A Systematic Review and Meta-analysis on the association between orthostatic hypotension and mild cognitive impairment and dementia in Parkinson's Disease

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Abstract

Background. Cognitive impairment is a frequent disabling feature of Parkinson's disease (PD). Orthostatic hypotension (OH) is treatable and may be a risk factor for cognitive impairment.

Objective. We conducted a Systematic Review and Meta-analysis to examine the relationship between OH with PD-associated Minimal Cognitive Impairment (PD-MCI) and Dementia (PDD) and assess the mitigating effects of potential confounding factors.

Methods. Observational studies published in English, Spanish, French, or Portuguese up to January 2022 were searched for in PubMed, EBSCO, and SciELO databases. The primary aim of this study was to revise the association between OH with PD-MCI and PDD. Alongside, we assessed OH as related to cognitive rating scales. Fixed and random models were fitted. Meta-regression was used to assess the mitigating effects of confounding variables.

Results. We identified 18 studies that reported OH association with PDD or PD-MCI, 15 of them reporting OH association with cognitive rating scales. OH was significantly associated with PDD/PD-MCI (OR, 95% CI: 3.31, 2.16-5.08; k=18, n=2251; p<0.01). OH association with PDD (4.64, 2.68-8.02; k=13, n=1194; p<0.01) was stronger than with PD-MCI (1.82, 0.92-3.58; k=5, n=1056; p=NS). The association between OH and PD-MCI/PDD was stronger in studies with a higher proportion of women and in those with a lower frequency of supine hypertension. Global cognition rating scale scores were lower in patients with OH (SMD, 95% CI: -0.55, -0.83/-0.26; k= 12, n= 1427; p<0.01).

Conclusions. Orthostatic hypotension shows as a significant risk factor for cognitive impairment in PD, especially in women and patients not suffering from hypertension**.**

Keywords: Parkinson's disease; Dementia; Minimal Cognitive Impairment; orthostatic hypotension; hypertension; sex

Introduction

Cognitive impairment is six-fold more frequent in patients with Parkinson's Disease (PD) than in otherwise healthy individuals and includes subjective cognitive decline, mild cognitive impairment (PD-MCI), and dementia (PDD) [1]. Its progression shows great heterogeneity as subjective cognitive decline or PD-MCI may precede PD diagnosis or appear several decades later [1]. In 50 to 70 years old patients at PD diagnosis, PDD cumulative prevalence is 17% and 83% in the 5 and 20 years after [2, 3]. Cognitive impairment can severely affect the quality of life and daily performance, with serious economic consequences [4, 5], calling for early diagnosis and intervention. Male sex, low education level, and disease severity are major factors of cognitive impairment and are non-modifiable [1].

Orthostatic hypotension (OH) affects 30% to 80% of PD individuals and is an allegedly modifiable risk factor for cognitive impairment [6]. Yet, certain issues were not adequately addressed. In the first place, the association of PD-MCI has not been examined. Furthermore, to what extent sex, age, disease duration, or comorbidities affects association strength of OH-cognitive impairment also remains unexplored. The present Systematic Review and Meta-analysis revises the relationship of OH with PD-MCI and PDD and examines the moderating effects of potential confounding factors.

Methods

Search strategy

This Systematic Review and Meta-analysis was conducted under the Guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 [7]. The protocol for this study was registered at PROSPERO (CRD42021245947).

We searched PubMed, EBSCO, and SciELO databases for studies published in English, Spanish, French, and Portuguese up to September 2022. The complete search strategy is online shared as Supplemental Material. Reference lists of relevant reviews and original articles were considered for more studies as well.

Selection criteria

We included observational studies that assessed the relationship between OH and impaired cognition in PD with or without prospective or retrospective follow-up. Dementia could be defined by the DSM-IV [8], the MDS criteria [9], or by a validated global cognitive rating scale like the Mini-Mental State Examination [10]. PD-MCI had to be diagnosed following the MDS criteria [11]. Studies using validated scales to assess global cognitive function or relevant cognition subdomains were included as well [10].

Only studies that defined OH based on blood pressure changes after standing up or during a till-test were considered. When available, Consensus was used to define OH, v.g.: systolic blood pressure or diastolic blood pressure fall of at least 20 mm Hg or 10 mm Hg within 3 minutes of standing [12, 13]. Studies that defined OH only based on systolic or diastolic blood pressure changes were also considered.

Data extraction and Quality assessment

We retrieved the following information from each study: authors, year of publication, country, PD diagnosis criteria, OH diagnosis and assessment, PDD, PD-MCI, cognition rating scales used and the corresponding outcome, study design, follow-up duration (if any), sample size,

male participants proportion, participants mean age, secondary causes of OH (i.e., diabetes and other polyneuropathies, exposure to drugs with hypotensive side-effects, amyloidosis, and alcoholism), tobacco use, antiparkinsonian treatments, including L-DOPA-equivalent daily dose, age at PD diagnosis, PD duration, mean UPDRS II, III, and II+III scores, and Hoehn & Yahr scores.

The risk of bias assessment was performed with the ROBINS-I ("Risk Of Bias In Non-randomized Studies - of Interventions") scale [14].

Data extraction and risk of bias assessment were conducted by two independent investigators, any disagreement being resolved by a third party.

Statistical analysis

The main outcome of this study was the association between OH with PD-MCI and PDD. The summary measure was the Odds ratio with 95% confidence interval. We also assessed the association between OH and cognitive rating scales. We analyzed the scales, evaluating global cognitive function or attention, frontal executive function, memory, and visuospatial function subdomains. Results were expressed as standardized mean differences and averaged when multiple scales were used to evaluate global function or subdomains. Missing data were not imputed. When available, adjusted data were also analyzed.

Mantel-Haenszel and inverse variance estimators were used to calculate summary measures in fixed-effects models of binary and numeric variables, respectively. Random-effects models were calculated using the DerSimonian-Laird estimator. Analyses were performed using R 4.1.1 (R Foundation, Vienna, Austria) "meta" and "metasens" packages [15]. If significant heterogeneity was found, as measured with the Q-test and I^2 statistic [16], random effect models were used. Funnel plots and Egger regression were used to evaluate publication bias. The following subgroup analyses were scheduled: cross-sectional vs. cohort studies, OH as by the Consensus [12, 13] vs. other definitions, dementia by the MDS criteria [9] vs. other criteria, and patients on antiparkinsonian medications vs. "de novo" patients. Meta-regression was used to assess moderating effects of the year of publication, the male proportion among

participants, mean age of participants, proportion of patients with OH-related comorbidities, mean L-DOPA-equivalent daily dose (LDED), mean PD duration, mean UPDRS II, III, or II+III scores, and mean Hoehn & Yahr score.

Results

Our bibliographical searches identified 25 studies fulfilling all inclusion and exclusion criteria (Figure 1) [17-39], involving 3156 patients, with a mean n=121 per study (range 18-456, Table 1). Of them, 18 studies reported the association between OH and PDD or PD-MCI, whereas 15 reported the association between OH and cognitive rating scales. Table 1 shows the characteristics of these studies. Four studies were prospective cohorts, and the rest used a cross-sectional design. Twenty-two studies used the Consensus to diagnose OH; 6 and 3 studies used the MDS criteria to define PDD and PD-MCI, respectively.

A random-effect analysis found a significant association between OH and PDD or PD-MCI (OR, 95% CI: 3.31, 2.16-5.08; k=18, n=2251; p<0.01, Figure 2). Heterogeneity was high (I^2=66%). The association between OH and PDD (4.64, 2.68-8.02; k=13, n=1194; p<0.01) was stronger than with PD-MCI (1.82, 0.92-3.58; k=5, n=1056; p=NS), as revealed by a test for subgroup differences (Chi-sq= 4.43, p=0.04, Figure 2). A Harbord test did not suggest any significant publication bias (t=1.45, df=16, p=0.16). The funnel plot is available in the Online Supplemental Material (Figure E-1).

Adjusted data were available only in 4 studies of PDD (Hussain et al., 2018; Daida et al., 2018; Tanaka et al., 2020; Longardner et al., 2022) and 1 of PD-MCI (Kang et al., 2021). The most significant confounding variables were age, sex, education, comorbidities, and disease severity or duration. A random-effects model showed a significant association between OH and PD-MCI/PDD (1.76, 1.36-2.27; k=5, n= 821; p<0.01, Figure E-2). The unadjusted association between OH and PD-MCI/ PDD in this dataset was (5.51, 3.26-8.65; k=5, n=821, p<0.01).

Meta-regression analysis found that the proportion of male sex in the sample of each study, the proportion of subjects with supine hypertension in the sample of each study, and the mean PD duration affected the strength of the association between OH and PD-MCI and PDD (Table E-1). A final meta-regression analysis showed that when all these variables were considered at the same time, PD duration was not significant anymore (Table 2). Furthermore, this model accounted for all heterogeneity. A subgroup analysis confirmed that the association between

OH and cognitive impairment was stronger in those studies with a proportion of males < 55% in their samples (Figure 3). Furthermore, as shown in Figure 4, the association was also stronger in studies with a proportion of participants with supine hypertension below 31%.

Figure 5 depicts the associations between OH and cognitive assessment outcomes. Scores of global cognition rating scales were lower in patients with OH, as disclosed by a random-effect analysis (SMD, 95% CI: -0.55, -0.83/-0.26; k= 12, n= 1427; $p<0.01$). Heterogeneity was high ($I^2=73\%$, $p<0.01$). No significant effects of OH on attention, executive, memory, or visuospatial orientation subdomains were found.

Discussion

In our systematic review and meta-analysis, we observed a significant association between OH and cognitive decline in PD patients, thus confirming previous findings [40, 41]. The association was statistically significant for PDD, but not for PD-MCI. Statistically significant associations were found for OH with global cognitive scores, but not with scores for cognition subdomains. When women not suffering from supine hypertension prevailed, the association between OH and PDD or PD-MCI was stronger.

The main limitation of our study is that most reports analyzed were cross-sectional, more prone to bias than others. Yet, our meta-regression analysis did not reveal any design effect. As every study examined had a high risk of bias, at least in one domain, well-designed, prospective studies will be necessary to confirm our findings. We could not assess the effects of other important confounding factors like depression, detrimental to cognitive function [42]. Finally, most of the reviewed studies did not segregate the effect of neurogenic OH vs. OH secondary to drugs or other conditions (i.e., non-neurogenic OH). The studies from Longardner et al. [38] and Kang et al. [37] focused on patients with neurogenic OH and found significant associations with PDD and PD-MCI, respectively. Tanaka et al. found an increased risk of PDD both in patients with neurogenic and non-neurogenic OH [21].

The mechanisms underlying OH effects on cognitive impairment are not clear. A recent study showed that white matter hyperintensities (WMH), which reflect small vessel disease, are involved in the effects of diastolic orthostatic hypotension and autonomic dysregulation, partly in this case, on cognitive decline in PD patients [32] likely due to brain hypoperfusion. Brain hypoxia leads to cerebrovascular damage and favors neurodegenerative processes in patients with dementia [43]. Notwithstanding, one trial found that cerebral microbleeds, related to small vessel disease, could not fully account for OH association with PDD [27]. Similarly, Pilotto et al, could not demonstrate a relationship between WMH and OH in a sample of 384 patients suffering from PD or DLB [44]. More research is therefore needed to clarify the mechanism mediating the effect of OH on cognitive function. Interestingly, we observed that the effects of OH were independent from those of hypertension, which is also known to cause vascular damage and increase the risk of dementia [45]. One study reported that the effects of supine hypertension on the risk of PDD disappeared when the variable was placed into a multivariate model including OH [21]. These findings suggest that the presence of supine hypertension cannot explain the effects of OH.

We observed that OH association with PD-MCI was less strong than with PDD. While curious, this may suggest that OH might influence progression rather than initiation of the degenerative process leading to PDD.

We also found that OH related more closely with cognitive impairment in studies with lower men proportion. Sex differences in blood pressure effects on cognitive impairment have been rarely studied. This is, to the best of our knowledge, the first time these are observed in PD. In agreement with our observation, one systematic review disclosed that at high midlife systolic blood pressure, women had a greater risk of all-cause dementia compared with men [46]. The reasons for this remain obscure. As cerebral small vessels disease is more frequent in males [47], our observations should be related to non-vascular factors. More research is warranted.

We also analyzed the association between OH and scores of cognition rating scales. While the expected association with global rating cognition scales was confirmed, no correlation was observed with cognition subdomains rating scales. Two studies reported data on the scores

of both global and subdomain cognition rating scales [26, 48] and found that OH effects on global cognition were larger than on cognition subdomains. These results are difficult to interpret, deserving further research.

Finally, it is worth mentioning that autonomic dysfunction leading to OH is not the only factor connected with cognitive impairment in neurodegenerative diseases. A recent study in patients with idiopathic autonomic failure, a condition that may convert into other forms of neurodegenerative disease, found no relationship between OH and WMH, which were connected with cognitive impairment [49].

Conclusion

Our systematic review and meta-analysis disclosed a significant association between OH and cognitive impairment in PD. As it might be more striking in women, earlier and more aggressive interventions should be encouraged upon OH development in them. Our results also suggest that, for unknown reasons, OH may have a mild effect at the beginning of the neurobiological process leading to PDD.

Statements and Declarations

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Author roles

Research project= SPLL, OJP

Data collection and evaluation= DL, RB

Data analysis= SPLL, SB, LG

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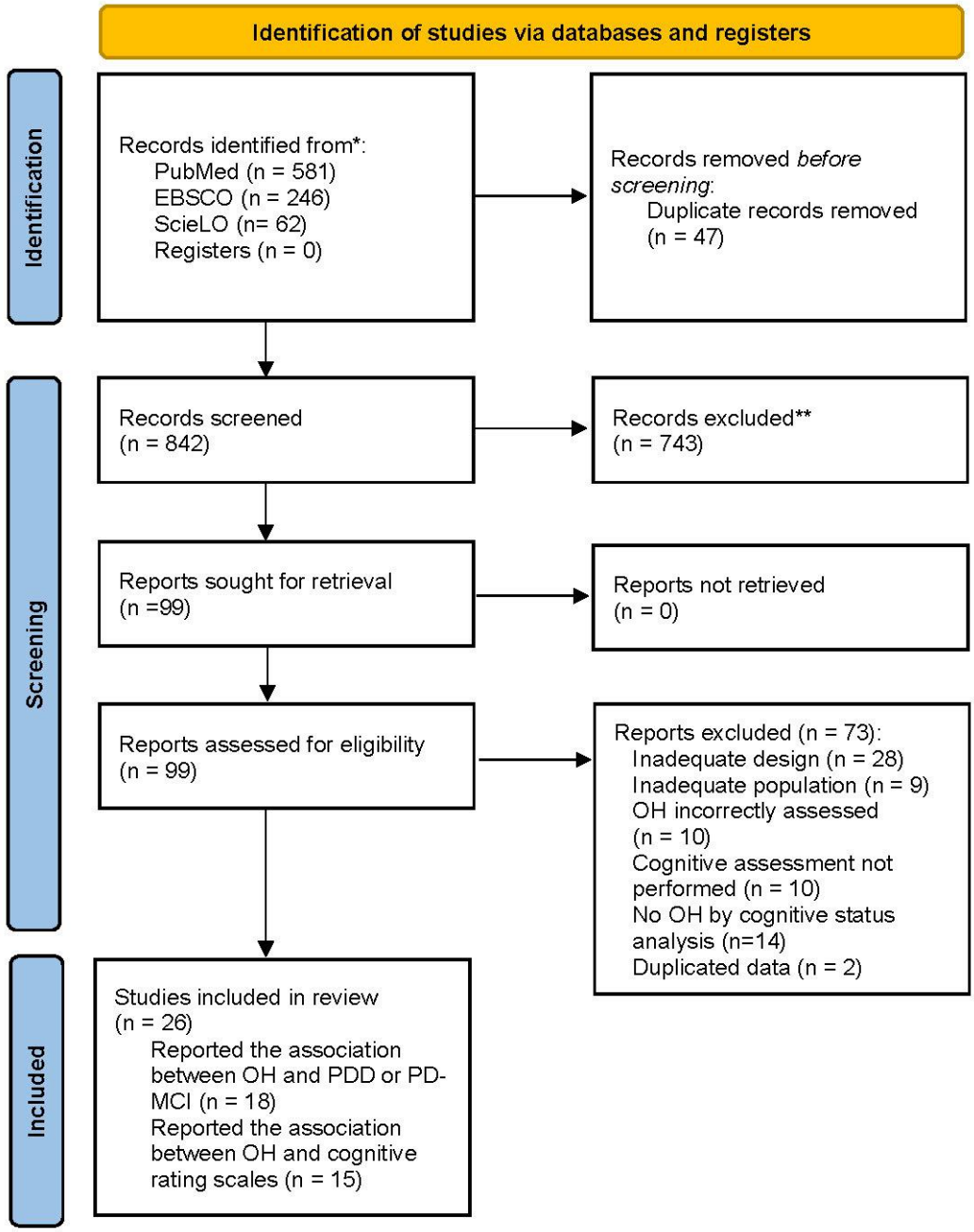


Figure 1. PRISMA flow diagram

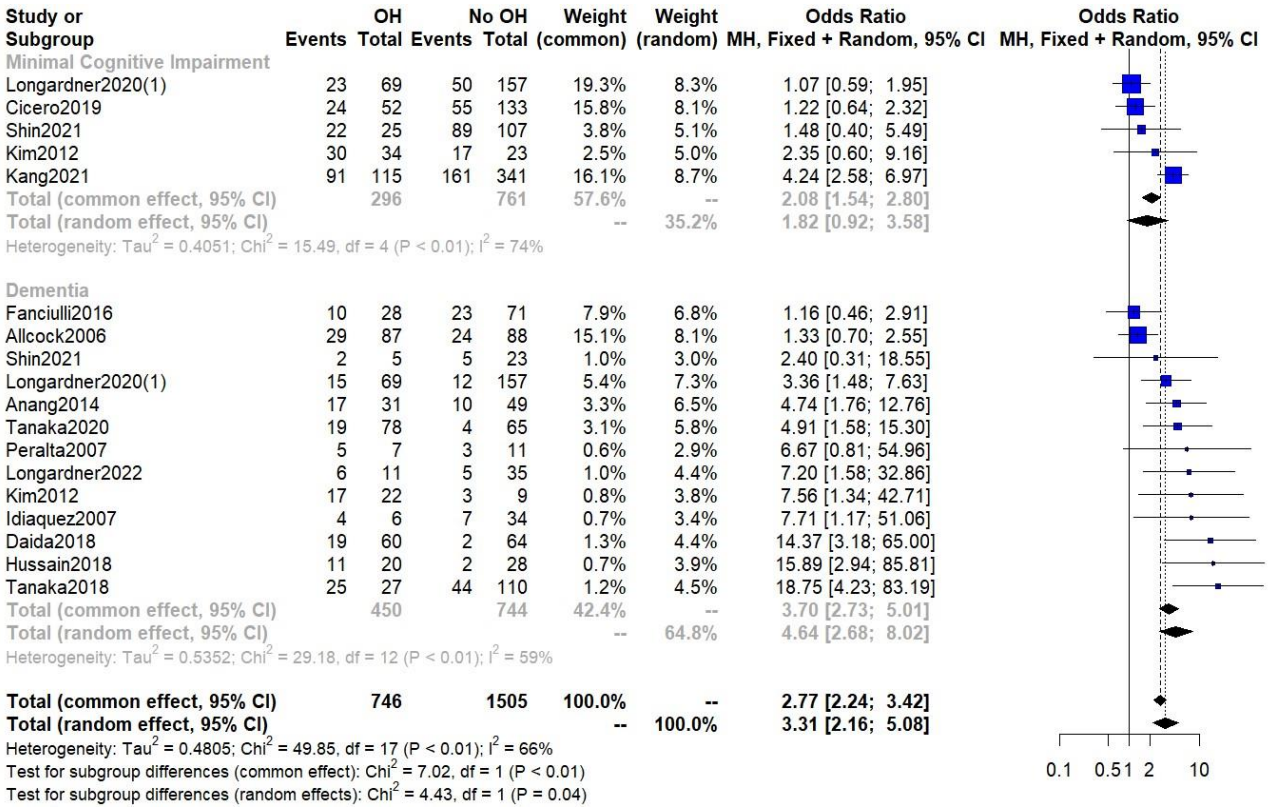


Figure 2. Forest plot of the association between orthostatic hypotension and cognitive impairment in PD.

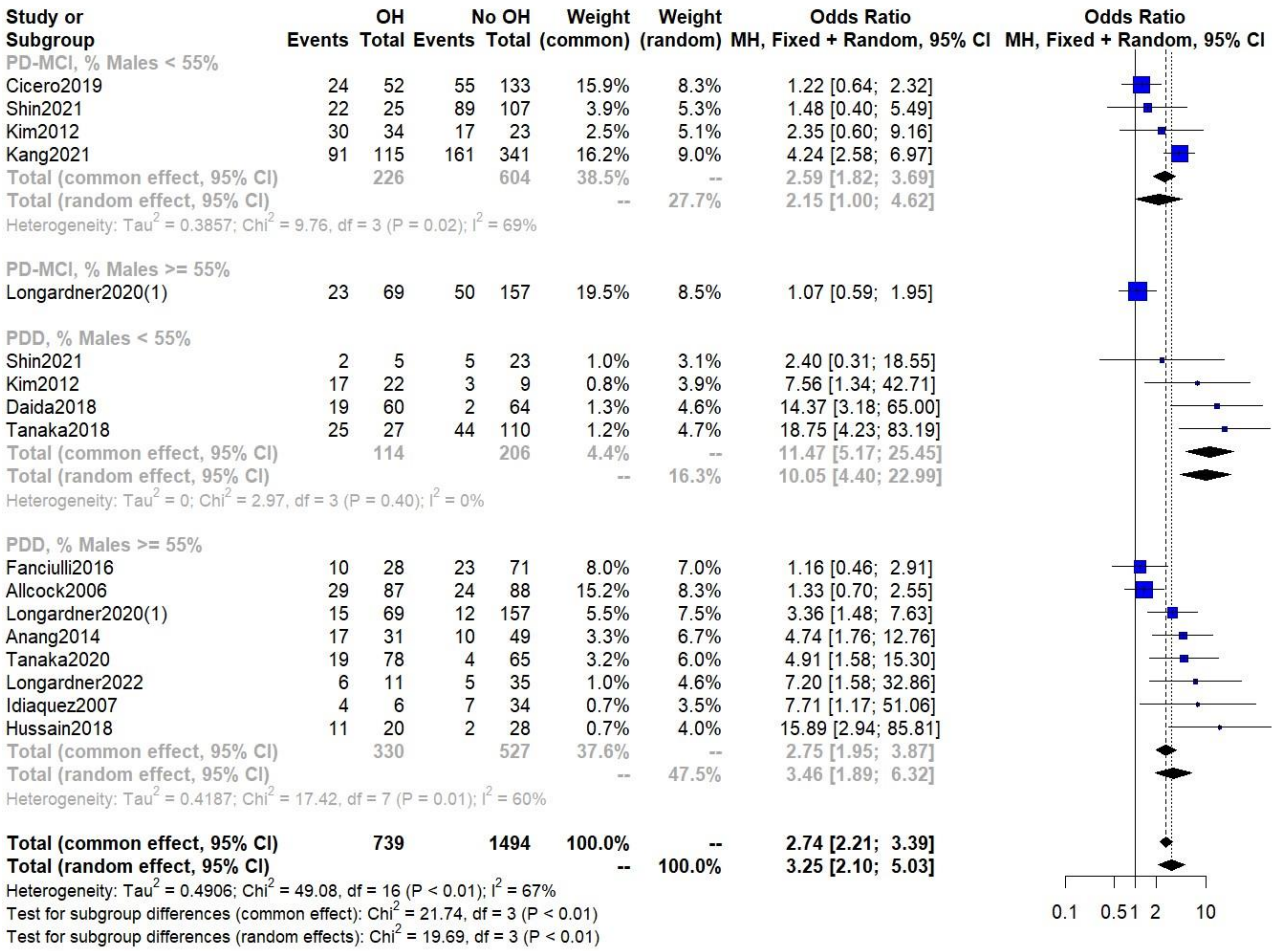


Figure 3. Forest plot of the association between orthostatic hypotension and cognitive impairment (subgroup analysis). The subgroups were defined according to the type of cognitive disorder and the median value of the % of males in the sample (i.e., 55%).

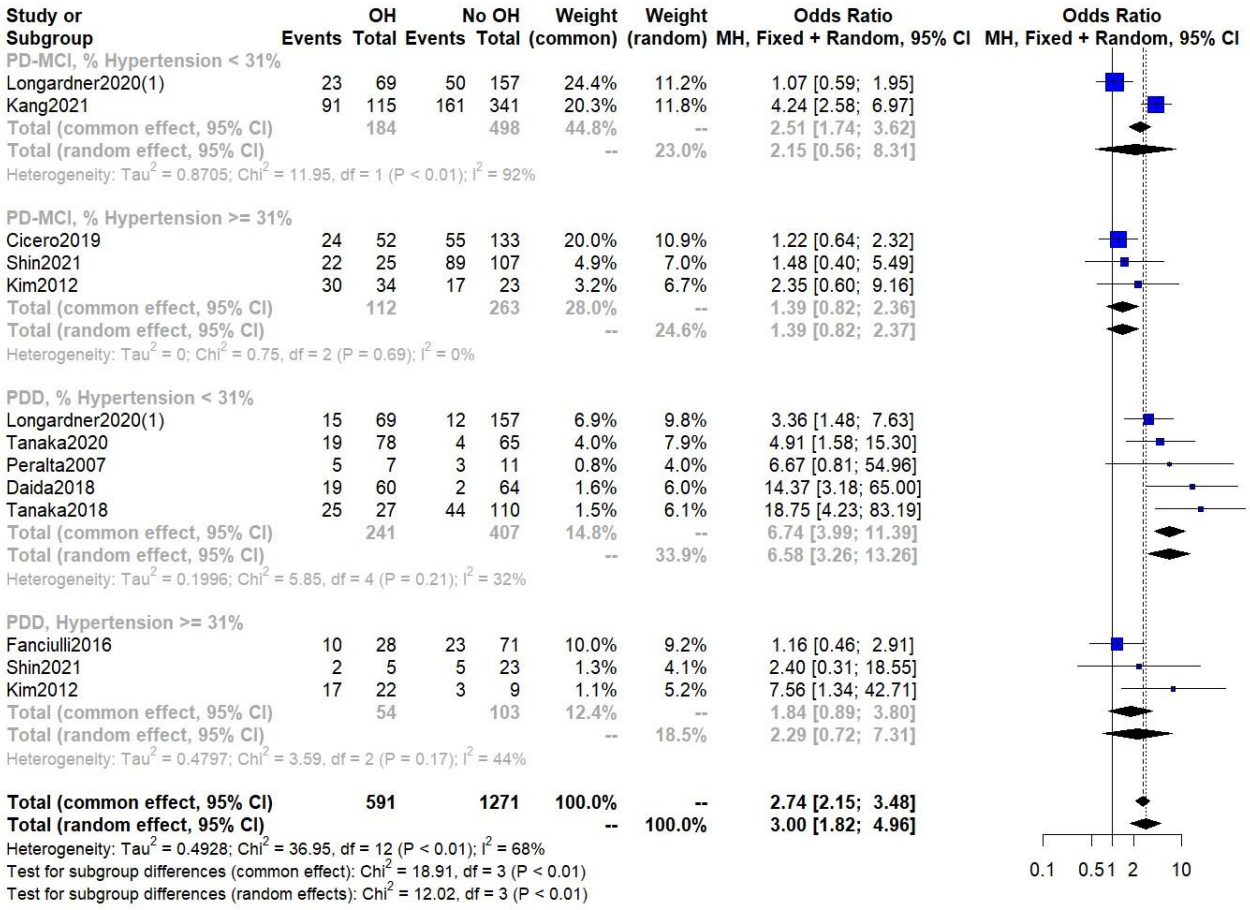
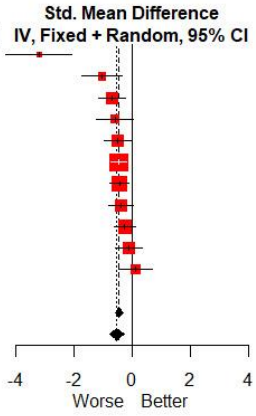


Figure 4. Forest plot of the association between orthostatic hypotension and cognitive impairment (subgroup analysis). The subgroups were defined according to the type of cognitive disorder and the median value of the % of hypertension in the sample (i.e., 31%).

A. Global cognitive assessment

Study	TE	SE	Weight (common)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
Shin2021	-3.22	0.5851	1.4%	3.7%	-3.22 [-4.37; -2.07]
Centi2017	-1.04	0.3506	3.8%	7.0%	-1.04 [-1.73; -0.36]
Chen2020	-0.71	0.2330	8.5%	9.7%	-0.71 [-1.17; -0.25]
Longardner2020(2)	-0.60	0.3259	4.4%	7.6%	-0.60 [-1.23; 0.04]
Yin2022	-0.51	0.2304	8.7%	9.8%	-0.51 [-0.96; -0.06]
Longardner2020(1)	-0.47	0.1461	21.7%	11.9%	-0.47 [-0.76; -0.18]
Tanaka2020	-0.45	0.1700	16.0%	11.3%	-0.45 [-0.78; -0.11]
Kim2012	-0.39	0.2243	9.2%	10.0%	-0.39 [-0.83; 0.05]
Umehara2018	-0.26	0.1932	12.4%	10.8%	-0.26 [-0.64; 0.12]
Oka2020	-0.13	0.2330	8.5%	9.7%	-0.13 [-0.58; 0.33]
Pilleri2013	0.12	0.2892	5.5%	8.4%	0.12 [-0.45; 0.68]
Total (fixed effect, 95% CI)			**100.0%**	**--**	**-0.46 [-0.59; -0.33]**
Total (random effects, 95% CI)			**--**	**100.0%**	**-0.53 [-0.79; -0.28]**

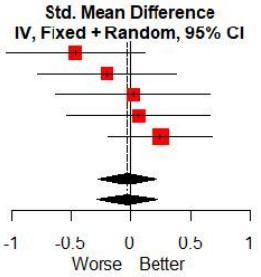
Heterogeneity: $Tau^2 = 0.1248$; $Chi^2 = 33.61$, df = 10 (P < 0.01); $I^2 = 70\%$



B. Attention Domain

Study	TE	SE	Weight (common)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
Pilleri2013	-0.46	0.2952	18.3%	18.5%	-0.46 [-1.04; 0.11]
Yoo2019	-0.20	0.2963	18.2%	18.3%	-0.20 [-0.78; 0.38]
Centi2017	0.02	0.3301	14.7%	14.9%	0.02 [-0.62; 0.67]
Bae2014	0.07	0.3070	16.9%	17.1%	0.07 [-0.54; 0.67]
Kim2012	0.25	0.2237	31.9%	31.2%	0.25 [-0.19; 0.69]
Total (fixed effect, 95% CI)			**100.0%**	**--**	**-0.03 [-0.27; 0.22]**
Total (random effects, 95% CI)			**--**	**100.0%**	**-0.03 [-0.28; 0.22]**

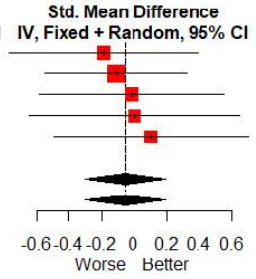
Heterogeneity: $Tau^2 = 0.0037$; $Chi^2 = 4.18$, df = 4 (P = 0.38); $I^2 = 4\%$



C. Executive domain

Study	TE	SE	Weight (common)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
Yoo2019	-0.19	0.2962	18.0%	18.0%	-0.19 [-0.77; 0.39]
Kim2012	-0.11	0.2231	31.8%	31.8%	-0.11 [-0.55; 0.32]
Pilleri2013	-0.01	0.2899	18.8%	18.8%	-0.01 [-0.58; 0.55]
Centi2017	0.00	0.3301	14.5%	14.5%	0.00 [-0.64; 0.65]
Bae2014	0.11	0.3056	16.9%	16.9%	0.11 [-0.49; 0.70]
Total (fixed effect, 95% CI)			**100.0%**	**--**	**-0.05 [-0.30; 0.19]**
Total (random effects, 95% CI)			**--**	**100.0%**	**-0.05 [-0.30; 0.19]**

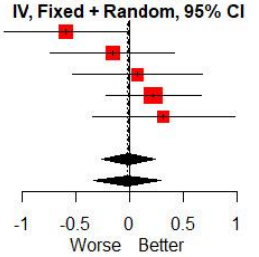
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.59$, df = 4 (P = 0.96); $I^2 = 0\%$



D. Memory domain

Study	TE	SE	Weight (common)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
Pilleri2013	-0.59	0.2965	18.4%	19.3%	-0.59 [-1.17; -0.01]
Yoo2019	-0.16	0.2958	18.5%	19.4%	-0.16 [-0.74; 0.42]
Bae2014	0.08	0.3069	17.1%	18.4%	0.08 [-0.53; 0.68]
Kim2012	0.23	0.2251	31.9%	26.7%	0.23 [-0.22; 0.67]
Centi2017	0.32	0.3376	14.2%	16.2%	0.32 [-0.34; 0.98]
Total (fixed effect, 95% CI)			**100.0%**	**--**	**-0.01 [-0.26; 0.24]**
Total (random effects, 95% CI)			**--**	**100.0%**	**-0.02 [-0.33; 0.30]**

Heterogeneity: $Tau^2 = 0.0459$; $Chi^2 = 6.22$, df = 4 (P = 0.18); $I^2 = 36\%$



E. Visuospatial orientation domain

Study	TE	SE	Weight (common)	Weight (random)	Std. Mean Difference IV, Fixed + Random, 95% CI
Kim2012	-0.19	0.2228	37.1%	37.1%	-0.19 [-0.63; 0.24]
Yoo2019	-0.13	0.2955	21.1%	21.1%	-0.13 [-0.71; 0.45]
Pilleri2013	-0.05	0.2890	22.0%	22.0%	-0.05 [-0.62; 0.52]
Bae2014	0.18	0.3049	19.8%	19.8%	0.18 [-0.42; 0.77]
Total (fixed effect, 95% CI)			**100.0%**	**--**	**-0.07 [-0.34; 0.19]**
Total (random effects, 95% CI)			**--**	**100.0%**	**-0.07 [-0.34; 0.19]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.00$, df = 3 (P = 0.80); $I^2 = 0\%$

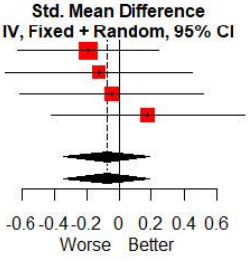


Figure 5. Forest plots of the associations between OH and results of the cognitive assessment tests.

Table 1. Characteristics of th [17]e studies included in the systematic review.

ID	Study design	OH assessment	Cognitive rating scales available	Dementia assessment	MCI assessment	Sample size	Males (%)	Mean age	Diabetes (%)	Hypertension (%)	"De novo" population	Mean LDED	Mean PD duration	Mean UPDRS III score
Kim 2012	Cross-sectional	Consensus	MMSE, CDR	MDS criteria	>1 alteration in a cognitive domain	87	35 (40%)	67.5	19 (22%)	27 (31%)	Yes	-	1.8	22.4
Li 2019	Cross-sectional	Consensus	MoCA	No	No	150	78 (52%)	64.7	33 (22%)	60 (40%)	No	351.0	4.0	27.3
Peralta 2007	Cross-sectional	Consensus	-	MMSE < 24 1-y after PD diagnosis	No	18	-	75.5	1 (6%)	2 (11%)	No	-	7.0	-
Pilleri 2013	Cross-sectional	Consensus	MMSE, FAB, TMT B-A, Corsy test, Verbal Fluency, ROCF, RAVLT	No	No	48	26 (54%)	65.3	-	9 (19%)	No	966.6	11.6	37.6
Tanaka 2018	Cross-sectional	Consensus	-	MDS criteria	No	137	74 (54%)	64.1	14 (10%)	29 (21%)	No	957.0	10.9	-
Umehara 2018	Cross-sectional	Consensus	MMSE	No	No	110	37 (34%)	74.0	-	50 (45%)	Yes	-	1.7	21.6
Anang 2014	Cohort	Consensus (1 min)	-	MDS criteria	MDS criteria	80	51 (64%)	66.2	-	-	No	-	5.7	24.0
Hussain 2018	Cohort	Consensus	-	Decline in neurpsy-chological assessment	No	48	27 (56%)	71.5	-	-	No	632.0	8.9	16.6
Idiaquez 2007	Cross-sectional	Consensus	-	DSM-IV	No	40	26 (65%)	69.0	-	-	No	-	11.2	27.2
Centi 2017	Cross-sectional	Consensus	WTAR, Digit Span, Arithmetic test, verbal fluency, Symbol Search test, CERAD, Hemifield Line Test, Line Bisection Test	No	No	35	22 (63%)	65.0	-	13 (37%)	No	553.1	6.2	-
Daida 2018	Cross-sectional	Consensus	-	MDS criteria	No	124	57 (46%)	63.6	11 (9%)	29 (23%)	No	960.0	10.9	-
Fanciulli 2016	Cross-sectional	Consensus	-	MDS criteria	No	99	66 (67%)	74.0	-	66 (67%)	No	450.0	4.3	-
Allcock 2006	Cross-sectional	SBP drop >= 20 mmHg or SBP	MMSE, Working memory, verbal memory	MMSE < 24	No	175	109 (62%)	70.8	-	-	No	349.7	4.3	17.7

		standing <= 90 mmHg												
Bae 2014	Cross-sectional	Consensus	-	No	No	45	17 (38%)	63.8	-	-	Yes	-	1.3	-
Chen 2020	Cross-sectional	Consensus	MMSE, MoCA	No	No	101	58 (57%)	66.6	-	35 (35%)	No	277.0	3.0	19.5
Cicero 2019	Cross-sectional	Consensus	-	No	MDS criteria	185	102 (55%)	64.6	27 (15%)	66 (36%)	No	355.0	5.6	31.7
Dadar 2020	Cohort	Consensus	MoCA	No	No	365	251 (69%)	60.5	16 (4%)	95 (26%)	Yes	-	0.6	20.7
Longardner 2020 (1)	Cross-sectional	Consensus	MoCA	MoCA < 21	MoCA < 26	226	149 (66%)	66.7	-	69 (31%)	No	-	5.2	27.1
Longardner 2020 (2)	Cohort	Consensus	MoCA	MoCA < 21	MoCA < 26	42	29 (69%)	61.2	-	-	No	-	2.9	21.1
Oka 2020	Cross-sectional	Consensus	MMSE	No	No	75	27 (36%)	72.2	0 (0%)	30 (40%)	Yes	-	1.6	20.3
Shin 2021	Cross-sectional	Consensus	MMSE	MDS criteria	MDS criteria	154	79 (51%)	70.2	27 (18%)	66 (43%)	No	50.0	1.0	14.9
Tanaka 2020	Cross-sectional	Consensus	MMSE, MoCA	MDS criteria	No	143	80 (56%)	63.7	-	32 (22%)	No	956.3	10.9	-
Yoo 2019	Cross-sectional	Not defined	MMSE, CDR, Seoul Battery, Digit Span, Trail Making test, Stroop test, COWAT, TMT, BNT, Rey Complex Figure test, Seoul Verbal learning test	No	No	47	25 (53%)	69.5	4 (9%)	19 (40%)	Yes		1.0	14.1
Kang 2021	Cross-sectional	Consensus	-	No	MDS criteria	456	198 (43%)	70.8	104 (23%)	111 (24%)	No	-	-	23.9
Longardner 2022	Cohort	Consensus	MoCA	MoCA < 21	No	50	30 (60%)	64.3	-	-	No	935.1	12.8	28.2
Yin 2022	Cross-sectional	Consensus	MMSE; MoCA	No	No	116	67 (57%)	66.8	13 (11%)	27 (31%)	No	340.0	3.23	26.9

Table 2. Final meta-regression model

Variable	Estimate	Standard Error	p-value
% of hypertensives in the sample	-3.50	1.32	0.008
% of males in the sample	-4.64	1.55	0.003
Mean PD duration	0.04	0.08	0.59
PDD vs PD-MCI	1.21	0.30	<0.001

R^2 (amount of heterogeneity accounted for)= 100%, I^2 (residual heterogeneity)=0%.

Supplemental Online Material

Table E-1. Results of meta-regression testing

Variable	Beta coefficient (SE)	p-value	Number of studies
Cohort vs cross-sectional design	0.63 (0.73)	0.39	17
Year of publication	0.05 (0.04)	0.29	17
OH defined by the consensus vs other	0.84 (0.62)	0.19	17
Dementia defined by the MDS criteria vs other	0.31 (0.53)	0.55	15
Proportion of males in the sample	-6.24 (2.04)	<0.01	16
Mean age of the sample	-0.07 (0.06)	0.29	17
Proportion of diabetes in the sample	2.90 (5.90)	0.63	9
Proportion of hypertension in the sample	-4.61 (1.42)	<0.01	13
De novo population	0.42 (0.78)	0.58	17
Mean PD duration of the sample	0.14 (0.06)	0.01	17
Mean LDED of the sample (adjusted for disease duration)	-0.003 (0.005)	0.54	9
Mean UPDRS III score of the sample	-0.002 (0.05)	0.95	12

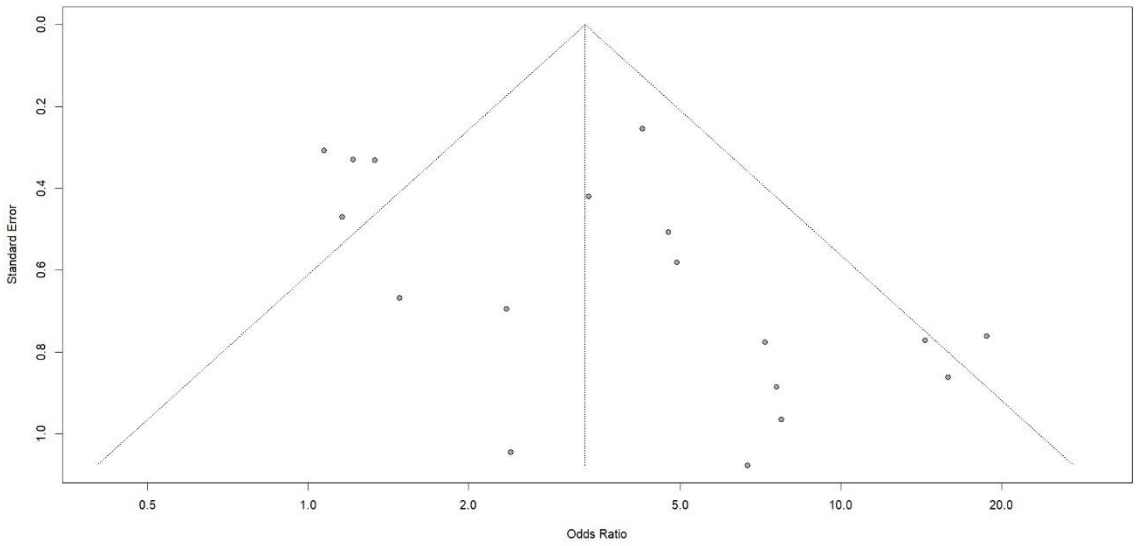


Figure E-1. Funnel plot of the association between orthostatic hypotension and cognitive impairment in PD. A Harbord test failed to disclose a significant asymmetry in the plot (p=0.24).

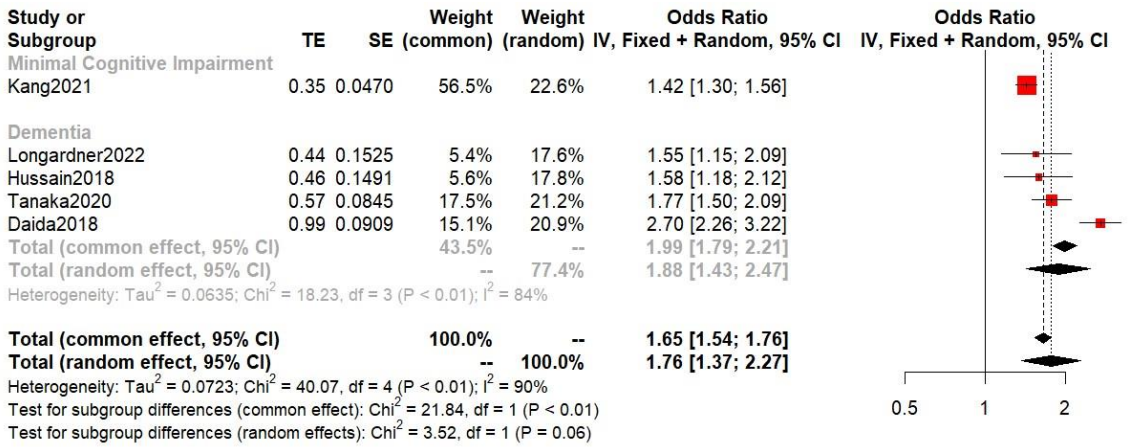


Figure E-2. Forest plot of the association between orthostatic hypotension and cognitive impairment in PD adjusting for covariates.