic recording at the baseline evaluation in the sleep laboratory.

*2 Depression and anxiety were evaluated in 113 and 111 patients, respectively.

*3 Depression and anxiety were evaluated in 858 and 545 patients, respectively.

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Figure Legends:

Patients with Parkinson's disease were intermixed in the patient population: 5 studies

Patients with iRBD with psychiatric comorbidities were excluded: 4 studies

Idiopathic RBD was unclearly defined: 3 studies

Unclear diagnostic criteria for depression, anxiety, and alexithymia: 3 studies

Only iRBD patients with psychiatric disorders or degenerative disease were included: 3 studies

Only family members of patients were assessed: 1 study

Patients overlapped with other studies: 1 study

Abbreviations:

iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; RBD, rapid eye movement sleep behavior disorder.

Figure 2. Prevalence of depression or depressive state in patients with iRBD

Abbreviations:

UPDRS, Unified Parkinson's Disease Rating Scale; BDI, Beck Depression Inventory; DSM, The Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; GDS-K, Korean version of GDS; iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; PHQ-9, Patient Health Questionnaire-9.

Figure 3. Odds ratio in pooled prevalence of depression or depressive state for patients with iRBD and controls.

Abbreviations:

BDI, Beck Depression Inventory; DSM, The Diagnostic and Statistical Manual of Mental Disorders; iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder.

Figure 4. Meta-regression analysis for depressive-state scores in patients with iRBD

Abbreviations:

iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; RBD, rapid eye movement sleep behavior disorder.

Figure 5. Prevalence of apathy in patients with iRBD

Abbreviations:

iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; UPDRS, Unified Parkinson's Disease Rating Scale; LARS, Lille apathy rating scale.

Figure 6. Prevalence of anxiety in patients with iRBD

Abbreviations:

HADS-A, Anxiety subscale of Hospital Anxiety and Depression Scale; BAI, Beck Anxiety Inventory; DSM, The Diagnostic and Statistical Manual of Mental Disorders; iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; NPI, Neuropsychiatric Inventory; STAI, State-Trait Anxiety Inventory; LAS, Leeds Anxiety Scale; NMS-Q, Non-Motor Symptoms Questionnaire; GAD, Generalized Anxiety Disorder

Supplementary Material

Figure S1. Funnel plots

Figure S2. Mean difference in depressive-state scores between patients with iRBD and controls (BDI and BDI-II)

Abbreviations:

BDI, Beck Depression Inventory;

iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder.

Figure S3. Mean difference in alexithymia scores between patients with iRBD and controls (TAS-20)

Abbreviations:

iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder; TAS-20, the 20-Item Toronto Alexithymia Scale.

Figure S4. Mean difference in anxiety scores between patients with iRBD and controls (HADS-A)

Abbreviations:

HADS-A, Anxiety subscale of Hospital Anxiety and Depression Scale; iRBD, isolated/idiopathic rapid eye movement sleep behavior disorder.

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