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REVIEW

Neuropsychological Changes in Isolated REM Sleep Behavior Disorder: A Systematic Review and Meta-analysis of Cross-sectional and Longitudinal Studies

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Abstract

The aim of this meta-analysis is twofold: (a) to assess cognitive impairments in isolated rapid eye movement (REM) sleep behavior disorder (iRBD) patients compared to healthy controls (HC); (b) to quantitatively estimate the risk of developing a neurodegenerative disease in iRBD patients according to baseline cognitive assessment. To address the first aim, cross-sectional studies including polysomnography-confirmed iRBD patients, HC, and reporting neuropsychological testing were included. To address the second aim, longitudinal studies including polysomnography-confirmed iRBD patients, reporting baseline neuropsychological testing for converted and still isolated patients separately were included. The literature search was conducted based on PRISMA guidelines and the protocol was registered at PROSPERO (CRD42021253427). Cross-sectional and longitudinal studies were searched from PubMed, Web of Science, Scopus, and Embase databases. Publication bias and statistical heterogeneity were assessed respectively by funnel plot asymmetry and using I^2. Finally, a random-effect model was performed to pool the included studies. 75 cross-sectional (2,398 HC and 2,460 iRBD patients) and 11 longitudinal (495 iRBD patients) studies were selected. Cross-sectional studies showed that iRBD patients performed significantly worse in cognitive screening scores (random-effects (RE) model = –0.69), memory (RE model = –0.64), and executive function (RE model = –0.50) domains compared to HC. The survival analyses conducted for longitudinal studies revealed that lower executive function and language performance, as well as the presence of mild cognitive impairment (MCI), at baseline were associated with an increased risk of conversion at follow-up. Our study underlines the importance of a comprehensive neuropsychological assessment in the context of iRBD.

Keywords Meta-analysis · REM sleep behavior disorder · Cognitive functions · Neuropsychological assessment · Mild cognitive impairment · Synucleinopathies

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Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by repeated episodes of complex motor behaviors or vocalizations enabled by the presence of REM sleep without atonia (RSWA) (American Academy of Sleep Medicine, 2014). RBD is defined as secondary when it is caused by a neurological or medical condition, or isolated (iRBD) when it occurs in the absence of other disorders (Högl et al., 2018). Importantly, several studies demonstrated that most iRBD patients will eventually develop a neurodegenerative disorder, primarily synucleinopathies, such as Parkinson's disease (PD) and dementia with Lewy body (DLB) (Galbiati et al., 2019; Postuma et al., 2019). For this reason, a great effort has been

made towards the identification of sensitive biomarkers able to predict phenoconversion in iRBD (Ferini-Strambi et al., 2019; Iranzo et al., 2016).

Cognitive impairment has been frequently observed in a large portion of iRBD patients, with longitudinal studies demonstrating that cognitive performance worsens over time. These findings suggest that neuropsychological profile could play a crucial role as prodromal marker of neurodegeneration (Gagnon et al., 2012; Marchand et al., 2017, 2018; Massicotte-Marquez et al., 2008; Terzaghi et al., 2019; Zhang et al., 2019). Nevertheless, results vary across studies. On one hand, the majority of cross-sectional studies agree that the most affected cognitive domains in iRBD are memory and executive functions (Massicotte-Marquez et al., 2008; Rolinski et al., 2016a, b). Other studies also report poorer performance in visuospatial abilities in iRBD patients compared to healthy controls (HC) (Fantini et al., 2011; Ferini-Strambi et al., 2004), but this difference is not universally confirmed (Gagnon et al., 2009; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). On the other hand, longitudinal studies showed that only the baseline performance on executive functions consistently predict the conversion into neurodegeneration, thus highlighting its role as a cognitive marker of conversion (Marchand et al., 2017, 2018; Youn et al., 2016). The cognitive deficits reported by studies in iRBD patients are similar to those observed in PD and DLB (Fantini et al., 2011). Indeed, executive functions (Kudlicka et al., 2011), verbal memory (Assogna et al., 2010; Bohlhalter et al., 2009; Galtier et al., 2014; Hanoğlu et al., 2019), and visuospatial abilities (Chastan et al., 2019; Gullett et al., 2013; Montse et al., 2001) are the most affected domains in PD (Aarsland et al., 2021; Curtis et al., 2019). In DLB, prominent executive and visuospatial dysfunctions are observed, with memory being affected to a variable degree (Goldman et al., 2014; Gomperts, 2016; Sanford, 2018; Walker et al., 2015).

Despite accumulating evidence of cognitive impairment in iRBD, results remain highly heterogeneous. This heterogeneity might be ascribed to the use of different neuropsychological tests and the limited sample sizes of patients. Therefore, a meta-analytic evaluation of the cognitive alterations occurring in iRBD patients is required to identify a neuropsychological profile associated with subsequent phenoconversion.

The present meta-analysis has two main goals: (a) to assess cognitive impairments in iRBD patients in comparison with HC; (b) to quantitatively estimate the risk of developing a neurodegenerative disease in iRBD patients based on the baseline cognitive assessment.

Methods

The search process and meta-analysis were performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Liberati et al., 2009; Moher et al., 2009; Radua, 2021).

Protocol and Registration

The research methodology and protocol for this meta-analysis was registered at the prospective register of systematic reviews (PROSPERO) with the following registration number: CRD42021253427. PRISMA Protocol (PRISMA-P) was used to determine whether all the relevant items were included in the protocol (Moher et al., 2015).

Search Procedure

Cross-sectional and longitudinal published studies were searched from PubMed, Web of Science, Scopus, and Embase databases. Two researchers (C.L. and G.D.) independently carried out the systematic search, first targeting titles and abstracts, then full text reports. The systematic literature search was performed by entering the following keywords: "rapid eye movement sleep behavior disorder", "iRBD" in combination with "cognition", "MCI", "mild cognitive impairment", "neuropsychological". These terms could appear everywhere in the manuscript. The last date of database searches was December 18, 2020. Authors were contacted when additional information from studies were needed - however, for various reasons, it was not always possible to reach the authors or access the raw data. This was done to resolve questions about eligibility, specifically regarding possible overlaps between samples of different studies. Disagreements were discussed and resolved between all authors. Only studies published in the English language were included.

Risk of Bias

To reduce publication bias, both publications in peer-refereed journals and conference abstracts were considered. Specifically, special issues of journals reporting conference abstracts were searched, namely the European Journal of Neurology, Sleep, Journal of Sleep Research, Sleep Medicine, and Journal of Neurology. Then, the publication bias was assessed by funnel plot asymmetry using Egger's test (Egger et al., 1997). To address the multiple publication bias, when two studies provided data from the same database, the study with the highest number of patients was selected and the other was excluded.

The heterogeneity between studies was assessed separately for cross-sectional and longitudinal studies using prediction intervals (PI) and I^2 statistic (Borenstein et al., 2017; Higgins & Thompson, 2002; Higgins et al., 2003). The RE-model was employed because of the considerable heterogeneity between studies (variability in the participant characteristics, variability in neuropsychological tests, variability in the follow-up duration, etc.).

Study Eligibility

The cross-sectional studies that met the following criteria were included:

- The studies had to include patients with a diagnosis of iRBD confirmed by PSG according to the standard criteria from the international classification of sleep disorders-third edition (ICSD-3) (American Academy of Sleep Medicine, 2014).
- The studies had to include the scores of at least one neuropsychological test performed in both iRBD and HC groups; this included experimental tasks or clinical tasks that assessed at least one of the following domains: cognitive screening, language, memory, executive functions, or visuospatial abilities.

The exclusion criteria for cross-sectional studies were:

- Literature review, meta-analysis, single-case study.
- Non-iRBD patients or iRBD patients not confirmed using PSG.
- Cross-sectional studies without HC.

The longitudinal studies that met the following criteria were included:

- The studies had to include patients with a diagnosis of iRBD confirmed by PSG according to standard criteria of the ICSD-3 (American Academy of Sleep Medicine, 2014).
- The studies had to include the baseline scores of at least one neuropsychological test for converted and still-isolated patients separately, including experimental tasks or clinical tests assessing at least one of the following domains: cognitive screening, language, memory, executive functions, or visuospatial abilities.
- The studies had to report the follow-up time and the phenoconversion rate of the sample.

The exclusion criteria for longitudinal studies were:

- Literature review, meta-analysis, single-case study.
- Non-iRBD patients or iRBD patients not confirmed by PSG.
- Retrospective studies investigating only RBD patients with an outcome of neurodegenerative disease, as the conversion rate would necessarily be 100%.
- Studies not reporting neuropsychological data for converted and still-isolated patients separately at baseline.
- Studies not reporting the rate of phenoconversion.

Data Extraction

For each eligible cross-sectional study, the following information was extracted: (1) characteristics of the publication: authors, year of publication, title, journal, country; (2) characteristics of the sample: number of iRBD patients, number of HC, age, gender, presence/absence of iRBD patients with MCI, mean iRBD duration, age at onset of iRBD; (3) neuropsychological tests assessing the different cognitive domains (i.e., cognitive screening, language, memory, executive functions, visuospatial abilities). The tests used to assess the different cognitive domains are reported in Table 1 for each study. The test selection for each domain followed the criteria suggested by the Italian Neuropsychological Society (SINP) (Barletta-Rodolfi et al., 2011). When missing, the study authors were contacted to obtain the required data.

For each eligible longitudinal study, the following information was extracted: (1) characteristics of the publication: authors, year of publication, title, journal; (2) characteristics of the sample: number of iRBD patients who remained still-isolated at follow-up, number of iRBD patients who converted to a neurodegenerative disease at follow-up and, when reported, the conversion subtype (i.e., PD, DLB, multiple system atrophy (MSA), Alzheimer's disease (AD), other), age, gender, presence/absence of iRBD patients with MCI, mean iRBD duration, age at onset of iRBD; 3) mean follow-up duration; (4) neuropsychological tests assessing the different cognitive domains (i.e., cognitive screening, language, memory, executive functions, visuospatial abilities). The tests used to assess the different domains are reported in Table 2 for each study. The test selection for each domain followed the criteria suggested by the Italian Neuropsychological Society (SINP) (Barletta-Rodolfi et al., 2011). Finally, study authors were contacted when the required information was missing.

Quality Check

To assess the quality of the studies, the critical appraisal skills programme (CASP) checklist for cohort studies was assessed independently by two raters (C.L. and G.D.). In this study, the following points were investigated: clarity of the focused issue (question 1); cohort recruitment (e.g., accuracy of inclusion and exclusion criteria) (question 2), bias selection (e.g., validated and standardized measures and diagnostic criteria) (question 3), outcome measures (e.g., measure similarity between HC and iRBD, for cross-sectional studies, and between baseline and follow-up, for longitudinal studies (Question 4), confounding factors (e.g., control or adjust for education and years of illness) (Question 5, a &

Table 1 Tests used for the different Domains for each Cross-sectional Study (in descending chronological order)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Byun et al., 2020	MoCA; MMSE	VF; BNT	WL memory, recall, recognition; CPR; memory (MDRS)	TMT A; TMT B; attention, initiation, conceptualization (MDRS)	CP copy
Biondetti et al., 2020	MoCA; MDRS	/	/	/	/
Sasai-Sakuma et al., 2020	MoCA; ACE-R	/	/	/	/
Ehgoetz Martens et al., 2020	MMSE; MoCA	BNT; sem and ph VF	DGS-F; DGS-B; logical memory I and II; ROCF immediate and delayed recall	TMT A; TMT B	CDT
Lanza et al., 2020	MMSE	/	/	/	/
Cochen De Cock et al., 2020	MoCA	/	/	/	/
Jun et al., 2020	MoCA	/	/	/	/
Stær et al., 2020	MMSE; MoCA	/	/	/	/
Sunwoo et al., 2020	MMSE; MoCA	/	/	/	/
Kim et al., 2020	MMSE	COWAT; BNT	SVLT immediate and delayed recall, recognition	TMT A; TMT B; SCWT reading	ROCF copy
Li et al., 2020	MMSE; MoCA	/	/	/	/
Chen et al., 2020a	MMSE	/	/	/	/
Chen et al., 2020b	MMSE; MoCA	/	/	/	/
Shin et al., 2020	MMSE	/	/	/	/
Stokholm et al., 2020	MMSE; MoCA	/	/	/	/
Ehgoetz Martens et al., 2019	MoCA	BNT; sem and ph VF	Logical memory I and II; DGS	TMT A; TMT B; SCWT 1,2,3,4	CDT
Dušek et al., 2019	MoCA	/	/	/	/
Her et al., 2019	MMSE; MoCA	Naming; language (MOCA); VF; BNT; WL recognition (CERAD)	Memory recall (MOCA); WL memory, recall, recognition; CR (CERAD)	Attention; visuospatial/ executive; abstraction (MOCA); TMT A; TMT B (CERAD)	CP (CERAD)
Mollenhauer et al., 2019	MoCA	/	HVLT	SDMT; LNS	BJLO
Shin et al., 2019	MMSE	COWAT sem and ph	SVLT immediate and delayed recall, recognition	TMT-A; TMT-B; SCWT	ROCF copy
Li et al., 2019	MMSE	/	/	/	/
Lee et al., 2019	MMSE	Sem and ph COWAT; BNT	SVLT delayed recall, recognition; DGS-B	TMT A, TMT B, SCWT	ROCF copy
Campabadal et al., 2019	MMSE	BNT; sem and ph VF	RAVLT total, recall, recognition; DGS-F; DGS-B	SDMT; TMT A; TMT B; SCWT Word, C, WC	BJLO; VFD; FRT
Yoon et al., 2019	MMSE	/	/	/	/

Table 1 (continued)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Zhang et al., 2019	MMSE	sem VF; BNT	RAVLT sum of trials 1–5, short and long delay recall, recognition; ROCF delayed recall	SDMT; TMT A; TMT B; SCWT A, B, C, interference effect	ROCF copy; CDT
Sunwoo et al., 2019	MoCA; MMSE	sem VF; BNT	WL Memory; WL recall; WL recognition; CPR	TMT A; TMT B	CP
Arnaldi et al., 2019	MMSE	/	/	/	/
Pereira et al., 2019	MoCA	sem VF	HVLT immediate and delayed recall, recognition	LNS; SDMT	BJLO
Liguori et al., 2019	MMSE	/	/	/	/
Yamada et al., 2019	MMSE	/	/	/	/
Marcone et al., 2019	MoCA	/	/	Executive functioning	/
Li et al., 2018a	MMSE; MoCA	Sem VF; BNT	DGS-F; RAVLT sum of trials 1–5, delayed recall, recognition; ROCF	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)	ROCF copy; block design (WAIS- RC); CDT
Rahayel et al., 2018	MoCA	/	/	/	/
Li et al., 2018b	MMSE; MoCA	Sem VF; BNT	DGS-F; RAVLT sum of trials 1–5, delayed recall, recognition; ROCF	TMT-A; TMT-B; SCWT A, C; SDMT (WAIS-RC)	ROCF copy; block design (WAIS- RC); CDT
Stokholm et al., 2018	MoCA	/	/	/	/
Meles et al., 2018	MoCA	/	/	/	/
Barber et al., 2018	MoCA	/	/	/	/
Bezdicek et al., 2018	MoCA	/	RAVLT total immediate and delayed recall, recognition	TMT A; TMT B; LNS; SCWT interference condition	/
Heintz-Buschart et al., 2018	MMSE; MoCA	/	/	/	/
Byun et al., 2017	MoCA; MMSE	Naming, language (MoCA); VF, BNT (CERAD)	Memory recall (MOCA); WL memory, recall and recognition (CERAD); CR (CERAD)	Attention, visuospatial/ executive, abstraction (MOCA); TMT-A, TMT-B (CERAD)	Visuospatial/executive (MOCA); CP (CERAD)
Barber et al., 2017	MoCA; MMSE	Sem and ph VF	/	/	/
Sunwoo et al., 2017	MoCA	/	/	/	/
Sasai-Sakuma et al., 2017	ACE-R	Language (ACE-R); VF (ACE-R)	Memory (ACE-R)	Attention (ACE-R)	Visuospatial perception (ACE-R)
Bang et al., 2017	MMSE	Sem VF	DGS-F; DGS-B; WL recall; CPR	TMT A; TMT B; FAB; SCWT	CP; CDT
Meles et al., 2017	MoCA	/	/	/	/
Boura et al., 2017	MMSE	/	/	/	/

Table 1 (continued)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Li et al., 2016	MMSE, MoCA	Sem VF; BNT	RAVLT sum of trials 1 to 5, immediate and delayed recall, recognition; DGS-F; DGS-B; immediate and delayed ROCF; SDMT	TMT A; TMT B; SCWT; SDMT	ROCF copy; CDT; block design (WAIS-RC)
Ehrminger et al., 2016	MoCA	/	/	/	/
Rolinski et al., 2016a	MMSE	/	VSTM task	/	/
Rolinski et al., 2016b	MMSE, MoCA	Sem and ph VF	/	/	/
Zhang et al., 2016	MMSE, MoCA	Sem VF	RAVLT immediate and delayed recall, recognition; DGS-F; DGS-B; ROCF	TMT A; TMT B; SCWT; SDMT	ROCF copy; CDT
Aguirre-Mardones et al., 2015	MoCA	/	/	/	/
Rahayel et al., 2015	MoCA	/	/	/	/
Compta et al., 2015	MMSE	/	/	/	/
Antonell et al., 2014	MMSE	/	/	/	/
Plomhause et al., 2014	MMSE, MDRS	Lexis picture naming test	/	/	/
Lee et al., 2014	MMSE	/	/	/	/
Sasai et al., 2013	MMSE, MoCA	/	/	/	/
Ellmore et al., 2013	MoCA	/	/	/	/
Terzaghi et al., 2013	MMSE	Sem and ph VF	Logical Memory; WL immediate, delayed recall; DGS-F; Corsi test; delayed ROCF	AM; CPM; WCST	ROCF copy
Videnovic et al., 2013	MMSE	/	/	/	/
Delazer et al., 2012	/	/	/	IGT, IST, IED, OTS, Go-NoGo Task	/
Sasai et al., 2012	/	/	/	IGT	/
Vendette et al., 2012	MMSE	Sem and ph VF	RAVLT sum of trials 1–5, list B, immediate recall, delayed recall, recognition; DGS-F	SCWT; TMT B	ROCF copy; block design (WAIS-III); bells test
Nardone et al., 2012	MMSE, MDRS	Sem and ph VF	/	/	/
Hanyu et al., 2012	MMSE	/	/	/	/
Fantini et al., 2011	MMSE	Sem and ph VF	DGS-F; DGS-B; Corsi test; story recall; Corsi supraspan learning test; delayed recall of ROCF	AM; CPM; SCWT interference Test; TMT A; TMT B; TMT B/A	ROCF copy
Marques et al., 2010	MMSE, MDRS	Sem and ph VF	DGS-F; DGS-B; WL Learning and Recall Test	SCWT; SDMT	/

Table 1 (continued)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Gagnon et al., 2009	/	Sem and ph VF	RAVLT sum of trials 1 to 5, list B, immediate and delayed recall, recognition; DGS	TMT B; SCWT	ROCF copy; block design; bells test
Postuma et al., 2009	MMSE	/	/	/	/
Massicotte-Marquez et al., 2008	MMSE	Sem and ph VF; similarity subtest (WAIS-III)	RAVLT total words of trial 1–5, list B, retention, delayed recall, correct recognitions, false positive recognitions; DGS-F; DGS-B	TMT A; TMT B; SCWT Interference condition, flexibility condition; SDMT	ROCF copy; block design (WAIS-III)
Terzaghi et al., 2008	MMSE	Sem and ph VF	DGS-F; WL immediate and delayed recall; Corsi's Test; logical Memory; delayed recall of ROCF	AM; CPM; WCST	ROCF copy
Raggi et al., 2007	MMSE	/	/	AM	/
Postuma et al., 2006	MMSE	/	/	/	/
Ferini-Strambi et al., 2004	MMSE	Sem and ph VF	DGS-F; DGS-B; Corsi block-tapping task; Corsi supraspan learning; logical memory	AM; SCWT interference condition; CPM; TMT A; TMT B	ROCF copy

ACE-R Addenbrooke cognitive examination-revised, *AM* attentive matrices, *BJLO* Benton judgment of line orientation, *BNT* Boston naming test, *CDT* clock-drawing test, *CERAD* consortium to establish a registry for Alzheimer's disease, *COWAT* controlled oral word association test, *CP* constructional praxis, *CPM* Raven's coloured progressive matrices, *CPR* constructional praxis recall, *DGS-B* digit span backward, *DGS-F* digit span forward, *FAB* frontal assessment battery, *FRT* facial recognition test, *HVLT* Hopkins verbal learning test, *IED* intra/extra dimensional shift, *IGT* Iowa gambling task, *IST* information sampling task, *LNS* letter-number sequencing test, *MDRS* Mattis dementia rating scale, *MMSE* mini-mental state examination, *MoCA* Montreal cognitive assessment, *OTS* one touch stockings of Cambridge, *RAVLT* Rey auditory verbal learning test, *VSTM* visual short-term memory, *ROCF* Rey complex figure, *SCWT* color word stroop test, *SDMT* symbol digit modalities test, *SVLT* Seoul verbal learning test, *TMT* trail making test, *VF* verbal fluency, *Ph VF* phonemic verbal fluency, *Sem VF* semantic verbal fluency, *VFD* visual form discrimination, *WAIS* Wechsler adult intelligence scale, *WCST* Wisconsin card-sorting test, *WL* word list

Table 2 Tests used for the different Domains for each Longitudinal Study (in descending chronological order)

First Author and Year	Cognitive Screening	Language	Memory	Executive Functions	Visuospatial Abilities
Arnaldi et al., 2021	/	Sem and ph VF	RAVLT immediate, delayed recall; DGS; Corsi Span	SCWT; TMT A; TMT B; SDMT	CDT
Kogan et al., 2020	MoCA	/	/	/	/
Campabadal et al., 2020	/	/	/	/	/
Feng et al., 2020	MoCA	/	/	/	/
Miyamoto et al., 2020	MMSE	/	/	/	/
Kim et al., 2020	MMSE	Sem and ph COWAT, BNT	SVLT immediate recall, delayed recall, recognition	TMT A; TMT B; SCWT	ROCF copy
Terzaghi et al., 2019	MMSE	Sem VF	DGS-F; Corsi test; WL immediate and delayed recall; logical memory; ROCF delayed recall	AM; Weigi's sorting test; FAB; CPM	ROCF copy; CP
Pereira et al., 2019	MoCA	Sem VF	HVLT immediate recall, delayed recall, recognition	LNS; SDMT	BJLO
Nepozitek et al., 2019	MoCA	/	/	/	/
Marchand et al., 2018	MMSE	Sem VF	DGS-F; DGS-B; WL recall test; CPR	TMT A; TMT B;	CP; CDT
Youn et al., 2016	MMSE, MoCA	Sem and ph VF	DGS; RAVLT sum of trials 1–5, list B, immediate and delayed recalls, recognition	TMT A; TMT B; FAB; SCWT	ROCF copy, block design; bells test

AM attentive matrices, *BNT* Boston naming test, *BJLO* Benton judgment of line orientation, *CDT* clock-drawing test, *COWAT* controlled oral word association test, *CP* constructional praxis, *CPM* Raven's coloured progressive matrices, *CPR* constructional praxis recall, *DGS-B* digit span backward, *DGS-F* digit span forward, *FAB* frontal assessment battery, *FRT* facial recognition test, *HVLT* Hopkins verbal learning test, *LNS* letter-number sequencing test, *MMSE* mini-mental state examination, *MoCA* Montreal cognitive assessment, *RAVLT* Rey auditory verbal learning test, *ROCF* Rey complex figure, *SCWT* color word stroop test, *SDMT* symbol digit modalities test, *SVLT* Shiraz verbal learning test, *TMT* trail making test, *VF* verbal fluency, *Sem VF* semantic verbal fluency, *Ph VF* phonemic verbal fluency, *VFD* visual form discrimination, *WCST* Wisconsin card-sorting test

b), follow-up completeness and length (only for longitudinal studies) (Question 6a & b), relevance of the results (e.g., presence of considerable differences between the groups: HC VS iRBD for cross-sectional studies and converted VS non converted for longitudinal studies) (Question 7); precision/accuracy of the results (e.g., the type of provided data: mean and standard deviations or other statistics) (Question 8); credibility of the results (e.g., study design, check for confounding factors, use of standardize and validated measures, effect sizes) (Question 9), applicability of the results (e.g., reliability of inclusion, exclusion criteria and sample size) (Question 10), fitness of the results within other available evidence (Question 11), and lastly practice implications (e.g., completeness and reliability of neuropsychological data) (Question 12). Each study could reach a maximum value of 14, reflecting the highest methodological quality. The scores between raters were compared and disagreements were solved by discussion.

Specific Methods for Meta-analysis

Data analyses were performed using the software R studio supporting R version 4.0.5 (RStudio Team, 2020; http://www.R-project.org/).

For cross-sectional analyses, effect sizes (ES) were calculated for each cognitive domain to quantify the difference in cognitive performance between iRBD patients and HC. A random effects (RE) model was used for the analyses. The *metafor* package was used for these analyses (Viechtbauer, 2010).

For the analyses of longitudinal studies, to estimate the survival function for the different phenoconversion trajectories, the *survival* package (Therneau, 2015) was used in R. Specifically, a Kaplan–Meier survival analysis with stratification factors, which indicated the different types of conversion (i.e., PD, DLB, MSA, AD, other), was applied. A dichotomous variable was used to describe the status of the patients at follow-up (0: still-iRBD patients; 1: patients

who converted) and the mean follow-up time was used as the timing variable.

To identify a baseline neurocognitive profile associated with phenoconversion, the cognitive performance of iRBD patients and the rate of phenoconversion at follow-up time were analyzed. As for cross-sectional studies, ES were calculated using the *metafor* package. Moreover, a Cox proportional hazards analysis using simulated data was performed to evaluate how cognitive status predicted the development of a neurodegenerative disease (*survival* package). This analysis required a time variable (follow-up time), a dichotomous status variable (0: still-iRBD patients; 1: patients who converted), and a factor, which in this case was represented by the simulated neuropsychological score for each cognitive domain, given the impossibility of getting access to single-subject data. The *runuran* R package (Leydold et al., 2012) was used to simulate single-subject data since these were necessary to perform the survival analyses. Specifically, the function *urnorm* was used to generate a normal distribution of random numbers with means and standard deviations equal to those provided by the different longitudinal studies.

Furthermore, we also used a Cox proportional hazards analysis to investigate the presence of MCI at baseline as a predictor of phenoconversion. This analysis was conducted using the three studies (Arnaldi et al., 2021; Nepozitek et al., 2019; Terzaghi et al., 2019) that provided information on the number of patients that presented with MCI at baseline, and whether they converted or not at follow-up. Taken together, these studies included 163 iRBD patients, of which 40 were iRBD patients with MCI.

Finally, additional analyses were conducted to probe whether our criteria to select tests and define the cognitive domains may have influenced our results. More specifically, we noticed domain inconsistencies in the neuropsychological tests reported by some studies, for example in two cross-sectional studies (Li et al., 2018a; Zhang et al., 2019) verbal fluency tests were used to assess language ability, whereas in other two cross-sectional studies (Ehgoetz Martens et al., 2020; Gagnon et al., 2009) verbal fluency tests were used to assess attention and executive functions. Therefore, we modified the domains to which these tests were assigned and calculated additional ES for language and executive domains. More specifically,

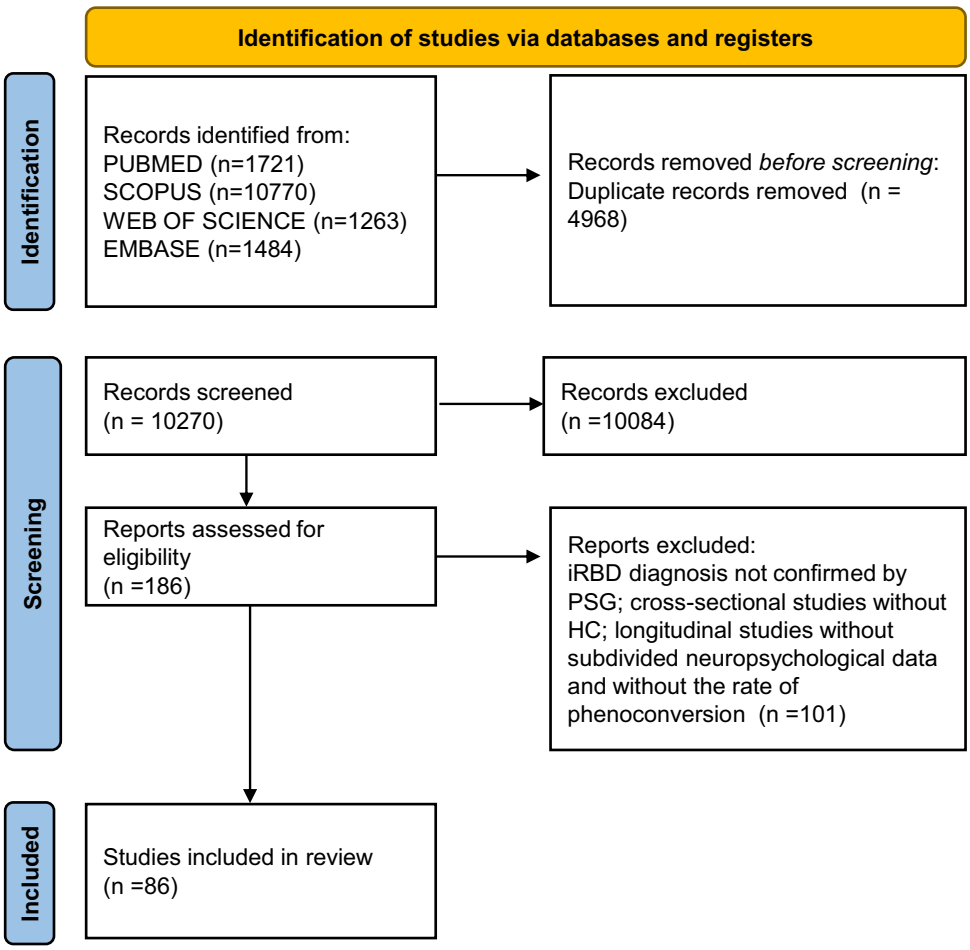

Fig. 1 PRISMA Flow Diagram Summarizing the Selection Procedure (*Note*. HC: healthy controls; iRBD: isolated Rapid Eye Movement (REM) sleep behaviour disorder; PSG: polysomnography)

these modifications targeted those neuropsychological tests where the included studies showed domain inconsistencies. Specifically, phonemic Controlled Oral Word Association Test and phonemic Verbal Fluency tests were moved from the language to the executive domain. The tests used to evaluate the two modified domains are reported in Supplementary Table 2. In addition, because of the heterogeneity inherent to the executive domain, we analyzed attention and processing speed separately. This latter analysis was only performed on the cross-sectional studies given the limited number of longitudinal studies available for secondary analyses of cognitive domains.

Results

Study Selection

Figure 1 shows the flow diagram according to the PRISMA statement summarizing the selection procedure.

Systematic Review Results

The systematic review analyzed 75 cross-sectional studies. These studies assessed the cognitive performance of 2,398 HC (1,397 males, 941 females; mean age 65.66 ± 3.28) and 2,460 iRBD patients (1,867 males, 562 females; mean age 66.80 ± 3.06). A total of 61 out of 75 cross-sectional studies reported either the mean age of iRBD symptoms onset (59.67 ± 3.33), the mean RBD duration from symptoms onset (6.47 ± 2.67), or the mean RBD duration from PSG diagnosis (2.99 ± 1.20). The selected cross-sectional studies were conducted in 16 different countries: South Korea (14 studies), Italy (10 studies), China (nine studies), Canada (seven studies), Japan (six studies), France (five studies), United Kingdom (four studies), Spain (four studies), Germany (three studies), United States (three studies), Australia (two studies), Czech Republic (two studies), the Netherlands (one study), Austria (one study), and Sweden (one study). The samples of three studies were composed of patients from both Denmark and Spain. These results are presented in Table 3.

The systematic review analysed 11 longitudinal studies, including 495 patients (non-converted n = 356; converted n = 139). The descriptive data for each group were provided in every study but one (Marchand et al., 2018). The 10 longitudinal studies that provided sociodemographic data included 370 males and 90 females, with a mean age of 67.57 ± 1.88 years. The mean follow-up of all 11 longitudinal studies was 3.2 ± 1.45 years (1.6–6.7 years). All studies provided the type of phenoconversion except one, which provided baseline iRBD cognitive performance scores separated between those who converted to PD versus DLB at follow-up (Marchand et al., 2018). Four studies (Campabadal et al., 2020; Kogan et al., 2020; Terzaghi et al., 2019; Youn et al., 2016) provided the mean age of iRBD symptoms onset (61.59 ± 1.19). The mean RBD duration from symptoms onset was 9.85 ± 4.72 (seven studies, presented in Table 4), whereas the mean RBD duration from PSG diagnosis was respectively 2.7 ± 3.5 and 1.2 ± 1.2 in the two studies that reported this information (Feng et al., 2020; Miyamoto et al., 2020). Furthermore, one study reported the age at onset of neurodegenerative disease (73.8 ± 7.6) (Feng et al., 2020). The selected longitudinal studies were conducted in 9 different countries: South Korea (two studies), Italy (two studies), Spain (one study), China (one study), Japan (one study), Sweden (one study), Czech Republic (one study), and Canada (one study). Lastly, one study was a collaboration between the Netherlands and Germany. Specifically, in the last study, the patients were provided by both countries. These results are presented in Table 4.

Risk of Bias within Studies

To evaluate the publication bias, a funnel plot for each cognitive domain, for both cross-sectional and longitudinal studies, was inspected. Plots showed few asymmetries, which appears consistent with the inference of publication bias, except for the longitudinal study domain of cognitive screening. Plots are reported in Supplementary Fig. 1.

PI and I^2 statistics were calculated to assess the heterogeneity across studies. Cross-sectional studies showed considerable heterogeneity levels (I^2 values from 65 to 100%) in every cognitive domain. Specifically, ranked by the extent of heterogeneity (I^2), cognitive screening came first (I^2 = 79.02%, PI = –1.7395 0.3563), followed by executive functions (I^2 = 78.58%, PI = –1.6327 0.6254), visuospatial abilities (I^2 = 65.39%, PI = –1.1656 0.3896), language (I^2 = 64.40%, PI = –1.1024 0.3401), and memory (I^2 = 62.13%, PI = –1.4122 0.1225). Longitudinal studies showed different heterogeneity levels across domains, ranging from low heterogeneity levels, such as for cognitive screening (I^2 = 11.64%, PI = –0.5759 0.0615) and visuospatial (I^2 = 32.03%, PI = –0.7392 0.2070) domains, to considerable heterogeneity values, such as for language (I^2 = 91.41%, PI = –3.3743 1.8179), memory (I^2 = 85.69%, PI = –2.0882 0.9665), and executive (I^2 = 87.17%, PI = –2.4378 1.0192) domains.

Quality Assessment

In terms of quality assessment of the studies, the agreement between the two raters was high (Cohen's K = 0.855, z = 14.2, p-value < 0.001; inter-rater reliability (IRR) = 89%). All the cross-sectional studies reached a cut-off score ≥ 10

Table 3 Cross-sectional Studies Characteristics (in descending chronological order)

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Byun et al., 2020	KOR	37 (12 F)	67.7 ± 7.1	/	6.8 ± 3.8	/	15 (6 F)	68.3 ± 3.3
Biondetti et al., 2020	FRA	42 (5 F)	67.7 ± 5.2	/	/	/	38 (21 F)	59.9 ± 9.3
Sasai-Sakuma et al., 2020	JPN	35 (10 F)	75.45 ± 0.95	/	/	/	11 (7 F)	69 ± 1.3
Ehgoetz Martens et al., 2020	AUS	30 (6 F)	66.7 ± 7.2	/	/	/	28 (14 F)	65.6 ± 8.1
Lanza et al., 2020	ITA	14 (3 F)	65.5	/	2.5 ± 0.89	/	14 (5 F)	65
Cochen De Cock et al., 2020	FRA	21 (4 F)	68.7 ± 6.9	/	11.4 ± 11.2	/	38 (7 F)	69.1 ± 7.2
Jun et al., 2020	KOR	94 (41 F)	67.6 ± 7.3	/	5.9 ± 4.6	/	50 (26 F)	65.4 ± 6
Stær et al., 2020	DNK and ESP	19 (2 F)	66.6 ± 6.3	62.2 ± 6.3	3.7 ± 3.5	/	27 (7 F)	65.55
Sunwoo et al., 2020	KOR	16 (2 F)	65.4 ± 6.6	/	3.7 ± 2	/	10 (3 F)	62.3 ± 7.5
Kim et al., 2020	KOR	30 (11 F)	68.6 ± 5.9	/	5.1 ± 4.5	/	12 (6 F)	67.9 ± 4.6
Li et al., 2020	CHN	15 (6 F)	64.27 ± 1.87	/	/	/	15 (6 F)	64.8 ± 1.83
Chen et al., 2020a	CHN	15 (5 F)	64.33 ± 12.16	/	4.33 ± 2.19	/	20 (5 F)	61.1 ± 8.04
Chen et al., 2020b	CHN	27 (5 F)	65.89 ± 8.54	/	11.09 ± 11.24	/	33 (13 F)	68.25 ± 7.8
Shin et al., 2020	KOR	39 (17 F)	69.37 ± 5.77	/	4.83 ± 3.63	/	19 (11 F)	69.38 ± 5.06
Stokholm et al., 2020	DNK and ESP	17 (2 F)	65.3 ± 6.3	/	3.5 ± 3.3	/	9 (0 F)	64.3 ± 6.9
Ehgoetz Martens et al., 2019	AUS	24 (6 F)	66.9 ± 7.6	/	/	/	14 (6 F)	67.4 ± 10.1
Dušek et al., 2019	CZE	74 (8 F)	67.5 ± 6.3	/	6.5 ± 5.8	/	39 (7 F)	65.2 ± 8.2
Her et al., 2019	KOR	15 (3 F)	64.94 ± 6.92	/	/	/	19 (5 F)	63.47 ± 7.37
Mollenhauer et al., 2019	USA	32 (6 F)	69.3 ± 4.83	/	/	/	173 (63 F)	60.9 ± 11.3
Shin et al., 2019	KOR	25 (12 F)	69.6 ± 5.8	/	4.2 ± 3	/	13 (8 F)	68.8 ± 5.2
Li et al., 2019	CHN	83 (19 F)	67.87 ± 7	/	7.3 ± 6.16	/	79 (21 F)	66.65 ± 7.04
Lee et al., 2019	KOR	31 (14 F)	70.5 ± 5.9	/	4.3 ± 3	/	19 (12 F)	70.1 ± 4.8
Campabadal et al., 2019	ESP	20 (6 F)	71.3 ± 7.8	/	3.1 ± 3.5	/	27 (14 F)	66.4 ± 9.9
Yoon et al., 2019	KOR	28 (14 F)	69.8 ± 5.6	/	4.4 ± 3.9	/	24 (17 F)	69.5 ± 4.3
Zhang et al., 2019	CHN	15 (8 F)	64.93 ± 1.81	/	5.77 ± 1.4	/	23 (13 F)	63.39 ± 2.14
Sunwoo et al., 2019	KOR	13 (2 F)	66.3 ± 6.5	/	4 ± 2.1	/	10 (3 F)	62.3 ± 7.5
Arnaldi et al., 2019	ITA	36 (4 F)	64.1 ± 6	/	/	/	79 (26 F)	65.6 ± 9
Pereira et al., 2019	SWE	27 (5 F)	68.9 ± 5.5	/	/	/	31 (11 F)	58.5 ± 11
Liguori et al., 2019	ITA	54 (13 F)	69.75 ± 8.89	/	5.75 ± 2.57	/	35 (16 F)	67.89 ± 4.95

Table 3 (continued)

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Yamada et al., 2019	JPN	23 (11 F)	71.5 ± 3.8	/	5.01 ± 3.33	/	20 (9 F)	70.7 ± 3.6
Marcone et al., 2019	ITA	38 (10 F)	67.7 ± 8.45	/	4.39 ± 4.45	/	20 (15 F)	65.3 ± 8.5
Li et al., 2018a	CHN	42 (10 F)	70.88 ± 8.29	/	8.81 ± 12.01	/	45 (33 F)	69.36 ± 10.04
Rahayel et al., 2018	CAN	52 (10 F)	65.5 ± 6.6	/	11.7 ± 11.9	1.6 ± 2.2	41 (16 F)	63.2 ± 8.2
Li et al., 2018b	CHN	28 (7 F)	72.32 ± 7.22	/	9.87 ± 13.59	/	21 (14 F)	69.81 ± 10.24
Stokholm et al., 2018	DNK and ESP	21 (3 F)	66.2 ± 6.3	/	/	3.6 ± 3.4	29 (8 F)	65.7 ± 4.8
Meles et al., 2018	DEU	21 (3 F)	61.9 ± 5.4	55 ± 7.1	5.88 ± 1.13	/	19 (10 F)	62.4 ± 7.5
Barber et al., 2018	GBR	88 (5 F)	66.9 ± 7.62	/	8.5 ± 6.7	3 ± 2.5	33 (18 F)	68.4 ± 8.94
Bezdicek et al., 2018	CZE	60 (5 F)	68.08 ± 7.91	/	4.49 ± 5.33	/	30 (4 F)	66.63 ± 7.43
Heintz-Buschart et al., 2018	DEU	21 (9 F)	66.1 ± 7.9	/	/	/	78 (32 F)	68.4 ± 6.7
Byun et al., 2017	KOR	14 (4 F)	62.5 ± 6.5	/	4.9 ± 4.1	/	14 (3 F)	64 ± 5.5
Barber et al., 2017	GBR	171 (20 F)	64.7 ± 9	/	7.07 ± 6.3	/	296 (151 F)	64.9 ± 10.2
Sunwoo et al., 2017	KOR	16 (5 F)	64.3 ± 7.4	/	4.8 ± 3.7	/	16 (3 F)	62 ± 6.9
Sasai-Sakuma et al., 2017	JPN	202 (58 F)	66.8 ± 8	/	6.8 ± 7.1	/	46 (14 F)	64.7 ± 5.8
Bang et al., 2017	KOR	57 (24 F)	66 ± 6.09	/	5.66 ± 8.45	/	33 (15 F)	63.88 ± 5.61
Meles et al., 2017	NLD	21 (3 F)	61.9 ± 5.4	55 ± 7.1	6.9 ± 5.4	/	19 (10 F)	62.4 ± 7.5
Boura et al., 2017	DEU	14 (2 F)	65.6 ± 7	/	6.8 ± 4.7	/	27 (16 F)	63.7 ± 11.5
Li et al., 2016	CHN	23 (4 F)	72.48 ± 6.78	/	6.89 ± 8.1	/	23 (4 F)	72.52 ± 6.72
Ehrminger et al., 2016	FRA	21 (6 F)	67.4 ± 7.6	/	5.9 ± 3.8	/	21 (5 F)	67.6 ± 6.3
Rolinski et al., 2016a	GBR	21 (2 F)	66 ± 9	/	/	2.7 ± 1.9	26 (8 F)	66 ± 7
Rolinski et al., 2016b	GBR	26 (4 F)	67 ± 7.7	/	6.3 ± 3.2	5.3 ± 3.01	23 (NA)	NA
Zhang et al., 2016	CHN	15 (4 F)	61.7 ± 12.7	/	12.4 ± 14.5	/	36 (17 F)	62.7 ± 8.1
Aguirre-Mardones et al., 2015	ESP	44 (9 F)	70.89 ± 6.12	61.16 ± 8.08	9.64 ± 6.25	/	40 (11 F)	70.13 ± 6.08
Rahayel et al., 2015	CAN	24 (4 F)	64.2 ± 7	/	9.3 ± 9	2.1 ± 3.1	42 (14 F)	63.3 ± 7.1
Compta et al., 2015	ESP	23 (7 F)	70.33	/	10.65	/	13 (6 F)	71.5
Antonell et al., 2014	ESP	12 (1 F)	69 ± 5.6	/	/	/	43 (31 F)	61.6 ± 7.6
Plomhause et al., 2014	FRA	15 (1 F)	66.7 ± 5.9	/	/	/	20 (5 F)	64.8 ± 7.6
Lee et al., 2014	KOR	15 (5 F)	62.8 ± 7.41	/	5.93 ± 3.22	/	20 (8 F)	59.95 ± 6.41

Table 3 (continued)

First Author and Year	Country	N of iRBD (Gender)	iRBD Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of HC (Gender)	HC Mean Age ± sd
Sasai et al., 2013	JPN	31 (7 F)	67 ± 7.5	/	5.4 ± 3.9	/	17 (NA)	59.5 ± 5.6
Ellmore et al., 2013	USA	10 (4 F)	57 ± 2.7	/	/	/	10 (6 F)	57 ± 2.4
Terzaghi et al., 2013	ITA	20 (1 F)	66.1 ± 7.1	60 ± 9.1	7 ± 8.5	/	20 (NA)	NA
Videnovic et al., 2013	USA	10 (4 F)	61.5 ± 8.6	58.5 ± 9.3	1.3 ± 0.9	/	10 (2 F)	62.7 ± 11.5
Delazer et al., 2012	AUT	16 (3 F)	65.2 ± 7.6	/	8.9 ± 7.1	/	45 (23 F)	63.9 ± 9.6
Sasai et al., 2012	JPN	38 (7 F)	64 ± 4.8	/	5.2 ± 3.7	/	34 (13 F)	66.4 ± 7.6
Vendette et al., 2012	CAN	20 (8 F)	67.06 ± 6.97	/	/	/	20 (5 F)	67.35 ± 6.38
Nardone et al., 2012	ITA	10 (0 F)	64.6 ± 7	/	1.23 ± 0.46	/	15 (0 F)	63.7 ± 6.4
Hanyu et al., 2012	JPN	20 (3 F)	68 ± 7	/	6 ± 5	/	18 (9 F)	71 ± 8
Fantini et al., 2011	ITA	24 (6 F)	69.5 ± 7.3	/	7.6 ± 7.3	/	12 (3 F)	69.3 ± 6.3
Marques et al., 2010	FRA	10 (2 F)	59 ± 2.4	/	4.5 ± 1.7	/	8 (3 F)	64 ± 2
Gagnon et al., 2009	CAN	32	65.69 ± 8.52	/	11.27 ± 8.56	/	40 (19 F)	65.78 ± 8.82
Postuma et al., 2009	CAN	68 (15 F)	68 ± NA	/	9.3 ± 1.1	2.6 ± 0.62	36 (8 F)	65.8
Massicotte-Marquez et al., 2008	CAN	14 (0 F)	66.6 ± 7.7	/	11.2 ± 6.7	/	14 (0 F)	65.6 ± 6.5
Terzaghi et al., 2008	ITA	23 (2 F)	67 ± 7	61.2 ± 5.9	6.6 ± 3.6	/	23 (2 F)	67 ± 6
Raggi et al., 2007	ITA	16 (3 F)	66.37 ± 6.14	/	3.43 ± 2.58	/	16 (3 F)	67.56 ± 5.25
Postuma et al., 2006	CAN	25 (3 F)	69.2 ± NA	/	10.5 ± 7	/	25 (3 F)	69.2
Ferini-Strambi et al., 2004	ITA	17 (4 F)	70 ± 7.3	64.31 ± 7.45	5.69 ± 5.31	/	17 (3 F)	69.5 ± 7.1

Table 4 Longitudinal Studies Characteristics (in descending chronological order)

First Author and Year	Country	N of Patients (Gender)	Mean Age ± sd	Mean age of symptoms onset ± sd	Mean RBD duration, symptoms ± sd	Mean RBD duration, diagnosis ± sd	N of Non-Converted (Gender)	Mean Age and sd Non-Converted	N of Converted (Gender)	Mean Age ± sd Converted	Mean Follow-up Time	MCI Included/ Excluded
Arnaldi et al., 2021	ITA	44 (6 F)	69 ± 6.95	41.06 ± 16.94	/	/	34 (4 F)	68.09 ± 7.54	10 (2 F)	69.9 ± 6.12	2.21	1
Kogan et al., 2020	NLD and DEU	20 (2 F)	66,37 ± 5.17	56.64 ± 6.7	6.02 ± 2.48	/	16 (2 F)	66.86 ± 4.58	4 (0 F)	64.4 ± 6.19	3.7	NA
Campabadal et al., 2020	ESP	13 (3 F)	70.1 ± 6.9	65.65 ± 7.5	4.5 ± 3.4	/	13 (3 F)	NA	0	NA	1.6	0
Feng et al., 2020	CHN	88 (17 F)	69.8 ± 7.7	/	/	2.7 ± 3.5	66 (18 F)	70.9 ± 7.5	22 (6 F)	72.1 ± 7.6	2	1
Miyamoto et al., 2020	JPN	24 (3 F)	65.4 ± 5.5	/	7.3 ± 6.2	1.2 ± 1.2	13 (1 F)	67.1 ± 4.2	11 (2 F)	63.5 ± 6.3	2.3	0
Kim et al., 2020	KOR	30 (11 F)	68.6 ± 5.9	/	5.1 ± 4.5	/	22 (6 F)	67.6 ± 6	8 (5 F)	71.3 ± 5.1	3.4	0
Terzaghi et al., 2019	ITA	63 (8 F)	66.46 ± 6.83	62.43 ± 8.32	14.54 ± 19.05	/	33 (2 F)	66.09 ± 7.48	30 (6 F)	66.87 ± 6.13	6.7	1
Pereira et al., 2019	SWE	27 (5 F)	68.9 ± 5.5	/	/	/	21 (3 F)	69.2 ± 5.9	6 (2 F)	67.8 ± 4.1	2.8	1
Nepozitek et al., 2019	CZE	55 (5 F)	65.7 ± 9.1	/	9.9 ± 9.3	/	46 (NA)	65 ± 9.5	9 (NA)	68.9 ± 6.5	2.3	1
Marchand et al., 2018	CAN	47 (NA)	NA	/	/	/	26 (NA)	NA	21 (NA)	NA	4	1
Youn et al., 2016	KOR	84 (30 F)	65.41 ± 5.83	60.75 ± 8.32	/	/	66 (18 F)	64.98 ± 7.21	18 (8 F)	65.83 ± 4.45	4.24	1

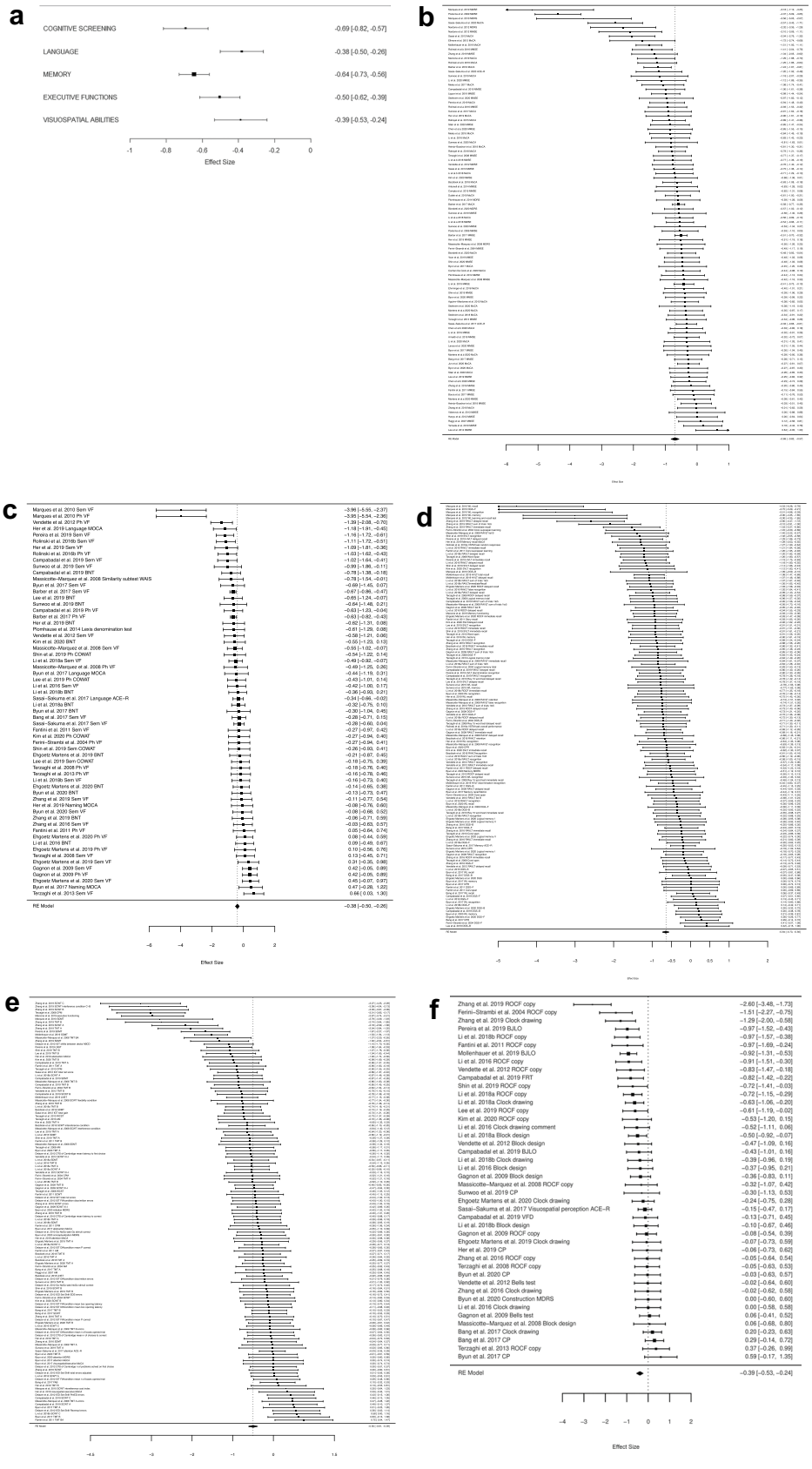

Fig. 2 Graphical Representation of the Main Results for Cross-sectional Studies: **a** Cognitive Domains Summary Forest Plot for Cross-sectional Studies, **b** Cognitive Screening Forest Plot for Cross-sectional Studies (*Note*. ACE-R: Addenbrooke Cognitive Examination-Revised; MDRS: Mattis Dementia Rating Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment), **c** Language Forest Plot for Cross-sectional Studies (*Note*. BNT: Boston Naming Test; COWAT: Controlled Oral Word Association Test; Ph VF: Phonemic Verbal Fluency; Sem VF: Semantic Verbal Fluency; WAIS: Wechsler Adult Intelligence Scale), **d** Memory Forest Plot for Cross-sectional Studies (*Note*. CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey Complex Figure; SVLT: Shiraz Verbal Learning Test; WL: Word list), **e** Executive Function Forest Plot for Cross-sectional Studies (*Note*. CPM: Raven's Coloured Progressive Matrices; FAB: Frontal Assessment Battery; IED: Intra/Extra Dimensional Shift; IGT: Iowa Gambling Task; IST: Information Sampling Task; LNST: Letter-Number Sequencing Test; OTS: One Touch Stockings of Cambridge; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WCST: Wisconsin Card-Sorting Test), and **f** Visuospatial Abilities for Cross-sectional Studies (*Note*. BJLO: Benton Judgment of Line Orientation; CP: Constructional Praxis; FRT: Facial Recognition Test; ROCF: Rey Complex Figure; VFD: Visual Form Discrimination)

on the CASP checklist, whereas the longitudinal studies reached a cut-off score ≥ 11. In other words, no studies were excluded based on quality ratings.

Meta-analytic Results

With regards to the cross-sectional meta-analysis, the largest ES was found for cognitive screening (RE model = –0.69 [95% confidence interval (CI) −0.82, −0.57]), followed by memory (RE model = –0.64 [95% CI −0.73, −0.56]), and executive functions (RE model = –0.50 [95% CI −0.62, −0.39]). Smaller differences between iRBD patients and HC were found for language (RE model = –0.38 [95% CI –0.50, –0.26]) and visuospatial abilities (RE model = −0.39 [95% CI −0.53, −0.24]). This suggests that iRBD patients performed significantly worse compared to HC on every cognitive domain, but more so on cognitive screening, memory, and executive functions. These results are presented in Fig. 2.

No differences were found between the ES above reported and the ES calculated for domains where tests were re-attributed (i.e., modified language domain with RE model = –0.37 [95% CI –0.50, –0.23] and modified executive functions domain (RE model = –0.50 [95% CI –0.60; –0.39]).

In terms of the analyses of executive subdomains, processing speed showed the largest ES (RE model = –0.73 [95% CI −0.97, −0.48]), while a minor difference between HC and iRBD was found in the attention subdomain (RE model = −0.25 [95% CI −0.40, −0.10]). These results are presented in Fig. 3.

With regards to the longitudinal meta-analysis, the Kaplan–Meier survival analysis estimated a hazard rate of 73.7% after 7 years of follow-up (Fig. 4).

The most frequent conversion phenotype was represented by PD (56.83%), followed by DLB (31.65%), MSA (5.75%), other neurodegenerative diseases (i.e., non-specific parkinsonism, pure autonomic failure, spinocerebellar ataxia) (3.60%), and AD (2.16%) (Fig. 5). Of note, 6 of the 11 longitudinal studies had a follow-up duration shorter than three years.

The largest difference (i.e., ES) at baseline between patients who converted at follow-up and those who remained still-isolated was found in the executive function domain (RE model = –0.71 [95% CI –1.12, –0.30]). Of note, language was close to significance (RE model = –0.77 [CI –1.59, 0.04]). Smaller differences between patients who converted at follow-up and those who remained still-isolated were found for memory (RE model = –0.58 [95% CI –0.90, –0.26]), visuospatial abilities (RE model = −0.27 [95% CI −0.48, −0.05]), and cognitive screening (RE model = –0.26 [95% CI –0.47, –0.04]). These results were presented in Fig. 6.

No relevant differences were found between the ES above reported and the ES calculated for domains with re-attributed tests: the modified executive domain showed, as above, a large and significant difference between converters and non-converters (RE model = –0.78 [95% CI –1.17, –0.38]. As found previously, the modified language domain was not significant (RE model 95% CI –1.61, 0.44).

The Cox proportional hazards analysis showed that the domains that best predicted phenoconversion (i.e., the highest and significant hazard ratios (HR)) were executive

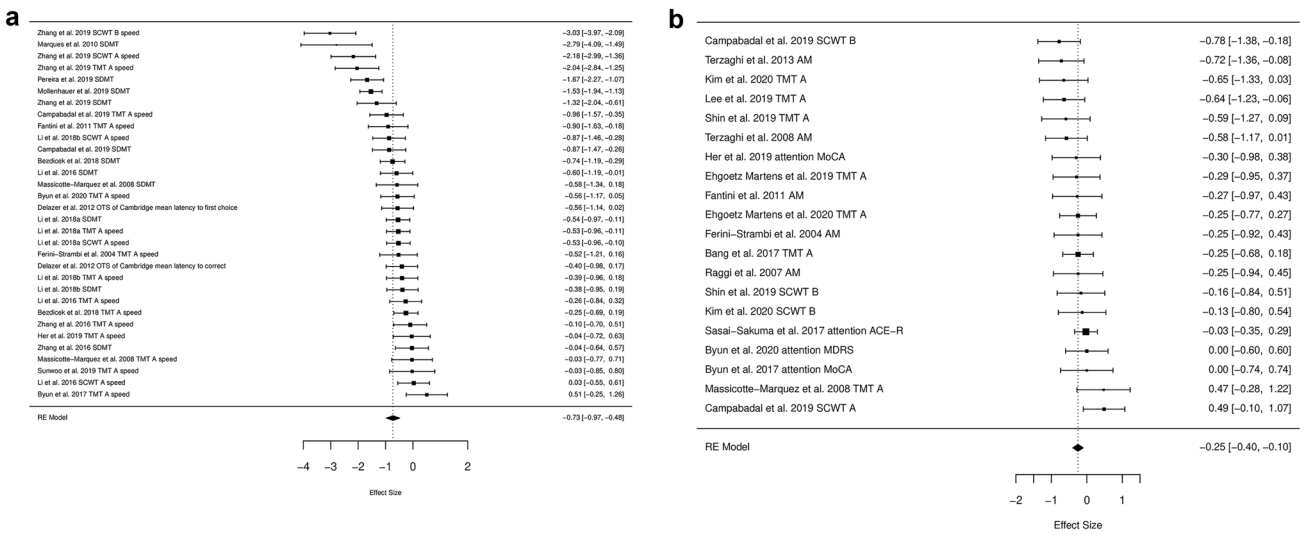

Fig. 3 Graphical Representation of the Executive Functions Subdomains Results for Cross-sectional Studies: **a** Speed Processing Forest Plot for Cross-sectional Studies, **b** Attention Forest Plot for Cross-sectional Studies

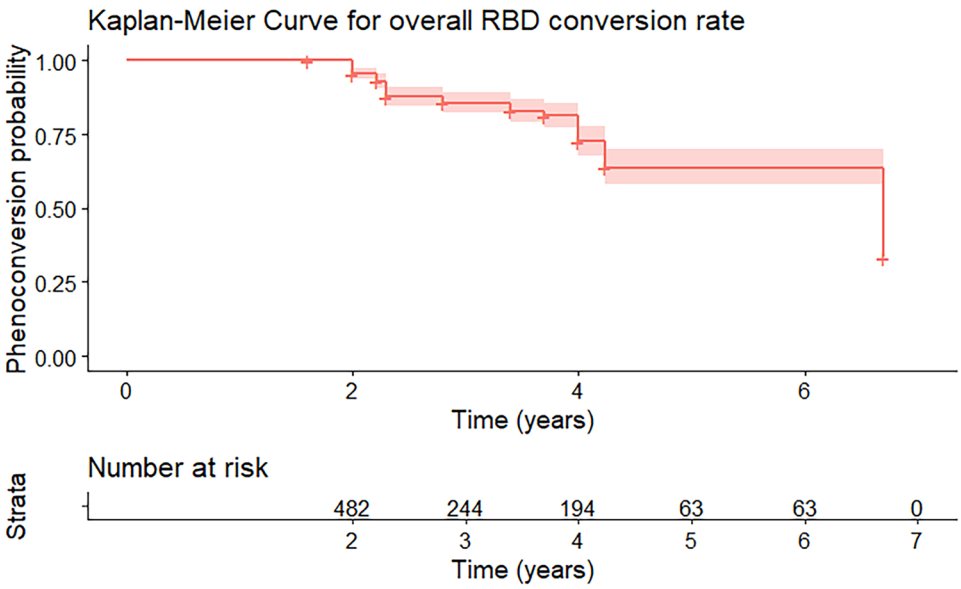

Fig. 4 Kaplan–Meier Analysis Plotting Disease-free Survival in iRBD Patients

functions and language. Each reduction of one unit in executive function performance (expressed in z-scores) increased the hazard by a factor of 0.4, equal to 60% (HR = 0.3992; 95% CI 0.309, 0.5157; p-value = 0.000) for the conversion to a neurodegenerative disorder, followed by language with a hazard of 0.7, corresponding to 24% (HR = 0.7628; 95% CI 0.6136, 0.9483; p-value = 0.01). Of note, memory was slightly above statistical significance threshold with a hazard of 0.64 (HR = 0.6379; 95% CI 0.3999, 1.018; p-value = 0.0592). There was no significant predictive value of either cognitive screening (p-value = 1) or visuospatial abilities (p-value = 0.47).

The Cox proportional hazards analysis that assessed MCI as a predictor of conversion showed that a patient with iRBD and MCI had a three-fold chance of converting compared to a patient with iRBD but no MCI (HR = 2.957; 95% CI 1.681, 5.201 p-value = 0.001).

Discussion

This meta-analysis aimed at evaluating the presence of cognitive impairment in iRBD patients in comparison with HC and at quantitatively estimating the risk of phenoconversion in iRBD patients based on their neuropsychological assessment.

The meta-analysis of cross-sectional studies showed that the most impaired cognitive domains in iRBD patients were cognitive screening, memory, and executive functions, which were associated with "medium" ES (Cohen, 1988; Vacha-Haase et al.,

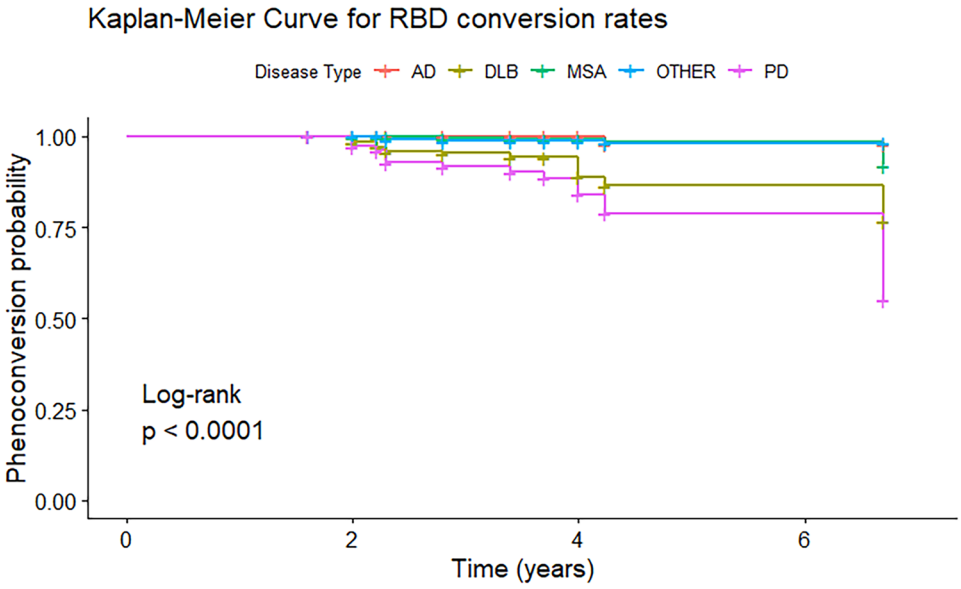

Fig. 5 Kaplan–Meier Analysis Stratified for Disease Type (*Note*. AD: Alzheimer's disease; DLB: dementia with Lewy bodies; MSA: multiple system atrophy; PD: Parkinson's disease)

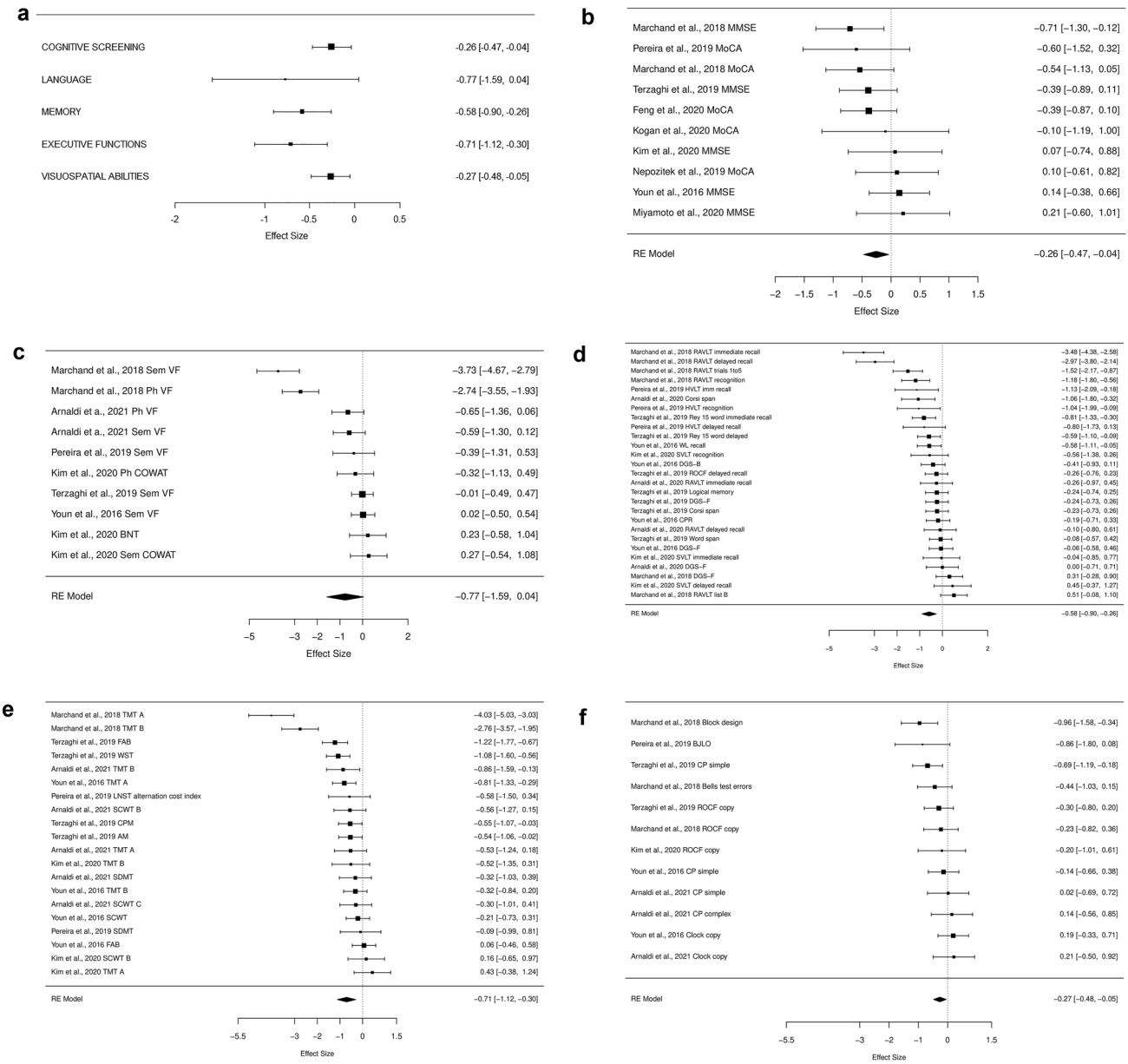

Fig. 6 Graphical Representation of the Main Results for Longitudinal Studies: **a** Cognitive Domains Summary Forest Plot for Longitudinal Studies, **b** Cognitive screening Forest Plot for Longitudinal Studies (*Note*. MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment), **c** Language Forest Plot for Longitudinal Studies (*Note*. BNT: Boston Naming Test; COWAT: Controlled Oral Word Association Test; Ph VF: Phonemic Verbal Fluency; Sem VF: Semantic Verbal Fluency), **d** Memory Forest Plot for Longitudinal Studies (*Note*. CPR: Constructional Praxis Recall; DGS-B: Digit Span Backward; DGS-F: Digit Span Forward; HVLT: Hopkins Verbal Learning Test; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey Complex Figure; SVLT: Shiraz Verbal Learning Test; WL: Word list), **e** Executive Function Forest Plot for Longitudinal Studies (*Note*. AM: Attentive Matrices; CPM: Raven's Coloured Progressive Matrices; FAB: Frontal Assessment Battery; LNST: Letter-Number Sequencing Test; SCWT: Color Word Stroop Test; SDMT: Symbol Digit Modalities Test; TMT: Trail Making Test; WST: Wisconsin Card-Sorting Test), and **f** Visuospatial Abilities Forest Plot for Longitudinal Studies (*Note*. BJLO: Benton Judgment of Line Orientation; CP: Constructional Praxis; ROCF: Rey Complex Figure)

2000). These results are partly in line with the previous literature. Indeed, the cognitive domains generally reported as most affected in iRBD are memory and executive functions (Ferini-Strambi et al., 2004; Gagnon et al., 2009; Li et al., 2016, 2018a, b; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). Some studies have also reported poorer performance in visuospatial abilities in iRBD patients compared to HC (Fantini et al., 2011; Ferini-Strambi et al., 2004; Youn et al., 2016), but this was not always observed (Gagnon et al., 2009; Massicotte-Marquez et al., 2008; Terzaghi et al., 2008). Here, we confirmed memory

and executive functions as two of the most impaired domains in iRBD patients compared to HC.

Since executive functions represent a broad and highly heterogeneous cognitive domain, we additionally performed an analysis based on its subdomains, showing that the most severe impairments within this category were specific to processing speed. This is in line with the slowness in information processing previously reported in DLB patients, which has been shown to be both a marker useful for differentiating synucleinopathy from AD and normal aging, as well as a marker of progression from MCI to DLB (McKeith et al., 2017). Moreover, speed processing alterations have been found in PD, even from the initial stages of the disease (Johnson et al., 2016). The PD literature coined two different terms to refer to speed processing alterations: "bradyphrenia" and "slowness in information processing" (Johnson et al., 2016; Shipley et al., 2002). Remarkably, a study of Arroyo and collaborators (Arroyo et al., 2021), which investigated the nature of this slowness, assessed different components of these processes in a stimulus–response pathway (i.e., motor, perceptual-alertness, response strategy-inhibition, decisional, visual search, and control of interference). They found an impairment in PD patients compared to HC in the simplest stages of processing, particularly in the motor and perceptual-alertness components. The results of our meta-analysis support this finding, and revealed the presence of speed processing impairment already in the prodromal stage of synucleinopathies. This result is important as it means that speed processing may play a role in the prediction of phenoconversion. Future longitudinal studies should investigate more in depth speed processing and its components as potential phenoconversion biomarkers.

We also found a large and unexpected difference in cognitive screening performance between iRBD patients and HC, which may be ascribed to several factors. One possible explanation is that studies including a comprehensive neuropsychological assessment generally do not discuss findings on cognitive screening, but rather insist on more specific, and consequently more informative, cognitive tests (Campabadal et al., 2019; Her et al., 2019; Marcone et al., 2019; Sasai-Sakuma et al., 2017). Second, cognitive changes based on screening tests in iRBD are subject to conflicting results in the literature due to the inclusion (Dušek et al., 2019; Mollenhauer et al., 2019; Sasai-Sakuma et al., 2020) or exclusion (Bang et al., 2017; Campabadal et al., 2019; Sunwoo et al., 2017) of iRBD patients with MCI. Future studies should investigate this issue more closely. Since MCI may be in some cases a reversible condition (Koepsell & Monsell, 2012; Lin & Chen, 2018; Postuma et al., 2012; Saredakis et al., 2019), it may be questionable to exclude MCI patients from iRBD samples; instead, it would be more appropriate to report the number of iRBD with concomitant MCI, if any. For example, in the cross-sectional studies included in our meta-analysis, the number of MCI patients included at baseline was often not reported (Cochen De Cock et al., 2020; Her et al., 2019; Pereira et al., 2019; Sasai-Sakuma et al., 2017). Another factor that may have led to conflicting results are the differences in the clinical characteristics of iRBD samples, especially the time passed since diagnosis. Given that cognitive performance worsens over time in iRBD (Marchand et al., 2017, 2018; Terzaghi et al., 2019; Zhang et al., 2019), the time that has passed since the diagnosis of iRBD is an important factor to consider. Yet, several of the cross-sectional studies in our meta-analysis did not specify the years since diagnosis (Ellmore et al., 2013; Her et al., 2019; Pereira et al., 2019; Vendette et al., 2012). Furthermore, none of the longitudinal studies provided information about the average age of symptoms onset for iRBD subjects who converted to a dementia-first versus a parkinsonism-first phenotype during follow-up. Future studies should provide a more detailed clinical characterization of patients that convert to the different phenotypes.

The second part of this study focused on longitudinal studies. First, we aimed to quantitatively estimate the phenoconversion risk in iRBD patients. The Kaplan–Meier survival analysis revealed an estimated hazard rate of 73.7% after 7 years of follow-up. The most frequent conversion phenotype was PD (56.83%), followed by DLB (31.65%), which is in line with a previous meta-analysis (Galbiati et al., 2019). Second, we aimed to evaluate the risk of phenoconversion based on neuropsychological assessment. In agreement with previous studies (Marchand et al., 2017, 2018; Terzaghi et al., 2019; Youn et al., 2016), our results showed that converted patients had lower scores at baseline in the executive domain compared with patients who did not yet convert. This may suggest a predictive role played by executive functions as a marker of progression. Another consideration regards cognitive screening, which despite the lower performance found in cross-sectional studies, did not allow to distinguish between converted and still-isolated patients at follow-up. Several studies found no significant changes from baseline to follow-up in cognitive screening in iRBD patients (Campabadal et al., 2020; Kogan et al., 2020; Pereira et al., 2019; Youn et al., 2016). This may be due to a possible test–retest effect on the major cognitive screening tests. Of note, 2 of the 11 longitudinal studies reported a positive trend from baseline to follow-up in the cognitive screening scores (Kogan et al., 2020; Youn et al., 2016). The lack of prediction from the cognitive screening tests may also be due to the fact that cognitive screening assessment is not sensitive enough to detect changes taking place over time on the alpha-synuclein spectrum.

Importantly, some studies reported an association between the presence of MCI at baseline and the future development of a neurodegenerative disease, particularly the dementia-first phenotype (Arnaldi et al., 2021; Marchand et al., 2017; Postuma et al., 2019; Rahayel et al., 2021; Terzaghi et al.,

2013). In this study, we therefore aimed to assess the role of MCI as a predictor of conversion. Only 3 of 11 longitudinal studies provided information about the number of MCI patients at baseline between those who converted to a manifest synucleinopathy during follow-up versus those who remained disease-free (Arnaldi et al., 2021; Nepozitek et al., 2019; Terzaghi et al., 2019). These 3 studies tested 163 iRBD patients, of which 40 had concomitant MCI. Importantly, because of the small sample size, our results should be interpreted with caution until more studies with larger sample sizes become available. In our analysis, we found that iRBD patients with MCI had a three-fold increased risk of phenoconverting compared to patients without MCI. MCI therefore represents a risk factor for phenoconversion, in line with the previous literature (Arnaldi et al., 2021; Marchand et al., 2017; Postuma et al., 2019; Terzaghi et al., 2019). Of note, only 2 of the 3 studies (Arnaldi et al., 2021; Terzaghi et al., 2019) adopted the same criteria for MCI, based on the guidelines from the Movement Disorder Society Task Force for the diagnosis of MCI (Litvan et al., 2012); the study by Nepozitek and collaborators instead used a MoCA cutoff for diagnosing MCI based on Czech normative data (Kopecek et al., 2017). Future work should aim at applying similar diagnostic criteria in order to ease comparability of findings between studies.

When considering longitudinal studies, one issue was the impossibility to compare patients who converted to a parkinsonism-first versus those who converted to a dementia-first phenotype since only two studies provided values for the conversion subtypes (Marchand et al., 2018; Terzaghi et al., 2019). The inability to assess conversion phenotypes separately may have prevented us from observing a differential pattern of cognitive impairments in those who developed DLB versus PD. An impairment in visuospatial and visuoperceptive abilities in iRBD patients, which have been observed along the spectrum of α-synucleinopathies, has been reported in several cross-sectional studies (Ehgoetz Martens et al., 2020; Fantini et al., 2011; Ferini-Strambi et al., 2004; Plomhause et al., 2014). In particular, DLB patients show lower performance on this cognitive domain (Beretta et al., 2019; Salmon et al., 2020). It is therefore possible that visuospatial deterioration may represent a specific feature of prodromal DLB but not of prodromal PD and that the inability to distinguish between the two groups may have explained the lack of an association between visuospatial performance and phenoconversion.

Future studies should report separate data for the type of conversion in order to identify neuropsychological measures able to predict dementia-first and parkinsonism-first patients. Moreover, the use of the same updated criteria for the definition of prodromal PD or DLB is of the utmost importance. Indeed, the longitudinal studies included in our meta-analysis employed different criteria to establish the type of phenoconversion: two out of ten longitudinal studies, including converted patients at follow-up, did not report the criteria used to assess the conversion (Pereira et al., 2019; Youn et al., 2016); the remaining eight studies applied different criteria for the parkinsonism diagnosis. In five studies (Feng et al., 2020; Kim et al., 2020; Kogan et al., 2020; Marchand et al., 2018; Terzaghi et al., 2019) parkinsonism was diagnosed according to the United Kingdom PD Society Brain Bank criteria (Gibb & Lees, 1988; Hughes et al., 1992). Finally, only three studies (Arnaldi et al., 2021; Miyamoto et al., 2020; Nepozitek et al., 2019) applied more recent PD criteria of the Movement Disorder Society (Postuma et al., 2015). Meanwhile, for the diagnosis of DLB all eight studies used the fourth consensus report of the DLB Consortium (McKeith et al., 2017). Therefore, in order to improve the accuracy of the diagnosis of PD and to obtain comparable data, future studies should apply up to date diagnostic criteria.

Another relevant aspect would have been the assessment of neuropsychological performance changes over time (from baseline to follow-up), separately for still-isolated patients, patients who converted first to PD, and those who converted first to DLB. Indeed, this would have been important in order to separate patients with similar neuropsychological profiles at baseline but with a different progression of cognitive impairment, which may have led to different phenoconversions. However, given that only one study provided this information (Marchand et al., 2018), neuropsychological trajectories could not be drawn.

The assessment of methodological quality and of risk of bias revealed some above-mentioned important aspects that we have considered to discuss our results: the variability in the inclusion/exclusion of MCI condition, the employment of different criteria to establish the type of phenoconversion, the incompleteness of clinical characterization of iRBD samples, especially concerning the time passed since diagnosis, and the use of different neuropsychological measures–probably the factor that caused the most heterogeneity. Indeed, the cognitive screening domain for longitudinal studies was the domain with the lowest value of heterogeneity and it was characterized by the highest level of homogeneity between neuropsychological questionnaires.

This meta-analysis had a statistical limitation to consider: to evaluate how cognitive status may predict the development of a neurodegenerative disease, we performed a Cox proportional hazards analysis using simulated data. Specifically, the use of artificially generated data comes with some disadvantages, because it can only approximate real-studies results. For this reason, a difference between real data and simulated data should be taken into account (see supplementary materials Table 1 for further details).

Finally, the present meta-analysis focused on the cognitive alterations occurring in iRBD patients. However, there are also many non-cognitive markers and risk factors related to phenoconversion in iRBD. A multicenter study published in 2019 (Postuma et al., 2019) tested 19 potential non-cognitive predictors. Of these, abnormal quantitative (adjusted HR = 3.16) and standardized (adjusted HR = 3.03) motor testing, olfactory impairment (adjusted HR = 2.62), erectile dysfunction (adjusted HR = 2.13), motor symptoms (adjusted HR = 2.11), abnormal DaT scan (adjusted HR = 1.98), color vision abnormalities (adjusted HR = 1.69), constipation (adjusted HR = 1.67), RSWA (adjusted HR = 1.54) and advanced age (adjusted HR = 1.54) were all associated with an increased risk of conversion during follow-up (Postuma et al., 2019). Additionally, a recent multicenter follow-up study explored the role of several environmental and life-style risk factors for phenoconversion in 281 PSG-confirmed iRBD patients. The authors concluded that only advanced age (adjusted HR = 1.05) and nitrate derivatives use (adjusted HR = 2.18) were associated with an increased risk of conversion at follow-up (Zhang et al., 2022). In both studies, patients who converted first to PD and those who converted first to dementia showed similar risk profiles (Postuma et al., 2019; Zhang et al., 2022), with the only difference being found for cognition (Postuma et al., 2019). Efforts have been made towards the identification of highly sensitive and specific markers that predict conversion phenotypes in iRBD, including electrophysiology (i.e., RSWA quantification, sleep micro- and macro- structure, wakefulness EEG activity), neuroimaging (i.e., ^{123}I-FP-SPECT, ^{18}F-FDG-PET, MRI), motor (i.e., motor scales, upper extremity alternate tap-test, gait dysfunction, speech abnormalities) and autonomic (i.e., autonomic questionnaires, ^{123}I-MIBG-SPECT) functioning, olfactory (i.e., odor identification tests) and ocular (i.e., optical coherence tomography, pupillometry) functions, genetic (i.e., GBA variants, SNCA variants), biofluid (i.e., CSF RT QuIC, nasal swabs RT QuIC, serum neuronal exosomal a-synuclein) and tissue biopsy (i.e., colon biopsy, tissue biopsy, major and minor salivary glands) (for a comprehensive review see Ferini-Strambi et al., 2019 and Miglis et al., 2021). The identification of both cognitive and non-cognitive risk factors and markers of conversion is crucial to monitor disease progression and to timely predict its future clinical trajectories.

In conclusion, our meta-analysis on cross-sectional studies identified lower cognitive performance in iRBD patients compared to HC in cognitive screening and memory. In longitudinal studies, iRBD patients who converted to a neurodegenerative disorder showed reduced performances in executive function at baseline. Moreover, our results highlighted the role of MCI at baseline as predictor of future conversion. Thus, iRBD patients with reduced performances in executive functions, as well as those with MCI, should be closely monitored because of their high conversion risk, as already suggested in previous studies (Marchand et al., 2017, 2018; Terzaghi et al., 2019; Youn et al., 2016). Further longitudinal studies reporting comprehensive neuropsychological assessment both at baseline and follow-up are needed to evaluate changes over a long time period in large cohorts of iRBD patients. This, together with a detailed characterization of iRBD samples, can provide a crucial insight into the dynamic of the neuropsychological changes that occur over time and their association with the future progression to a specific neurodegenerative disease.

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Author Contribution Andrea Galbiati devised and directed the study. Material preparation, data collection and analysis were performed by Caterina Leitner and Giada D'Este. Laura Verga and Shady Rahayel contributed to the interpretation of the results. The first draft of the manuscript was written by Caterina Leitner with support from Andrea Galbiati and Giada D'Este. All authors commented on previous versions of the manuscript, provided critical feedback, and helped shape the research. Finally, all authors read and approved the final manuscript.

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Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval This declaration is "not applicable".

Competing Interests We have no known conflict of interest to disclose.

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