REVIEW

Subjective Cognitive Complaints in Parkinson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT: Background: Subjective cognitive complaints (SCCs) in Parkinson's disease (PD) are reported frequently, but their prevalence and association with changes on objective testing are not fully known.
Objective: We aimed to determine the prevalence, clinical correlates, and predictive value of SCCs in PD.
Methods: We conducted a systematic review and meta-analysis. From 204 abstracts, we selected 31 studies (n = 3441 patients), and from these, identified the prevalence, clinical features, associations with neuropsychiatric symptoms, and predictive values of SCCs in PD.
Results: The meta-analysis showed an SCC prevalence of 36%. This prevalence, however, was significantly moderated by study heterogeneity regarding female sex, disease severity, levodopa equivalent daily dosage, exclusion from the overall sample of patients with objective cognitive impairment, and measurement instrument. SCC prevalence did not differ between de novo and treated PD patients. SCCs were weakly and negligibly associated with cognitive changes on objective testing in cross-sectional studies. However, in cognitively healthy patients, SCCs had a risk ratio of 2.71 for later cognitive decline over a mean follow-up of 3.16 years. Moreover, SCCs were moderately related to co-occurring symptoms of depression, anxiety, or apathy and were more strongly related to these neuropsychiatric symptoms than objective cognitive functioning.
Conclusion: Our analyses suggest that SCCs in patients with and without objective cognitive impairment are frequent, occurring in more than one third of PD patients. Establishing uniform measurement instruments for identifying PD-related SCCs is critical to understand their implications. Even in cases lacking evidence of objective cognitive impairment and where SCCs might reflect underlying neuropsychiatric symptoms, the possibility of later cognitive deterioration should not be excluded. Therefore, SCCs in PD patients warrant close monitoring for opportunities for targeted and effective interventions.

Key Words: Parkinson's disease; subjective cognitive complaints; mild cognitive impairment; cognitive; non-motor symptoms

Subjective cognitive complaints (SCCs) are defined as a concern of persistent cognitive decline in any domain, with or without objective cognitive deficits.[1,2] SCCs reported by the patient, caregiver, or clinician are a key diagnostic criterion for the diagnosis of mild cognitive impairment (MCI), a transitional stage between physiological aging and dementia.[3] To date, patient-reported SCCs are more frequently studied, as compared to the proxy-reported ones; therefore, in the present meta-analysis, we decided to focus exclusively on these studies on patients' reports.

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People with Parkinson's disease (PD) often report SCCs not only throughout the disease progression but also in the 2 years predating the onset of motor symptoms.[4] Despite the well-known clinical relevance of SCCs in PD, there remain inconsistencies regarding their prevalence and clinical correlates. Notably, prevalence estimates ranging from 15% to 83% have been reported.[5,6]

Cross-sectional studies exploring the association between SCCs and objective cognitive functioning have yielded conflicting results, showing either an association between SCCs and cognitive changes on objective testing[7,8] or no association.[1,9,10] Also, the few available longitudinal reports showed no conclusive evidence of the role of SCCs, in cognitively unimpaired patients, as risk factor for objectively identified cognitive impairment (ie, MCI or dementia).[11-14]

The relationship between SCCs and neuropsychiatric symptoms is also largely debated.[10,15] Some studies suggest that SCCs are associated with neuropsychiatric symptoms more strongly than (clinical or subclinical) cognitive changes on objective testing[1,5,9,16]; this association with neuropsychiatric symptoms persists even in studies excluding patients with clinically relevant neuropsychiatric disorders (eg, major depressive disorder).[9] Moreover, a growing body of evidence has suggested that the treatment of symptoms of depression, anxiety, or apathy can improve aspects of cognitive dysfunction in PD and increase the likelihood to revert from PD-MCI (defined by the co-occurrence of SCCs and objective cognitive impairment) to healthy cognition at follow-up.[17,18]

This high heterogeneity in the literature on SCCs in PD may be explained by differences in study characteristics, patient populations, and/or assessment instruments employed to measure them.[2] Yet a sound and thorough understanding of SCCs in PD is needed to identify patients at risk of cognitive decline and timely engage them with effective interventions and compensatory strategies.

With regard to the growing number of systematic reviews related to SCCs in PD,[2,19-21] a meta-analysis is recommended as a suitable and logical step for providing a statistical ground to any conclusion on this subject. Therefore, the present meta-analysis aimed (1) to provide a reliable estimate of the prevalence rate of SCCs in PD, exploring the role of potential moderators on its variability; (2) to explore the cross-sectional association and predictive value of SCCs for cognitive changes on objective testing; and (3) to investigate the cross-sectional association between SCCs and neuropsychiatric symptoms (ie, symptoms of depression, anxiety, or apathy). Moreover, we compared the strength of the association between SCCs and cognitive changes on objective testing and between SCCs and neuropsychiatric symptoms.

Patients and Methods

Data Collection

A systematic review of research-based literature catalogued in PubMed, Scopus, Web of Science, and PsycINFO (ProQuest) was restricted to peer-reviewed articles in English, supplemented by hand searches of reference lists of all included papers. The entire time scale was used up to June 2023 "Parkinson's disease," and synonyms were cross-referenced with "subjective cognitive complaints" (SCCs) and related search terms (eg, "subjective cognitive decline," "subjective cognitive impairment," "subjective cognitive complaints," "subject cog*," "subjective memory decline," "subjective memory impairment," or "subjective memory complaint") to explore the diverse facets of subjective cognitive functioning: memory, visuospatial abilities, language, and attention and executive functioning. The strings inserted in the search box for obtaining bibliographic materials are presented in Supplementary Material S1. Two independent authors (L.R. and M.S.) evaluated the research-based literature results addressing any disagreement about the eligibility of the studies by discussion or with recourse to two arbitrators (J.G.G. and F.M.). After excluding duplicates and articles judged irrelevant to the title or content of the abstract, we considered for a detailed inspection only studies regarding the SCCs (Fig. 1). The two authors employed an extraction form for deriving quantitative data from selected articles (Supplementary Material S2).

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) 2020 to develop the present systematic review and meta-analysis.[22] The PRISMA 2020 checklists are systematically presented in Supplementary Material S3 for the abstract and main text. However, we did not register our meta-analysis on an international prospective register of systematic reviews (eg, PROSPERO).[23]

Quality Assessment

As reported in previous meta-analyses,[24,25] the quality of primary studies was assessed using the modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.[26,27] QUADAS includes 10 criteria with a score ranging from 0 to 19 with a cutoff level higher than 13 points, meaning methodological acceptability.

Study Eligibility Criteria

In the present meta-analysis, we selected studies meeting these criteria: (1) recruiting adult patients with idiopathic PD, (2) examining the prevalence of SCCs or their (cross-sectional or longitudinal) associations with cognitive changes on objective testing, and (3) using independent samples. Conversely, we excluded studies that (1) included atypical PD or parkinsonian

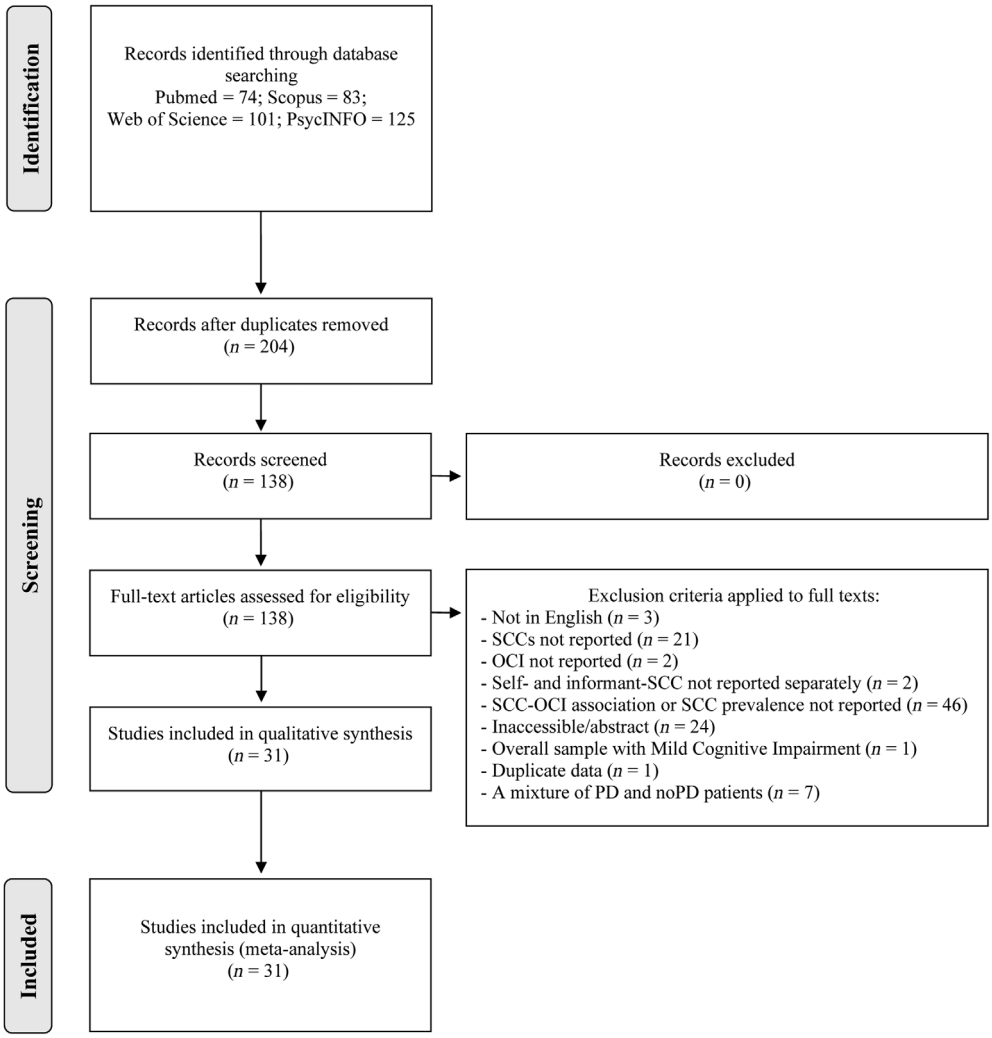

FIG. 1. Flow diagram based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement (www.prisma-statement.org). OCI, objective cognitive impairment; PD, Parkinson's disease; SCCs, subjective cognitive complaints.

syndromes; (2) comprised only PD patients with dementia, psychosis, or mood fluctuations; and (3) did not report the proportion of participants with cognitive impairment (eg, MCI, dementia), such as studies showing means and standard deviations exclusively. In the case of studies that stemmed from the same data set (as in cumulative databases), we included in the meta-analysis only the study with the largest sample size or that had a more extended follow-up period to prevent a disproportional influence of some databases on the results. When the primary studies examined subsamples of patients with and without cognitive impairments on objective testing separately, we selected only data derived from cognitively healthy participants. This strategy of selection was similar to a previous meta-analysis on the same topic[28] and was motivated from two main reasons: (1) to prevent a disproportional influence of some studies/databases on the results and (2) to balance the relative weight of objective cognitive status on the results so that studies including patients with cognitive impairment on objective testing did not overshadow the contributions of studies recruiting cognitively unimpaired patients exclusively.

Statistical Analysis

We analyzed data by random effects models using the inverse variance method. For the first aim, we analyzed prevalence rates reported in primary studies. For the second and third aims, we extracted from each included primary study the Pearson's product–moment correlation coefficients (r) between SCCs and measures of objective cognitive functioning (ie, global cognitive measure, attention and working memory, executive functions, language, memory, visuospatial abilities domains)[3] or neuropsychiatric symptoms (ie, depressive, anxious, and apathetic symptoms). When, in the same study, it was possible to extract more than one effect size for the same measure (eg, cognitive domain), we averaged the resultant effect sizes to obtain a

summary index for that measure. The effect size for r was defined by the following criteria: $r < 0.10$: negligible; $0.10 \leq r < 0.30$: weak; $0.30 \leq r < 0.50$: moderate; $r \geq 0.50$: strong.[29] We tested this part of the analysis using *ProMeta 3* (Intenovi, 2015).

To establish whether patients with SCCs at baseline were more likely than those without it to develop objective cognitive decline, we calculated the overall risk ratio (RR, using *meta* and *meta sense* packages implemented in the *R* software program).[30] RR >1 meant that SCCs were at risk of objective cognitive decline.

Moreover, we used a multivariate meta-analysis approach (using *metaSEM* package implemented in the *R* software program)[31] to test whether the average strength of the Pearson's r correlations of SCCs using the Global Composite Cognitive Score (calculated by averaging all Pearson's r correlations between SCCs and cognitive changes on objective testing) and the Global Composite Neuropsychiatric Score (calculated by averaging all Pearson's r correlations between SCCs and symptoms of depression and/or anxiety and/or apathy) was the same. Because the primary studies did not report the correlations between Global Composite Cognitive and Neuropsychiatric Scores, we used a correlation of 0.5 to calculate the sampling covariance between the effect sizes.[31]

We estimated the heterogeneity among primary studies using Q and I^2 statistic indices.[32] A P-value of Q-test <0.05 meant a lack of homogeneity in the study results. The I^2 expressed the proportion of observed variance that reflected real differences in effect sizes; values of 25%, 50%, and 75% corresponded to low, moderate, and high heterogeneity.[33]

A sensitivity analysis, consisting in estimating how the overall effect size changed when removing one study at a time, was utilized to check the stability of the primary study results.[34] Finally, we employed a funnel plot,[35,36] Egger's test,[37] and trim and fill procedure[38-40] to determine the presence of publication biases. For the categorical moderator analysis of the outcomes, we employed a meta-analytic procedure like a univariate analysis of variance, where the P-value related to the one-way analysis of variance Q-test lower than 0.05 indicated that effect sizes significantly differed among the levels of the moderator.

The categorical moderator analysis was considered only when the heterogeneity exceeded that expected by chance (Q-test <0.05).[34] For the prevalence of SCCs, the levels of categorical moderators (ie, age, education, sex or percentage of female, age at onset, disease duration, Unified Parkinson's Disease Rating Scale [UPDRS, Part III], Movement Disorder Society-UPDRS converted to UPDRS,[41] Hoehn and Yahr [HY] staging system, and levodopa equivalent daily dose [LEDD]) reflected median values or tertiles of primary study scores (if available for at least 90% of study participants), after den Brok et al.[42]

Results

Study Selection

Our search yielded 204 articles after duplicate removal (Fig. 1). Studies were reviewed in full when reporting the prevalence of SCCs, their cross-sectional or longitudinal association with cognitive changes on objective testing, or neuropsychiatric symptoms.

The quality of included studies, assessed using the modified version of the QUADAS tool, and their main characteristics are presented in Supplementary Material S4. In total, 31 studies obtained a QUADAS score higher than 13 points and were selected for our meta-analysis.[1,5-16,43-60] Of these, 15 studies included[6-8,10,12,13,43,47-51,53,55,59] and 9 excluded[9,11,14,15,44,46,54,56,57] patients with objective cognitive impairment, whereas the remaining 7 studies[1,5,16,45,52,58,60] analyzed the data separately for patients with and without objective cognitive impairment. As for this last group of studies, only data from cognitively intact participants were used. Therefore, of the 31 studies selected for our meta-analysis, 15 studies included patients with objective cognitive impairment and 16 studies included cognitively unimpaired patients.

Of the 31 included studies, 20 studies[1,6,9,11-16,43-46,49,60,52,54,56-58] reported the SCC prevalence (number of patients: 2350), 28 studies[1,5,7-11,13-16,43,44,46-60] explored the cross-sectional association between SCCs and cognitive changes on objective testing (number of patients: 3690) or neuropsychiatric symptoms (number of patients: 2438), 21 studies[1,5-11,14-16,43,44,47,49,51,52,56-58,60] investigated the association between SCCs and cognitive changes on objective testing in addition to the association between SCCs and neuropsychiatric symptoms (number of patients: 2362), and 5 studies[11-14,60] reported the risk of SCCs to progress to objective cognitive decline (number of patients: 435).

The assessment methods used for the evaluation of SCCs are presented in Supplementary Material S4.

In line with Burmester et al.,[28] included studies were categorized into three groups (ie, global measures, specific examples, or mixed) based on whether their measure of SCCs consisted of a global question (eg, "Do you feel that you have a declining memory?"),[9-11,14,15,46,54] several specific examples (eg, "Do you often forget appointments?"),[1,5,8,12,13,44,45,47-49,50,51,53,56,57,60] or a combination of both types.[6,7,16,43,52,55,58,59]

SCC Prevalence Estimates

The pooled SCC prevalence was 36% (n = 2350, 95% confidence interval [95% CI] = 30%, 42%) with

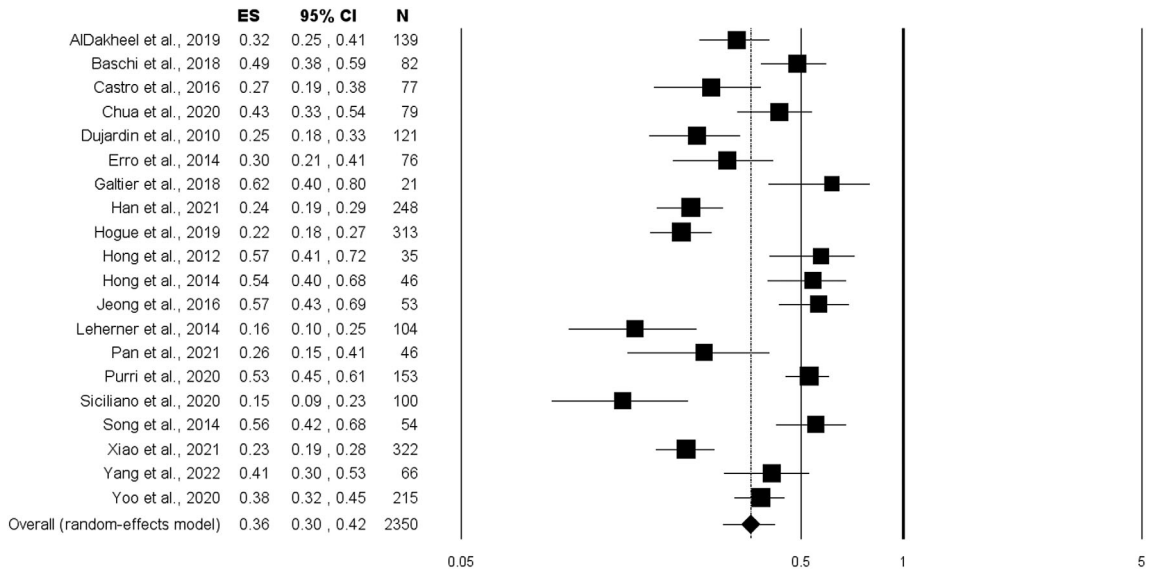

FIG. 2. Forest plot for subjective cognitive complaint prevalence. CI, confidence interval; ES, effect size; N, number of patients for each study.

a high heterogeneity ($Q = 162.12$, $P < 0.001$; $I^2 = 88.28\%$) (Fig. 2). Sensitivity analysis showed a stability of prevalence estimates. The funnel plot was reasonably symmetrical, Egger's test was not significant ($P = 0.117$), and no study was trimmed, consistent with a low risk of publication bias.

Moderators of SCC Prevalence Estimates

The search for the potential influence of variables on prevalence estimates using moderator analysis identified sex (female), HY, LEDD, exclusion of patients with objective cognitive impairment, and measurement instruments to assess SCCs as significant. Particularly, the prevalence of SCCs was higher in studies recruiting samples with a proportion of females higher than or equal to 50%, lower HY, or lower LEDD, excluding patients with objective cognitive impairment, and using global measures of SCCs (compared to specific examples or mixed instruments). Age, education, age at disease onset, disease duration, UPDRS Part III score, or study design did not exert significant effects on prevalence estimates. Moreover, we contrasted studies on de novo[12,45,52,56-58] versus studies on treated PD patients,[1,6,9,11,13-16,43,44,46,49,54,60] and we did not find differences in SCC prevalence estimates (Table 1).

Associations and Predictive Value of SCCs with Objective Cognitive Functioning

SCCs were associated with poor performance on global cognitive tests in 8[5,7,8,16,54-56,59] of 22 studies.[1,5,7-9,11,13-16,43,44,46,49,50,52,54-57,59,60] A separate meta-analysis revealed that SCCs were weakly associated with poor performance on global cognitive tests (Supplementary Materials S5 and S6).

SCCs were associated with poor performance in attention and working memory tests in 3[8,10,60] of 17 studies.[1,7,8,10,11,13-16,43,44,47,49,52,57,58,60] A separate meta-analysis showed that SCCs were weakly associated with attention and working memory functioning (Supplementary Materials S5 and S7).

SCCs were associated with worse performance in tests assessing executive functions in 3[7,8,13] of 19 studies.[1,7-11,13-16,43,44,47-49,52,57,58,60] A separate meta-analysis suggested that SCCs were weakly associated with poorer performance in executive functioning (Supplementary Materials S5 and S8).

SCCs were correlated with poor performance in tests measuring language functioning in 2[7,8] of 16 studies.[1,7-11,13-16,44,49,52,57,58,60] A separate meta-analysis revealed that SCCs were negligibly related to language functioning (Supplementary Materials S5 and S9).

SCCs were associated with detrimental performance in memory tests in 8[7,8,13,44,47,49,50,51] of 20 studies.[1,7,8,10,11,13-16,43,44,47,49,50-53,57,58,60] A separate meta-analysis confirmed a weak association between SCCs and poor memory functioning (Supplementary Materials S5 and S10).

SCCs were associated with detrimental performance in visuospatial abilities tests in 3[7,8,16] of 13 studies.[1,7,8,10,11,14-16,44,52,57,58,60] A separate meta-analysis did not demonstrate an association between SCCs and performance on visuospatial abilities tests (Supplementary Materials S5 and S11).

Sensitivity analysis indicated the stability of the aforementioned meta-analytical findings. Heterogeneity exceeded that expected by chance ($P < 0.05$) at a high level for global cognition and at a moderate level for visuospatial abilities. Trim and fill procedure and Egger's test suggested irrelevant publication bias for all outcomes.

TABLE 1 *Moderator analysis for SCC prevalence estimates*

Moderator	K	SCCs (%)	LL (%)	UL (%)	I^2	Q_w
Age						
High	9	40	30	52	89.35	75.13***
Low	8	29	24	35	74.68	27.65***
Model $Q_b = 3.05$, $P = 0.081$						
Education						
High	7	35	25	45	91.85	73.63***
Low	9	36	25	49	87.56	64.31***
Model $Q_b = 0.05$, $P = 0.827$						
Sex (female)						
Higher than or equal to 50%	5	50	38	62	77.04	17.42***
Lower than 50%	13	31	24	39	88.80	107.19***
Model $Q_b = 6.90$, $P = 0.009$						
Age at onset						
High	5	29	17	44	89.42	37.79***
Low	4	33	23	46	85.71	20.99***
Model $Q_b = 0.20$, $P = 0.657$						
Disease duration						
Long	4	31	18	48	92.00	37.51***
Middle	4	35	18	56	92.81	41.74***
Short	8	40	30	50	85.81	49.32***
Model $Q_b = 0.79$, $P = 0.673$						
UPDRS, Part III						
High	6	35	20	54	92.39	65.66***
Low	7	37	28	48	84.35	38.33***
Model $Q_b = 0.36$, $P = 0.828$						
HY						
High	2	25	20	30	0.00	0.38
Low	9	39	29	51	89.49	72.89***
Model $Q_b = 6.00$, $P = 0.014$						
LEDD						
High	3	25	16	36	77.72	8.98*
Low	5	44	30	60	89.26	37.23***
Model $Q_b = 4.44$, $P = 0.035$						
De novo						
Yes	6	29	23	37	80.18	25.23***
No	14	39	30	48	89.17	119.98***
Model $Q_b = 2.63$, $P = 0.105$						

(Continues)

TABLE 1 *Continued*

Moderator	K	SCCs (%)	LL (%)	UL (%)	I^2	Q_w
Exclusion of OCI						
No	4	23	15	33	79.04	14.31**
Yes	16	39	32	47	88.86	134.68***
Model $Q_b = 6.43$, $P = 0.011$						
Study design						
Multicenter	3	33	20	49	90.90	21.98***
Single center	15	35	28	43	88.87	125.75***
Model $Q_b = 0.06$, $P = 0.812$						
Instrument						
Global measures	6	50	40	60	72.00	17.86**
Specific examples	5	30	20	42	86.45	29.52***
Mixed	9	30	24	36	81.19	42.54***
Model $Q_b = 12.88$, $P < 0.002$						

Abbreviations: SCC, subjective cognitive complaint; K, number of studies; LL, lower limit on a 95% confidence interval; UL, upper limit on a 95% confidence interval; Q and I^2, heterogeneity statistics; UPDRS, Unified Parkinson's Disease Rating Scale; HY, Hoehn and Yahr; LEDD, levodopa equivalent daily dose; OCI, objective cognitive impairment; Q_w, measure of heterogeneity within group; Q_b, measure of heterogeneity between groups.
*P-value <0.05.
**P-value <0.01.
***P-value <0.001.

As for the predictive value of SCCs with objective cognitive decline, over a mean follow-up period of 3.16 years (range: 1–7.5 years), data from five studies for 435 patients[11-14,60] established that cognitively healthy patients with SCCs had an RR of 2.71 [95% CI: 1.82; 4.04] to progress to objective cognitive decline (ie, PD-MCI or PD-dementia diagnosed based on the Level I testing procedures).[3,61] The heterogeneity statistic I^2 is 0.00, and its 95% CI ranges from 0.00% to 79.2%, denoting potentially unimportant to substantial heterogeneity.

Association between SCCs and Neuropsychiatric Symptoms

SCCs were associated with a greater presence of depressive symptoms in 17[1,5,7-10,14,16,43,44,47,49,51,52,56-58] of 21 studies.[1,5,7-12,14-16,43,44,47,49,51,52,56-58,60] A separate meta-analysis revealed that SCCs were moderately associated with depressive symptoms (Supplementary Materials S5 and S12).

SCCs were associated with greater ratings of symptoms of anxiety in 5[1,16,47,56,57] of 9 studies.[1,5,9,12,16,47,52,56,57] A separate meta-analysis revealed that SCCs were moderately associated with anxiety (Supplementary Materials S5 and S13).

SCCs were associated with more marked apathetic symptoms in 3 studies.[1,5,56] A separate meta-analysis revealed that SCCs were moderately associated with apathy (Supplementary Materials S5 and S14).

Sensitivity analysis indicated the stability of the aforementioned meta-analytical findings. Heterogeneity exceeded that expected by chance ($P < 0.05$) at a high level for symptoms of depression, anxiety, and apathy. Trim and fill procedure and Egger's test suggested no publication bias for all outcomes.

As for the comparison between SCCs with cognitive changes on objective cognitive testing (regardless of the specific domain) and the association of SCCs with neuropsychiatric symptoms (independently of specific symptoms), there were 20 studies[1,5,7-11,14-16,43,44,47,49,51,52,56-58,60] from which it was possible to extract the association between SCCs and Global Composite Cognitive Score and between SCCs and Global Composite Neuropsychiatric Score. If we conducted two separate meta-analyses, the overall effects (and their standard errors) of the association between SCCs and Global Composite Cognitive Score and between SCCs and Global Composite Neuropsychiatric Score were 0.17 (0.04) and 0.38 (0.05), respectively. The estimated heterogeneity variances were 80.81 and 89.09 for the Global Composite Cognitive Score and the Global Composite Neuropsychiatric Score, respectively. The results of the multivariate meta-analysis showed that the SCCs were more strongly related to the Global Composite Neuropsychiatric Score than to the Global Composite Cognitive Score, χ^2 $(df = 2) = -7.04$, $P < 0.001$ (Fig. 3).

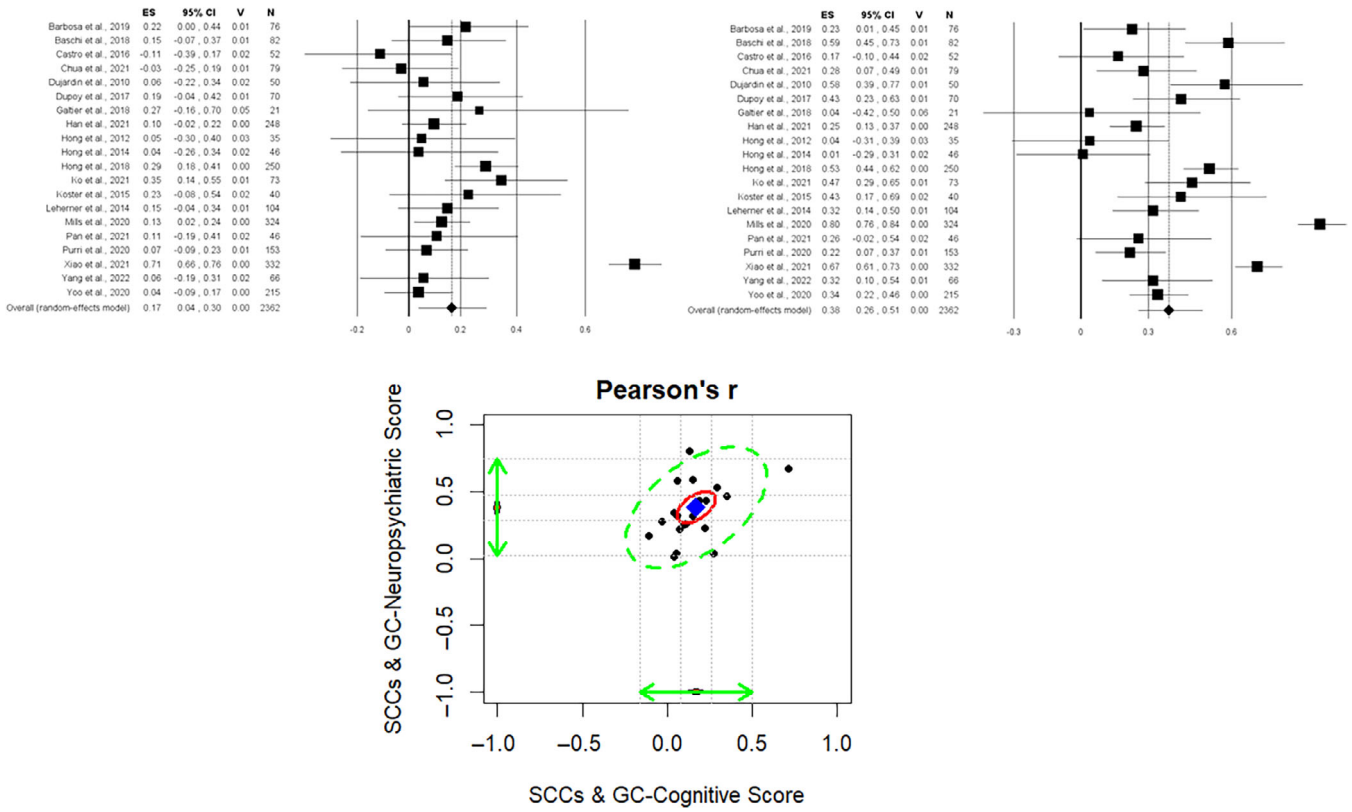

FIG. 3. Plot of multivariate effect sizes (bottom) and forest plots of the associations between subjective cognitive complaints and global composite cognitive score (top left) and between subjective cognitive complaints and global composite neuropsychiatric score (top right). GC, Global Composite; SCC, subjective cognitive complaints. [Color figure can be viewed at wileyonlinelibrary.com]

Moderators of the Associations between SCCs and Objective Cognitive Functioning or Neuropsychiatric Symptoms

The meta-analyses suggested that the subgroup of studies not excluding patients with objective cognitive impairments from the overall sample expressed a "cross-sectional" association stronger (although still weak) for some domains (ie, attention and working memory, language, memory, and visuospatial abilities) than studies that did exclude them. Exclusion of patients with objective cognitive impairment did not moderate the "cross-sectional" associations between SCCs and measures of global cognition, executive functions, and symptoms of depression, anxiety, or apathy (Supplementary Material S15).

The type of measurement instruments (ie, global measures, mixed, and specific examples) moderated the association between SCCs and cognitive changes on objective cognitive domains (ie, attention and working memory, language, memory, and visuospatial abilities) or neuropsychiatric symptoms (ie, depressive) (Supplementary Material S15).

When de novo PD patients were excluded from the study sample, the association between SCCs and cognitive changes on objective testing or neuropsychiatric symptoms did not change (Supplementary Material S15).

Because the exclusion of patients with objective cognitive impairments from the studies that have analyzed the subgroups separately[1,5,16,45,52,58,60] might potentially impact the cross-sectional associations between SCCs and cognitive changes on objective testing or neuropsychiatric symptoms, we also ran supplementary meta-analyses, including all the unselected patients, which confirmed our previous findings (Supplementary Material S16).

Discussion

Prevalence and Moderators of SCCs

The present meta-analysis demonstrated an estimate of SCC prevalence in PD of 36%. This overall prevalence estimate, however, was moderated by sex, measurement instruments, clinical profile, and the exclusion from the study sample of PD patients with objective cognitive impairment.

In detail, the moderator analysis highlighted that more severe cognitive impairment demonstrated by objective testing, greater disease severity, and higher LEDD were associated with a lower prevalence of SCCs. Indeed, the estimation of SCC prevalence decreased to 23% in studies not excluding patients with objective cognitive impairment and increased by 39% in studies recruiting cognitively unimpaired PD patients

exclusively (ie, this last percentage corresponds to patients with "subjective cognitive impairment," defined as the presence of SCCs without objective cognitive impairment on formal testing).[62-64] Our previous study[65] supported a close association between disease severity (ie, HY staging) and objective cognitive functioning; that is, more advanced disease and more severe motor symptoms were related to more marked objective cognitive impairment. Based on these premises, the lower prevalence of SCCs in patients with more severe disease and higher LEDD might be explained by several reasons, including more severe objectively demonstrated cognitive impairment being accompanied by reduced insight/awareness of cognitive changes (ie, fewer SCCs). Another explanation could be that people with advanced disease state and worse motor symptoms might focus more on their motor and other nonmotor issues rather than on SCCs. We did not find any difference in SCC prevalence between studies enrolling only de novo PD patients and those including both medically treated and de novo patients. Therefore, disease severity more than the exposure to dopaminergic therapy might impact on the presence of SCCs.

Measurement instruments to assess the presence of cognitive complaints are another potential moderator of SCC prevalence in PD. Indeed, when SCCs were assessed by questionnaires or interviews rather than one global question, the prevalence estimates decreased (ie, the longer, the more conservative). For example, studies using just one global question to assess SCCs (eg, "Do you feel that you have a declining memory?")[9-11,14,15,46,54] provided prevalence estimates of SCCs (50%) higher than studies relying on longer questionnaires (30%), including several specific examples (eg, "Do you often forget appointments?"),[1,5,8,12,13,44,45,47-49,50,51,53,56,57] or employing a combination of both global and specific questions (30%).[6,7,16,43,52,55,58] These results advocate the need for uniform and validated measurement instruments and diagnostic criteria for defining SCCs in PD[64] and also encourage the need to form a task force for this scope. Moreover, the lack of consensus on research or clinical criteria for SCCs in PD has engendered the use of several terms to refer to them (eg, subjective memory complaints,[15,16] subjective memory impairment,[12] and subjective cognitive decline).[11,19,46]

The moderator effect of sex on prevalence estimate suggests that the occurrence of SCCs is strongly associated with being female. Different interpretations can account for these results; for example, in the general population, SCCs[66,67] are closely related to the presence of neuropsychiatric disorders (eg, major depression), which are in turn twofold more prevalent in women than in men.[68] Therefore, it is likely that sex-related differences in the prevalence of neuropsychiatric disorders and related help-seeking behaviors, as reported in the general population,[69] may determine the higher prevalence of SCCs in female patients with PD. Notably, the association between cognitive impairment (including SCCs) and female sex has also been described in other neurological disorders (eg, Alzheimer's disease). The association between SCCs and sex is thus more likely to be a result of more general factors (eg, estrogen levels) than PD-specific factors.[70] Conversely, we did not find the moderator effect of other demographic variables in SCC prevalence, supporting the view of SCCs as a nonmotor symptom independent of aging or educational attainment.

Association and Predictive Value of SCCs for Objective Cognitive Functioning

We demonstrated that the cross-sectional value of SCCs for indicating concurrent cognitive changes on objective testing is weak. In detail, SCCs were significantly associated (although weakly) with objective cognitive changes on domains such as executive functions, attention/working memory, or memory and no association with more "posterior" cognitive domains (eg, language and visuospatial abilities). This result may be due to the nature of the measurement instruments used to identify SCCs. Indeed, most of the measurement instruments for SCCs in PD focus mainly on complaints related to dopaminergic-mediated fronto-striatal executive impairments or memory abilities, likely underestimating the complaints associated with the remaining cognitive domains, such as visuospatial abilities. This suggests that the available measurement instruments of SCCs in PD may not be sensitive enough to collect subjectively experienced cognitive symptoms in all cognitive domains. Another more speculative explanation of this result is that the presence of posterior cortical deficits is more associated than fronto-striatal impairment to the progression of PD dementia (PD-D),[71-74] which in turn reduces self-awareness of cognitive performance and engenders "cognitive anosognosia."[58]

However, apart from the specific domain, the strength of the "cross-sectional" associations between SCCs and objective cognitive changes did not vary substantially in relation to the exclusion from the study sample of patients with objective cognitive impairment (ie, with reference to the categorical moderator "Exclusion of Objective Cognitive Impairment"). Indeed, this association was low (ranging from weak to negligible), although the studies not excluding patients with objective cognitive impairments reported a "cross-sectional" association stronger for some domains (ie, attention and working memory, language, memory, and visuospatial abilities) compared to the studies that did exclude them. This low association suggests a weak cross-sectional value of SCCs in representing

concurrent (clinical or subclinical) cognitive changes on objective testing. This supports the recommendation that these two dimensions of cognitive functioning should be assessed in PD formally and separately. The absence of patient-reported SCCs cannot guide the choice of whether to perform a neuropsychological assessment. Moreover, SCCs are a criterion for the diagnosis of PD-MCI,[3] and these results support the notion that the inclusion of SCCs in PD-MCI diagnostic criteria (at least those reported by patients) may potentially cloud, rather than clarify, diagnosis and thereby possibly result in high rates of misclassification of PD-MCI, especially in settings where other PD-MCI criteria are not clearly or fully met. Thus, in accordance with the available diagnostic criteria,[3] there is the possibility that patients with mild impairments in cognitive functioning and without SCCs are excluded from PD-MCI diagnosis if informants do not report changes or are not available. Notably, the discrepancy between the patients' SCCs and cognitive changes on objective testing has been called into question by studies in both PD[58,75] and other neurological disorders.[66,67] Therefore, the results of the present meta-analysis, in conjunction with the recent literature, recommend a thorough, formal, and comprehensive assessment of SCCs but also indicate that the criterion of SCCs (at least those reported by patients) might need further consideration when applying the diagnostic criteria for PD-MCI.[67]

Notably, we found that the presence of SCCs, in cognitively healthy PD patients, at baseline has a threefold higher risk of progressing to MCI or dementia ~3 years later, which suggests the value of screening for SCCs as a potential risk marker of subsequent objective cognitive decline in PD.[11,12,14,60]

Association of SCCs with Neuropsychiatric Symptoms

A moderate and significant association was detected between SCCs and neuropsychiatric symptoms; indeed, SCCs were more strongly related to concurrent depressive, anxious, or apathetic symptoms (ie, Global Composite Mood Score) than objective changes on objective testing (ie, Global Composite Cognitive Score). This moderate "cross-sectional" association between SCCs and neuropsychiatric symptoms, regardless of the exclusion from the overall sample of the patients with objective cognitive impairment, suggests that the neuropsychiatric symptoms, and specifically depression, anxiety, and apathy, should always be assessed and managed when SCCs are considered in PD. Moreover, we found that the strength of the relationship between SCCs and neuropsychiatric disorders may change depending on the measurement instruments for SCCs, where more comprehensive measures (ie, questionnaires or interviews rather than one global question) resulted in more robust associations. This further underscores the need for validated and comprehensive measurement tools and diagnostic criteria for SCC.

Study Limitations

Although we used a comprehensive literature search and thoroughly analyzed our data, we are aware that the present meta-analysis has some limitations. First, the literature search was limited to English-language articles, as in large part of the published meta-analyses in PD,[76,77] and focused exclusively on patient-reported SCCs considering the scarce literature on proxy-reported SCCs. Second, the heterogeneity among the included studies in the measures of SCCs contributed to the caution with which conclusions can be drawn. Another limit might lie in the possibility of publication bias for several outcomes, but we found trivial differences between the observed and estimated effect sizes; therefore, the issue of publication bias had likely a limited impact on the present findings. Third, due to the high degree of heterogeneity among studies, some results (eg, the association between SCCs and global cognition) require a cautious approach to interpretation. Moreover, our result concerning the predictive value of SCCs for future cognitive impairments needs confirmation by future studies as it is derived from a small number of reports[11-14,60] that differed in the measurement of SCCs, follow-up duration, and assessment of cognitive performance. Finally, we did not register our meta-analysis on an international prospective register of systematic reviews (eg, PROSPERO),[23] though this registration is not strictly required based on the PRISMA 2020 guidelines.[22]

Conclusions and Future Directions

Our findings show that SCCs occur in more than one-third of patients with PD and might represent a potential risk marker of subsequent cognitive decline. Therefore, even in cases where there was no evidence of objective cognitive impairment and subjective changes in cognitive abilities might be thought to reflect neuropsychiatric symptoms in PD, the possibility of subsequent cognitive deterioration should not be excluded, and patients with SCCs must still be monitored for change and functional impact in PD.[28] In this regard, the early identification and treatment of neuropsychiatric symptoms in clinical care might help address the SCCs and increase the likelihood to prevent the cognitive decline.

In the future perspective, there is a need for recommendations and consensus on how to define and classify SCCs in PD, as different types of SCCs (eg, complaints related to slow thinking, attentive difficulties, or memory) may be differently related to the risk

of subsequent objective cognitive decline. In this context, our meta-analysis emphasizes the monitoring of SCCs as a mandatory step in PD assessment to ensure this symptom is not missed in clinical practice and subsequently managed with adequate protocols.

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Data Availability Statement

Data sharing not applicable-no new data generated.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution;
(2) Statistical analysis: A. Design, B. Execution, C. Review and critique;
(3) Manuscript: A. Writing of the first draft, B. Review and critique.
M.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
A.T.: 3B
F.M.: 3B
J.G.G.: 1A, 3B
L.R.: 1A, 1B, 2A, 3B

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