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Olfactory Impairment and Incident Cognitive Decline: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Olfactory impairment (OI) is associated with poor ageing outcomes. While cross-sectional studies found a high prevalence of OI among patients with neurodegenerative diseases, the temporal relationship remains unclear. This meta-analysis aims to synthesise the longitudinal association of OI with cognitive decline (CD).

Methods: PubMed, Embase and Web of Science were searched through August 9, 2024 for longitudinal studies reporting on self-reported and objectively measured OI in adults, in association with CD, measured using validated methods. The outcome of interest was incident CD. Independent authors extracted data, assessed for bias and graded the strength of evidence. A mixed-effects meta-analysis with subgroup, sensitivity and bias analyses was conducted. The population-attributable fraction (PAF) of OI-associated CD was calculated.

Results: This study included 48 articles and 37,783 participants. OI patients had a 2.06-fold greater risk of any CD (risk ratio [RR] = 2.06; 95% CI = 1.87–2.26, $I^2 = 0\%$), compared to individuals with normal olfaction. Patients with severe OI had a higher risk of any CD (RR = 2.60; 95% CI = 2.12–3.20, $I^2 = 0\%$) than patients with moderate OI (RR = 1.51; 95% CI = 1.23–1.85, $I^2 = 0\%$). The risk of any CD increased by 18% per 10% decrease in olfactory score (RR = 1.18; 95% CI = 1.14–1.22, $I^2 = 24\%$) and by 15% per point decrement on the Sniffin' Sticks Odor Identification Test (RR = 1.15; 95% CI = 1.11–1.18, $I^2 = 0\%$). These results remained robust to supplementary analyses. The PAF of OI-associated incident CD was 18%.

Conclusion: OI may increase the risk of CD, with poorer olfaction linked to greater risks. OI should be assessed as a potential cognitive screening tool, and cognitive screening should be considered in patients with long-standing OI.

Brian Sheng Yep Yeo, Harris Jun Jie Muhammad Danial Song and Benjamin Kye Jyn Tan are joint first authors.

1 | Introduction

Olfactory Impairment (OI) affects approximately one-fifth of individuals worldwide [1, 2]. It influences personal hygiene, food and gas safety, mental health and quality of life (QoL), among other issues [3]. With OI being a prominent symptom of COVID-19 [4], and a considerable number of patients experiencing persistent symptoms, this previously overlooked sensory impairment has been cast into the limelight [5–8]. Concurrently, the incidence of dementia is expected to triple to cross 150 million cases worldwide by 2050 [9]. Both cognitive impairment and dementia are debilitating conditions which may erode the QoL of patients and families, and raise healthcare expenses at individual and national levels [10]. Considering the lack of a definitive cure and the increasing public health concern regarding the burden of cognitive disorders, the identification of risk factors/predictors and emphasis on preventive health have become crucial components of public health strategy.

It has been known for some time now that neurodegenerative diseases and OI are interlinked [11, 12]. Up to 100% of patients with Alzheimer's disease (AD) and more than 95% of patients with Parkinson's disease (PD) have impaired olfaction [11, 12]. However, whether OI is a consequence of the underlying neurodegeneration, or a causal risk factor for neurodegeneration, remains unclear. Recently, some well-adjusted longitudinal studies found an association between baseline OI and the risk of subsequent cognitive decline (CD), cognitive impairment and dementia [13, 14]. While a prior meta-analysis of eight studies by Chen et al. found a 2.37-fold increased risk of CD associated with OI, the authors noted several limitations that constrained the generalisability of their findings, including reliance on unadjusted estimates, substantial heterogeneity, and a lack of bias or quality assessment [15].

The objective of this study was to synthesise the current literature in a systematic review and meta-analysis, to summarise the longitudinal association of olfactory impairment (OI) with CD. Considering the rising prevalence of OI, and the tremendous public health concerns for CD, a comprehensive review of existing evidence is both clinically relevant and timely.

2 | Materials and Methods

2.1 | Standard Protocol Approvals, Registrations and Patient Consents

This review's protocol was registered under PROSPERO (CRD42021279430) and adhered to the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [16]. The PRISMA checklist is reported in Table S1. As this was a meta-analysis of separate primary studies, no individual patient data were used and hence no Institutional Review Board approval or written informed patient consent was required for this study.

2.2 | Search Strategy

We searched PubMed, Embase and Web of Science using search terms related to OI and CD from database inception to August 9, 2024. The full search strategy can be found in Supporting Information.

2.3 | Study Selection

The selection of relevant articles, initially based on titles and abstracts and later through full-text evaluations, was carried out in a blinded manner by various independent authors (BSYY, AS and OTWH). Any disagreements were resolved through consensus with another independent author (HJJMDS). The study selection process was conducted using Rayyan—Intelligent Systematic Review [17], an online systematic reviews platform that allows authors to manually assess records in a blinded manner.

We included full-length peer-reviewed articles that assessed the association between OI and CD, among adults aged at least 18 years, compared to participants with normal olfactory function. We accepted validated measurements (e.g., standardised psychophysical tests such as the Brief Smell Identification Test and the University of Pennsylvania Smell Identification Test) or self-reported measurements of OI. The outcome of interest is incident CD, defined as a composite outcome comprising either an incident decline in test scores of general cognition, incident cognitive impairment, or incident dementia. The following definitions of CD were accepted for inclusion: (1) major neurocognitive disorders, such as dementia and its various subtypes, diagnosed based on clinical diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorder [DSM]); (2) any measure of cognitive function measured through validated tools (e.g., Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]); or (3) cognitive impairment, diagnosed based on accepted clinical diagnostic criteria or through standardised screening questionnaires. We only included observational studies that investigated a longitudinal association between OI and CD. We excluded case–control, cross-sectional or other observational designs that do not distinguish temporality. We also excluded case reports, reviews, meta-analyses, abstracts, conference proceedings, paediatric studies, animal studies and studies published in any language other than English.

2.4 | Data Extraction

The data of interest from included articles were extracted by various independent authors (AS, OTWH and JHC) into a structured format. The information extracted was verified by another independent author (BSYY and HJJMDS). We extracted key data from each article including first author, year published, study design, setting, country, sample size, duration of follow-up, percentage male, mean/median age, method of ascertainment of OI and any summary estimate of cognitive outcomes such as hazard ratios, odds ratios or cognitive test scores.

2.5 | Risk of Bias Assessment

The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale (NOS) by several independent authors (CJWT, AS and OTWH), with differences resolved by another independent author (BSYY and HJJMDS). The NOS employs a nine-point grading system, derived from an eight-item checklist,

to assess the degree of selection, information and confounding biases when evaluating the risk of bias of non-randomised studies [18]. The NOS examines several domains: sample framework, sampling methodology, ascertainment of exposure, demonstration that the outcome of interest was absent at the start of the study, comparability of cohorts, methods of outcome assessment, duration and adequacy of follow-up. The authors assigned a point for each criterion satisfied on the checklist. Studies were classified as having a low, moderate, or high risk of bias based on their scores of 8–9, 5–7 and 0–4 points, respectively.

2.6 | Statistical Analysis

We conducted all analyses using R Studio (version 1.4), using the *meta* and *metafor* packages [19]. We used mixed-effects models to pool maximally covariate-adjusted risk ratios (RRs) from each study to determine the longitudinal risk of CD. Given that hazard and odds ratios numerically approximate one another when follow-up duration, average rate of event and magnitude of risk is low [20], we pooled maximally adjusted hazard ratios and odds ratios together if the above conditions were met. Separately, the standardised mean differences (SMD) of cognitive test scores assessing general cognition were pooled between OI patients at baseline and follow-up, between OI patients and controls at both baseline and follow-up. Unless otherwise specified, we considered a two-sided p-value of ≤ 0.05 as statistically significant. We assessed and considered between-study heterogeneity as significant if the p-value of the Q-test was <0.10 or if the I^2 statistic was $\geq 50\%$ [21, 22].

To investigate potential sources of heterogeneity, we performed subgroup analyses, sensitivity analyses and meta-regression using the following pre-specified study-level characteristics—(1) type of cognitive outcome (decrease in cognitive test score, cognitive impairment and dementia), (2) PD, (3) study setting, (4) study design, (5) continent of study, (6) average age, (7) percentage male, (8) follow-up duration and (9) NOS score. Additionally, leave-one-out influence analyses and cumulative analyses were conducted to investigate the role of individual studies on the overall findings and determine the stability of published data over time, respectively. To investigate small-study effects, we assessed funnel plot asymmetry through visual inspection, imputing potentially missing studies using the trim-and-fill method if publication bias was suspected [23].

Finally, we computed the worldwide population-attributable fraction (PAF) of incident CD associated with OI using the formula: $\text{PAF}(\%) = \frac{p\times(\text{RR}-1)}{p\times(\text{RR}-1)+1} \times 100$, where p represents the global prevalence of OI (22.2%, 95% CI = 14.8%–30.6%) in 2020 reported in a meta-analysis [24], and RR represents the pooled relative risk of incident CD associated with OI based on our meta-analysis. The PAF estimates the percentage of incident CD cases potentially explained by OI, assuming the absence of confounding.

2.7 | Certainty of Evidence

We evaluated the overall certainty of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [25, 26].

3 | Results

The study selection process is summarised in Figure 1. A systematic search of databases identified 1961 records, of which 1250 unique articles were assessed for eligibility using titles and abstracts after de-duplication. The full texts of 85 articles were subsequently evaluated for inclusion. A total of 48 studies comprising 37,783 participants were included [14, 15, 27–72], of which 24 studies were quantitatively synthesised [14, 27–50]. Where multiple studies from the same overarching cohort reported the same outcome of interest, we meta-analysed the study with the largest sample size.

3.1 | Patient and Study Characteristics

Table S2 summarises the patient and study characteristics of included studies. The average age of participants was 68.8 years old, of which 47.2% were male. The mean follow-up duration ranged from 5 months to 10 years. All 48 studies were longitudinal in nature, of which 41 were prospective [14, 38–40, 43, 46–48, 50–72] and seven were retrospective cohort studies [15, 37, 41, 42, 44, 49]. Geographically, 23 studies were conducted in North America [27, 32, 34, 35, 38–42, 45, 46, 48, 52–54, 56, 58, 59, 61, 62, 64–67, 70], 10 in Asia [28, 36, 37, 43, 49, 55, 69, 71, 72], 11 in Europe [15, 29–31, 33, 44, 47, 51, 57, 60, 63, 68] and four in Australia [38, 50, 61, 62]. There were eight studies which investigated the association between OI and CD among patients with PD at baseline [28, 29, 33, 45, 49, 52, 57, 59]. Using the NOS scale, 36 studies had a low risk of bias [14, 15, 27–30, 32, 33, 35–37, 39–46, 48–53, 55, 57, 58, 61, 62, 65, 67, 69–72], 12 studies had a moderate risk of bias [31, 34, 38, 47, 54, 56, 59, 60, 63, 64, 66, 68] and none had a high risk of bias (**Table** S3).

3.2 | Assessment of Cognitive Outcomes

There were 27 studies which assessed dementia outcomes using validated diagnostic criteria such as the DSM [14, 15, 27, 29, 31, 32, 35, 39, 40, 44, 46–49, 53–55, 57, 60–62, 65, 68, 69, 71, 72]. Separately, 13 studies investigated the outcome of cognitive impairment [15, 28, 29, 35, 38–40, 46, 59, 62, 63, 69, 70], while 20 studies examined CD [30, 32, 34, 36, 37, 41–43, 45, 50–53, 58, 64, 66], employing various validated means of cognitive testing such as the MMSE and MoCA. The full list of the cognitive assessment tools used can be found in **Table** S2.

3.3 | Assessment of Olfaction

Olfaction was assessed via psychophysical tests such as the Sniffin' Sticks Smell Identification Test [15, 27, 29, 32, 35, 38–40, 46, 48, 50, 55–57, 60–65, 67, 68, 70–72], the University of Pennsylvania Smell Identification Test (UP-SIT) [36, 37, 45, 47, 51–54, 59], the San Diego Odor Identification Test [41, 42, 58], the revised version of the Scandinavian Odor Identification Test (SOIT) [30], the Odor Stick Identification Test for Japanese [28], the Culturally Adapted Smell Identification Test [31] and the Cross-Cultural Smell Identification Test (CC-SIT) [34, 49, 69]. Table S2 summarises a list of cut-off values used to define OI.

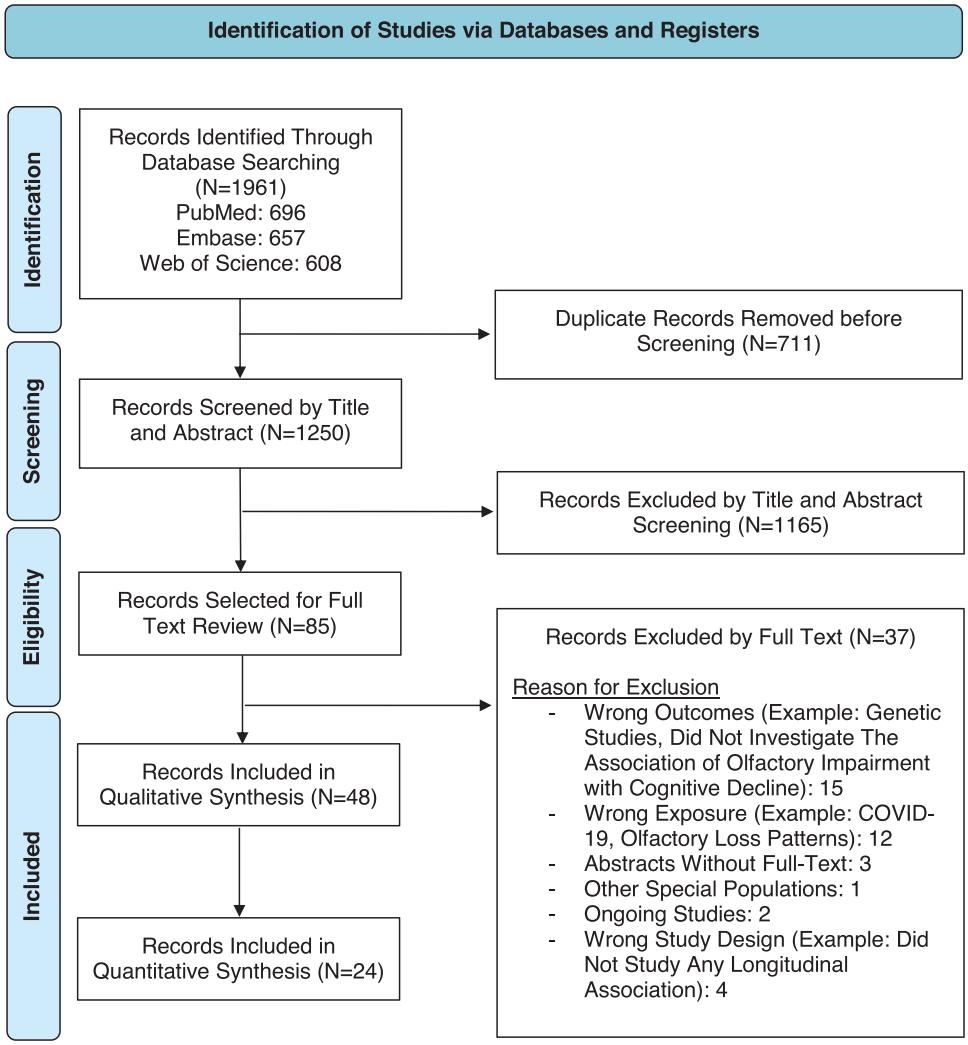

FIGURE 1 | PRISMA flowchart.

3.4 | OI and any CD

Among 15 studies comprising of 21,683 participants, participants with OI had a significantly higher risk of any CD (RR = 2.06; 95% CI = 1.87–2.26; $N = 16$), compared to patients with normal olfaction (Figure 2). Crucially, no between-study heterogeneity was observed ($I^2 = 0\%$). OI was associated with an increased risk of dementia (RR = 2.14; 95% CI = 1.88–2.44; $N = 9$), decrease in cognitive test scores (RR = 2.08; 95% CI = 1.67–2.59; $N = 7$) and cognitive impairment (RR = 1.85; 95% CI = 1.43–2.39; $N = 1$) (Figure 2). The list of pre-adjusted covariates in the pooled studies is available in Table S2.

3.5 | Categorical Dose–Response Relationship Between OI and Any CD

Among these 16 studies investigating the association between OI and any CD, four studies comprising of 4360 participants provided compatible summary estimates to evaluate the role of categorical OI severity on the risk of CD. We observed a categorical dose–response relationship where participants with severe OI had a higher risk of any CD (RR = 2.60; 95% CI = 2.12–3.20) compared to those with moderate OI (RR = 1.51; 95% CI = 1.23–1.85) (Figure 3). Severe OI was defined as scoring less than 5 on the CC-SIT, less than 8 on the B-SIT or less than 15 on the UP-SIT.

3.6 | Continuous Dose–Response Relationship Between OI and Any CD

The continuous dose–response relationship between olfaction and any CD was first elucidated by standardising the units of olfactory testing, with each unit corresponding to a 10% reduction in olfactory function. Among eight studies consisting of 5670 participants assessed olfaction using objective measures such as UP-SIT [45], 12-item Sniffin' Sticks Odor Identification Test [29, 35, 40], 16-item Sniffin' Sticks Odor Identification Test [46, 50], CC-SIT [49] and SOIT [44]. The risk of any CD increased by 18% per 10% decrease in olfactory score (RR = 1.18; 95% CI = 1.14–1.22; $N = 8$) (Figure 4). Additionally, the risk of cognitive impairment increased by 17% (RR = 1.17; 95% CI = 1.10–1.24; $N = 3$), the risk of dementia increased by 20% (RR = 1.20; 95% CI = 1.12–1.28; N

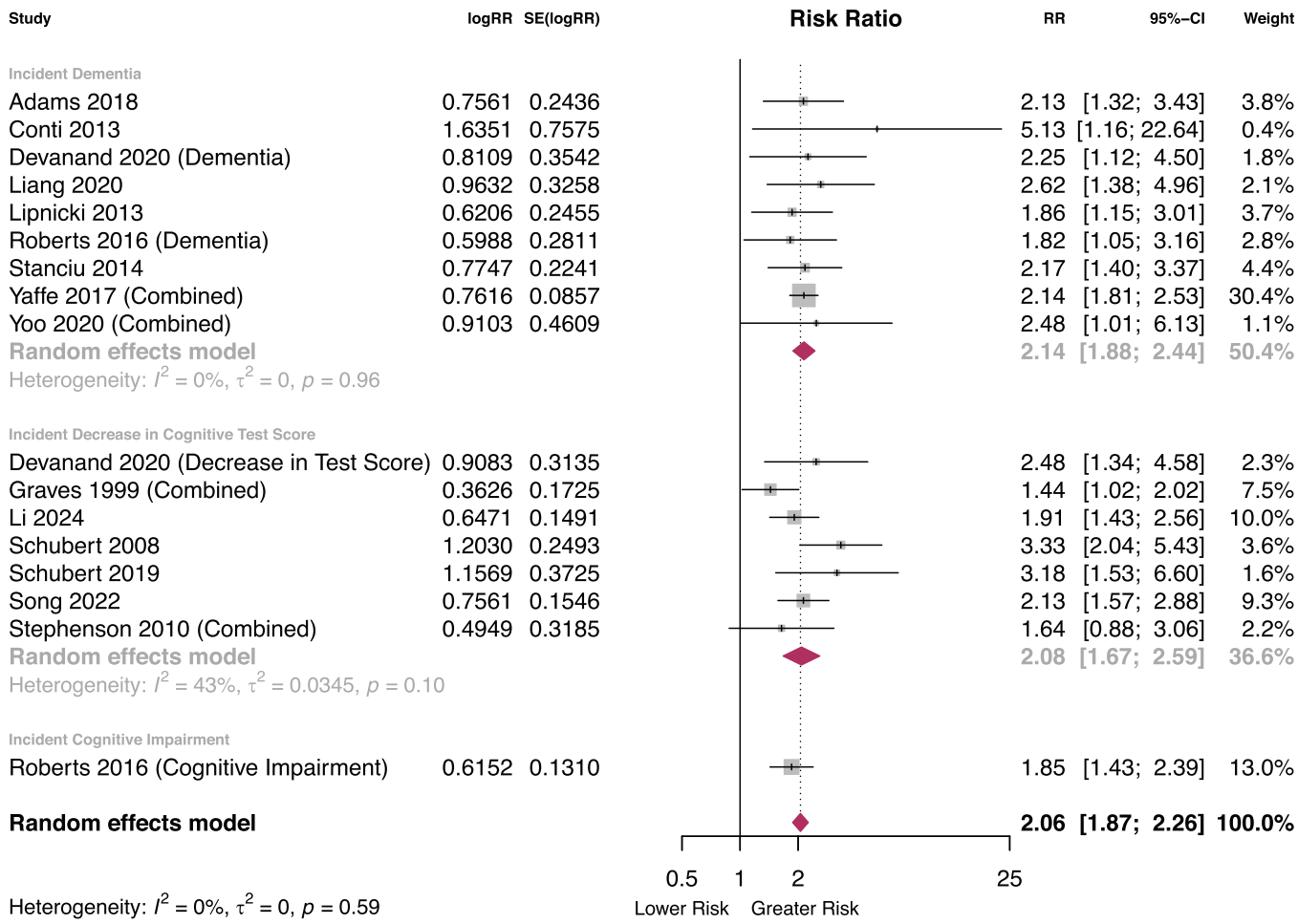

FIGURE 2 | Longitudinal association of olfactory impairment and any cognitive decline, stratified by type of cognitive outcome.
Legend: maroon diamonds are the estimated pooled risk ratios for each random-effects meta-analysis; grey boxes reflect the relative weight apportioned to each study.

= 5) and the risk of a decrease in cognitive test score increased by 21% (RR = 1.21; 95% CI = 1.04–1.42; N = 2) per 10% decrease in olfactory score (Figure 4). The list of pre-adjusted covariates in the pooled studies is available in Table S2.

Additionally, five studies comprising of 3813 participants that employed the Sniffin' Sticks Odor Identification Test were also exclusively pooled. The risk of any CD increased by 15% per point decrement on the Sniffin' Sticks Odor Identification Test (RR = 1.15; 95% CI = 1.11–1.18; N = 5) (Figure S1). There was no between-study heterogeneity (I^2 = 0%) identified.

3.7 | OI and Cognitive Test Scores

3.7.1 | Changes in Cognitive Scores Between Baseline and Follow-Up Among OI Patients

Additionally, cognitive test scores of 478 OI patients were compared between baseline and follow-up. Mean cognitive test scores from baseline to follow-up deteriorated by 57% (SMD: −0.57; 95% CI: −0.78 to −0.35; N = 7) (Figure S2). We did not observe any statistically significant between-study heterogeneity (I^2 = 48%, p = 0.08).

3.7.2 | Differences in Cognitive Scores Between OI and Controls at Baseline and Follow-Up

The differences in mean cognitive test scores between 478 patients with OI and 1614 participants with normal olfaction were also compared at baseline and follow-up separately. The cognitive test scores in OI patients were significantly lower at baseline (SMD = −0.36; 95% CI = −0.60 to −0.13; N = 7) (Figure S3) and follow-up (SMD = −0.77; 95% CI = −1.08 to −0.45; N = 7) (Figure S4), compared to those with normal olfaction, with the gap widening over time. We observed a moderate degree of heterogeneity in the pooled analyses at baseline (I^2 = 72%, p < 0.01) and follow-up (I^2 = 73%, p < 0.01).

3.8 | Population Attributable Fraction of Incident CD Associated With OI

The worldwide PAF of incident CD associated with OI was computed to be 18.17% (95% CI = 9.51%–28.93%).

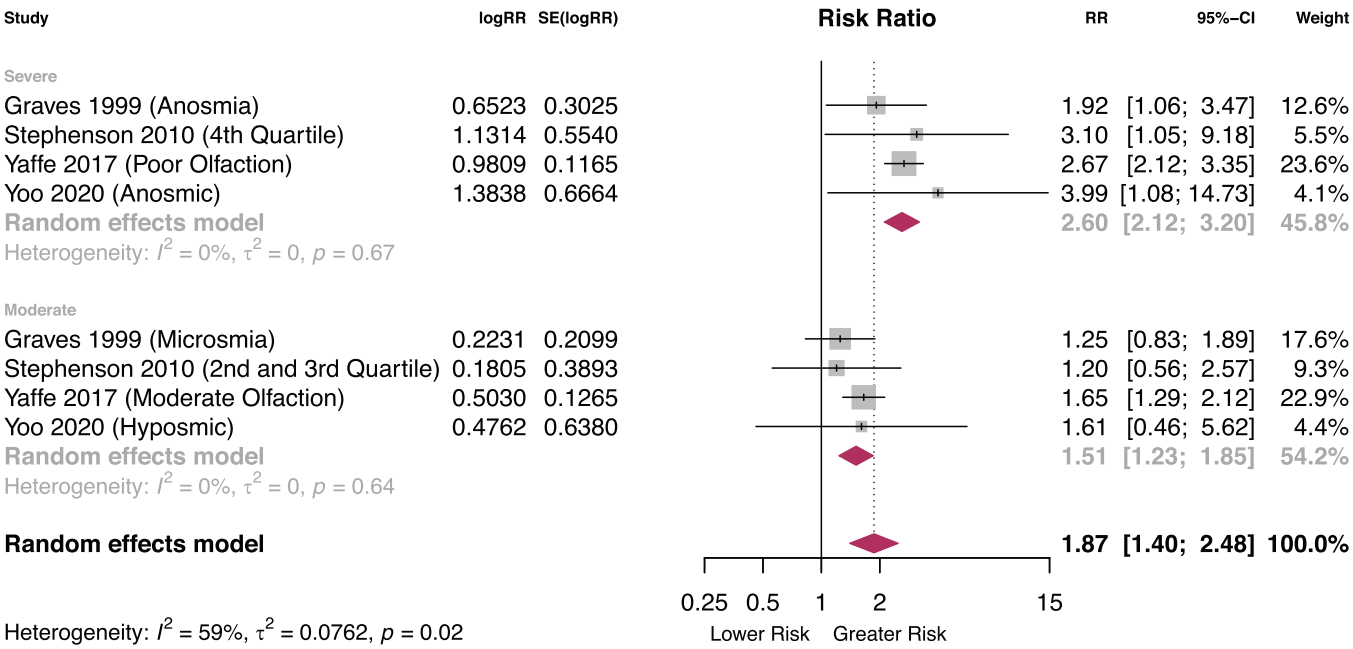

FIGURE 3 | Categorical dose–response relationship between olfactory impairment and any cognitive decline by categorical severity of olfactory impairment. Legend: maroon diamonds are the estimated pooled risk ratios for each random-effects meta-analysis; grey boxes reflect the relative weight apportioned to each study.

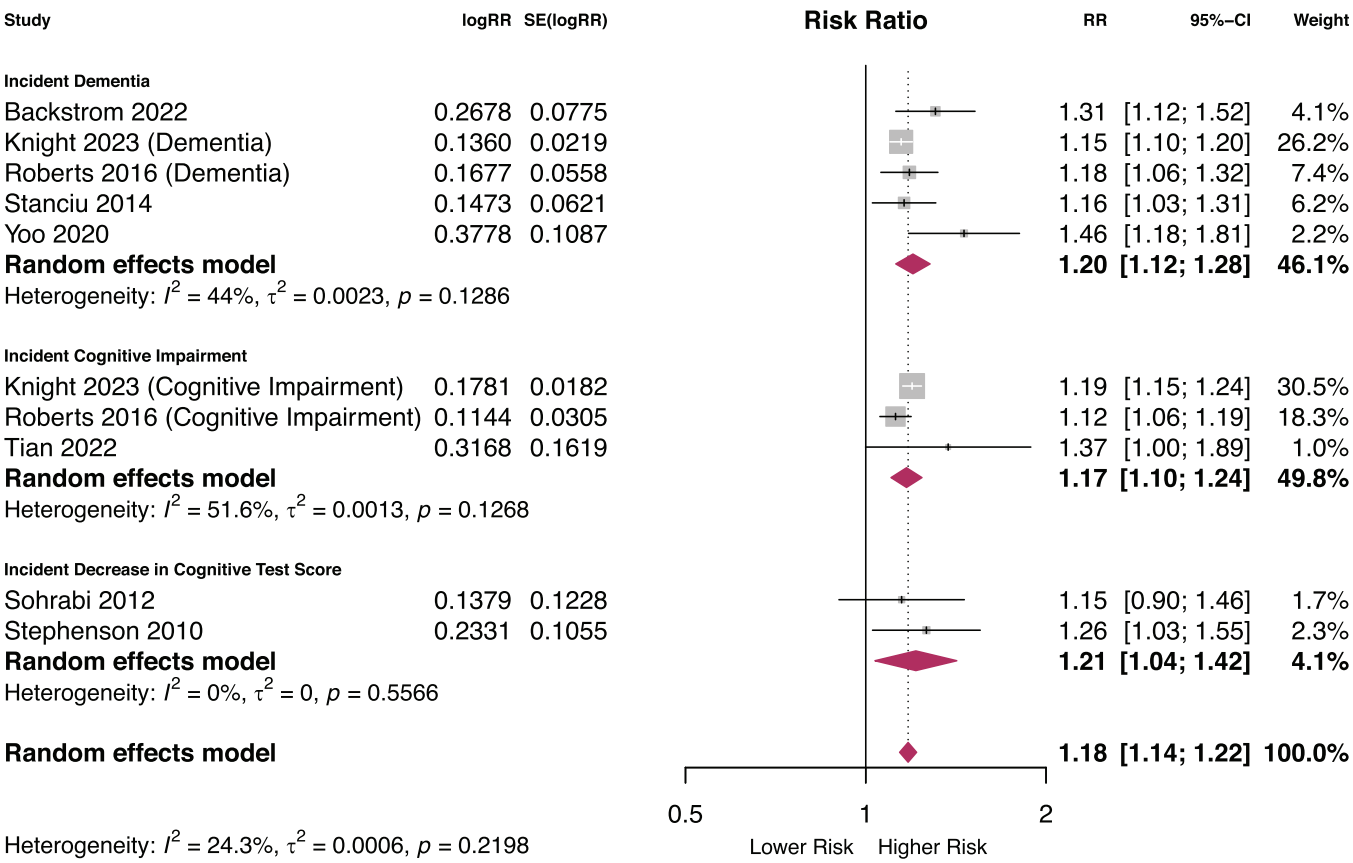

FIGURE 4 | Continuous dose–response relationship between olfaction and any cognitive decline, stratified by type of cognitive outcome. Legend: maroon diamonds are the estimated pooled risk ratios for each random-effects meta-analysis; grey boxes reflect the relative weight apportioned to each study.

3.9 | Subgroup, Sensitivity, Influence and Publication Bias Analyses

Additional subgroup stratification, based on the study design, study setting, continent of study and the PD status at baseline, was conducted for both the overall and the continuous dose–response analyses between OI and any CD. These results remained robust to geographical stratification, PD status at baseline, study design and study setting in all analyses (Figures S5–S12). The omission of any study did not influence the significance of the overall pooled effect size in leave-one-out analysis (Figures S13 and S14) and cumulative analysis highlighted a stable pooled effect size over time (Figures S15 and S16).

We assessed for small-study effects, such as publication bias, using a funnel plot when sufficient studies were available. Visual inspection of the funnel plot for the association between OI and any CD indicated potential asymmetry (Figure S17). Further trim-and-fill imputed three additional studies, but the recalculated summary estimate did not change the significance of our findings (RR = 1.87; 95% CI = 1.60–2.19). Separately, the funnel plot generated for the continuous dose–response relationship between OI and any CD also outlined possible asymmetry (Figure S18). While trim-and-fill analysis added three studies, the overall effect size remained statistically significant (RR: 1.16; 95% CI = 1.10–1.22).

Additionally, meta-regression for the association between OI and any CD was conducted on various pre-specified study-level characteristics, including average age, percentage male, average follow-up duration and NOS score, to determine their influence on the overall effect size (Table S4). The pooled RR increased by a factor of 0.68 (95% CI = 0.27–2.94) per year increase in mean age and 0.16 (95% CI = 0.28–0.89) per year increase in mean follow-up duration. However, the percentage of males and NOS score of studies did not influence the overall effect size.

3.10 | Systematic Review

There were 24 additional studies that fulfilled our inclusion criteria but were excluded from the meta-analysis due to incompatible data. These studies similarly suggest a significant association between OI and a decline in cognitive function [51–72].

3.11 | Overall Quality of Evidence

The overall quality of evidence per outcome was assessed using the GRADE framework (Table S5).

4 | Discussion

In this multi-adjusted, observational systematic review and meta-analysis of 48 longitudinal studies comprising 37,783 participants, patients with OI were found to have a 2.06-fold increased risk of subsequent CD, compared to participants with normal olfactory function. Furthermore, positive dose–response relationships were identified between both worsening categorical olfactory status and continuous changes in olfactory score, in relation to CD. The mean cognitive test scores of OI patients decreased by 57% from baseline to follow-up, and OI patients had a 36% and 77% lower cognitive test score than controls at baseline and follow-up, respectively. These associations remained robust to various subgroup analyses, sensitivity analyses and assessments of publication bias. Overall, this study provides compelling evidence that OI may be a risk factor for CD. Taking into account cumulative evidence from various studies regarding the effects of OI on negative outcomes in ageing, it is imperative for physicians and policymakers to pay closer attention to olfactory health, underscoring the importance of comprehensive geriatric assessments and the need for appropriate monitoring of older patients with OI [73, 74].

To the best of our knowledge, this is the most comprehensive evidence-based summary of the literature to date on the longitudinal relationship between olfaction and CD. While a previous meta-analysis by Chen et al. comprising eight studies found that OI was associated with a greater risk of CD [13], unadjusted associations were incorporated in their analysis, leading to numerous potential sources of confounding in their findings. Crucially, neither publication bias nor the quality of evidence was assessed. Given the greater availability of literature, only adjusted estimates were pooled to minimise heterogeneity, and comprehensive subgroup, sensitivity, meta-regression and publication bias analyses were performed to enhance the robustness of results. Crucially, no between-study heterogeneity was identified in the overall analysis between OI and CD. Additionally, our study assessed for both categorical and dose–response relationships, which provides insight into how the risk of CD may vary according to the severity of OI.

It has been reported that OI may be an indicator of underlying subclinical neurodegenerative diseases, with several studies showing the association between olfactory deficits and the onset of neurodegenerative diseases such as PD and AD [75]. While the exact pathophysiological mechanisms are unclear, there are several hypotheses which may explain this observed association. Figure 5 depicts a schematic diagram summarising these.

First, various neuropathological studies have demonstrated that pathologic processes, including the accumulation of neurofibrillary tangles and Lewy bodies within olfactory bulbs and tracts, emerge in the olfactory system prior to the onset of cognitive deficits. The inability to store and retrieve memories of smell and thereby correctly identify odours could indicate the presence of pathology in the entorhinal cortex, hippocampus and other temporal regions, even before the emergence of typical clinical manifestations [76].

Second, OI has been postulated to indirectly accelerate CD and neurodegeneration through various mechanisms. For example, a study found that patients with PD who suffered from OI had a greater risk of conversion to dementia, as worse olfaction may reflect early and extranigral Lewy body pathology in the cortical areas, accelerating the progression of CD [47]. Likewise, neuroimaging studies found that in patients with mild cognitive impairment and AD, poorer olfaction was directly correlated with lower volumes of the hippocampus, entorhinal cortex, fusiform, precentral and total middle temporal cortex on MRI, with subsequent steeper CD [77]. Moreover, it is imperative to consider the

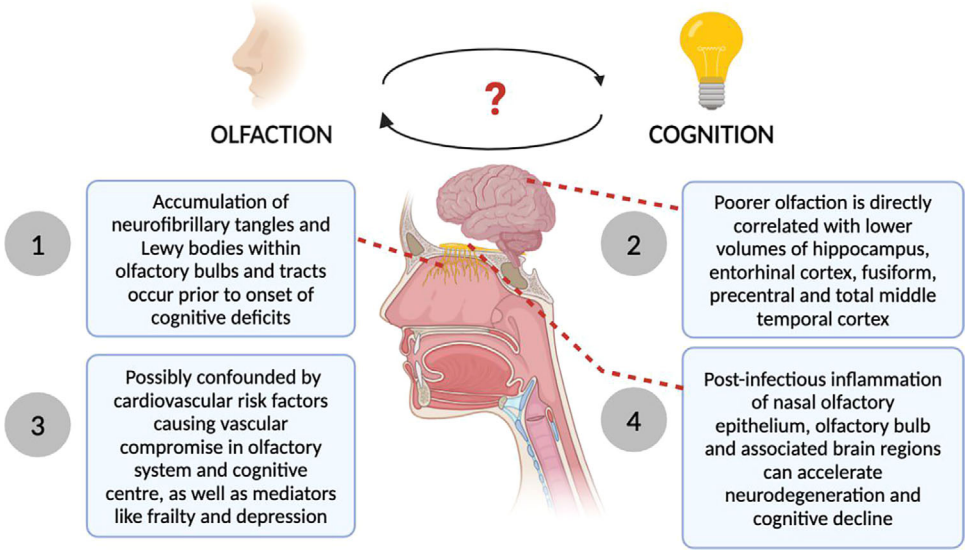

FIGURE 5 | Schematic diagram showing the proposed mechanisms between olfactory impairment and any cognitive decline.

possibility that OI is associated with frailty, which may accelerate CD [73, 78, 79]. OI can cause reduced food satisfaction and loss of appetite, subsequently leading to malnutrition. Additionally, OI may also be associated with depression, as studies have proposed that olfactory bulb ablation results in behavioural changes similar to that of depression. Both malnutrition and social isolation may increase the risk of frailty, which has strong associations with late-life CD [80].

Third, the relationship between OI and CD may be confounded by factors such as cardiovascular diseases, smoking and diabetes. OI may be caused by vascular compromise to regions of the brain involved in olfaction, with subclinical atherosclerosis being associated with CD. Furthermore, OI has also been proposed to be associated with diabetes, given its link with diabetic peripheral neuropathy, although this association is a matter of discussion [81–83]. Nevertheless, some of the included studies in this review still observed a positive association following adjustment for these confounders.

Fourth, it has been hypothesised that post-infectious inflammation of the nasal olfactory epithelium, olfactory bulbs and associated brain regions not only contribute to olfactory disturbances, but may also accelerate pathological processes responsible for the development and progression of neurodegenerative disorders [84, 85]. OI is well associated with COVID-19. The incidence of acute OI in patients with COVID-19 has been found to be 52.7%, with a large number of initially affected individuals later developing persistent smell dysfunction [5, 6, 8, 86, 87]. While our study did not include patients with COVID-19, it remains to be seen if the incidence of neurodegenerative disorders rises considering the surge in incidence of OI after the COVID-19 pandemic.

Unsurprisingly, age was identified as a significant effect modifier of the OI–CD association. This finding aligns with the well-established understanding that advanced age is the most significant risk factor for dementia, largely due to the cumulative effects of neurodegenerative changes that occur over time [88, 89]. Epidemiological studies have shown that the prevalence of cognitive impairment and dementia increases with age [90]. Considering a rapidly ageing global population, the identification of OI as a potential risk factor for CD becomes increasingly important [91]. Separately, follow-up duration was also a significant effect modifier of the association between OI and CD, where the risk of CD increased per year of mean follow-up duration. Given the chronic and insidious nature of cognitive impairment and dementia [92], an extended follow-up duration may allow for more cases to be diagnosed, which may otherwise remain undetected in studies with shorter follow-up periods.

This study contributes to the growing literature demonstrating the relationship between various special senses and adverse ageing outcomes. Approximately, 18% of CD may be associated with OI, a proportion comparable to the findings from other studies showing that 15.6% of dementia cases may be linked to hearing impairment, and 4%–19% to vision impairment [93, 94]. Crucially, both hearing loss and vision impairment are associated with cognitive impairment and dementia [95, 96], but hearing and vision interventions have shown potential cognitive benefits [97–102]. While some randomised studies have demonstrated certain benefits of olfactory training in older adults, such as enhanced verbal function and improved subjective well-being, future interventional studies may shed more light on whether OI may similarly be a modifiable risk factor for neurocognitive diseases [101–103].

The main strengths of our study are the systematic inclusion of a large number of new studies, increasing the generalisability of our findings. We employed a methodologically rigorous pre-specified protocol according to international guidelines and used thorough statistical methods to explore possible effect size moderators and dose–response relationships. Various subgroup analyses, sensitivity analyses and assessments of publication bias to enhance the strength of our results. We also pooled maximally covariate-adjusted effect sizes to reduce the effect of confounding. Crucially, no evidence of publication bias was found and overall quality of evidence was high, with no included studies assessed to have a high risk-of-bias. Furthermore, our study newly explored

dose–response relationships between OI and CD. Cumulatively, the rigorous methodology employed in our study appropriately addressed limitations from aforementioned meta-analyses.

Nonetheless, this study should be interpreted in the context of known and potential limitations. First, olfactory function was mainly assessed via olfactory identification tests which have inherent limitations, including cultural bias. To get a correct response, participants must be able to correctly recall the presented odour. However, participants from various ethnicities might not have been exposed to certain odours and would thus be unable to identify them. Furthermore, as these tests mainly focus on odour identification, other facets of olfactory function, such as olfactory discrimination and threshold could not be appropriately assessed. Hence, future studies investigating the role of specific olfactory domains on cognition may be valuable in guiding olfactory screening for at-risk individuals. For example, a study found that individuals with AD predominantly experience impairment in odour discrimination, while those with semantic, frontotemporal or corticobasal dementia have difficulty with odour identification instead [104]. Second, the studies utilised varying olfactory tests and methods for determining neurocognitive outcomes, which may have introduced measurement bias. The number of olfactory items assessed varied across different tests, and not all tests were based on a forced-choice task. Nonetheless, we attempted to minimise heterogeneity by only pooling maximally covariate-adjusted estimates, and employed a battery of subgroup analyses and meta-regression to detect any effect size moderators, which increases the reliability of our findings. Crucially, no heterogeneity was observed in the overall analysis between OI and CD. Third, as all included studies were observational, causative conclusions on the causal relationship between OI and CD should not be permitted due to the possibility of residual confounding. There is a potential for confounding effects from other sensory impairments, such as those related to vision and hearing, which may not have been accounted for in pre-existing studies. Similarly, the calculation of PAF also assumes a causal relationship. Nevertheless, it is a useful epidemiological estimate of the burden of CD associated with OI.

5 | Conclusion

In this multi-adjusted systematic review and meta-analysis of 48 longitudinal studies comprising 37,783 participants, OI was associated with an increased risk of CD. A positive categorical and continuous dose–response relationship was observed, where OI of greater categorical severity and worsening olfactory scores were associated with a greater risk of CD. Given the high prevalence of OI among the older adults, physicians should be mindful of the potential cognitive implications of OI. OI may be incorporated as an element of early cognitive screening in high-risk patients, and cognitive screening should be recommended for patients with long-term OI.

Author Contributions

B.S.Y.Y., H.J.J.M.D.S. and B.K.J.T. contributed equally to this paper and are joint first authors. B.S.Y.Y., H.J.J.M.D.S., B.K.J.T. and N.W.Y.T. conceptualised and designed the study. B.S.Y.Y., H.J.J.M.D.S., A.S., O.T.W.H., J.H.C. and E.Y.G. selected the articles and extracted data. B.S.Y.Y. and H.J.J.M.D.S. were responsible for statistical analysis. B.S.Y.Y., H.J.J.M.D.S., A.S., O.T.W.H., J.H.C., C.J.W.T. and C.B.T. wrote the first draft of the manuscript. All authors were involved in critical revision of the manuscript. All authors approved the final version of the manuscript. B.K.J.T. and N.W.Y.T. are joint corresponding authors. The corresponding authors attest that all authors meet authorship.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

The articles included in this study can be found on PubMed, Embase and Web of Science. Data may reasonably be requested from the corresponding authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: alr23635-sup-0001-SuppMat.docx