Temporal Association Between COVID-19 Infection and Subsequent New-Onset Dementia in Older Adults: A Systematic Review and Meta-Analysis

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Abstract

Background: The relationship between COVID-19 infection and the increased likelihood of older adults developing new-onset dementia (NOD) remains elusive. This review primarily aimed to investigate the potential role of COVID-19 in leading to NOD among older adults aged 60 years and older over various time intervals.

Methods: A thorough search was performed across several databases including MEDLINE/PubMed, PsycINFO, Scopus, medRxiv, and PQDT Global for studies published in English from January 2020 to December 2023. We assessed the risk of developing NOD, using Risk Ratio (RR) for measurement. The control groups were categorized as: (i) a non-COVID cohort with other respiratory infections [control group (C1)]; and (ii) a non-COVID cohort with otherwise unspecified health statuses [control group (C2)]. Follow-up periods were divided into intervals of 3, 6, 12, and 24 months post-COVID. The study protocol was registered with PROSPERO (CRD42023491714).

Results: Our review incorporated 11 studies, encompassing 939,824 post-COVID-19 cases and 6,765,117 controls. The overall pooled analysis revealed a significant link between COVID-19 infection and an increased risk of NOD (RR = 1.58, 95% CI 1.21–2.08). In subgroup analyses, NOD risk was significantly higher in the COVID-19 group compared to C2 at 12 months post-COVID (RR = 1.84, 95% CI 1.41–2.38), but not at 3 (RR = 0.87, 95% CI 0.46–1.65) or 6 months (RR = 1.73, 95% CI 0.72–4.14). Compared to C1, the risk increase was not significantly remarkable at 3 (RR = 0.94, 95% CI 0.35–2.57), 6 (RR = 1.13, 95% CI 1.07–1.20), and 12 months (RR = 1.12, 95% CI 0.91–1.38), and overall (RR = 1.13, 95% CI 0.92–1.38). Female had a significantly higher risk of developing NOD in the COVID-positive group (RR = 1.65, 95% CI

1.53–1.78) and C2 group (RR = 1.33, 95% CI 1.22–1.44). Patients with severe COVID-19, as classified by the American Thoracic Society guidelines, were significantly much more prone to developing NOD than those with non-severe infections (RR = 17.58, 95% CI 10.48–29.49). Cognitive impairment was nearly twice as likely in COVID-19 survivors compared to those uninfected (RR = 1.93, 95% CI 1.52–2.43).

Discussion: COVID-19 infection may be linked to a higher risk of NOD in recovered older adults at the subacute and chronic stages following COVID-19 diagnosis. This risk appears to be on par with that associated with other respiratory infections.

Keywords

Dementia, Alzheimer's Disease, COVID-19, , meta-analysis, respiratory infection, review

1. Introduction

The COVID-19 pandemic, precipitated by the emergence of the novel coronavirus SARS-CoV-2, has profoundly disrupted global health paradigms, extending its influence beyond acute illness to potentially shape long-term neurological trajectories (Parotto et al., 2023). Among the most scrutinized consequences in recent years is the heightened risk of cognitive impairment and the emergence or exacerbation of neurodegenerative conditions (Ceban et al., 2022; Shariff et al., 2023), including Alzheimer's disease and other types of dementia (Golzari-Sorkheh et al., 2023; Toniolo et al., 2021), in older adults following COVID-19 infection (Liu et al., 2021).

Emerging research has increasingly drawn attention to the correlation between COVID-19 infection and escalated risks of cognitive decline or "brain fog" in older adults, in

comparison with those affected by other respiratory diseases, or healthy ones who are otherwise characteristic-matched (Abdullah et al., 2023; Baker et al., 2021; Liu et al., 2021; Liu et al., 2022). Furthermore, some evidence suggests that COVID-19 may precipitate the new-onset of Alzheimer's disease and other dementia or exacerbate pre-existing neurodegenerative conditions within this demographic (e.g., Taquet et al., 2022; Xu et al., 2022). This conjecture was bolstered by neurobiological studies illustrating how SARS-CoV-2 could trigger central nervous system inflammation and dysregulation, trigger autoimmune responses detrimental to neurological function, and potentially expedite neurodegenerative processes (e.g., Monje & Iwasaki, 2022). More specifically, for instance, COVID-19 has been linked to the activation of the NLRP3 inflammasome, tau aggregation, neurodegeneration, and elevated levels of amyloid-beta deposition and cerebrospinal fluid markers such as neurofilament light chain, and tau, suggesting ties to Alzheimer's disease pathology (Gordon et al., 2022). Additionally, COVID-19's role in cerebral ischemia, thrombus formation, and hypoxia aligns with vascular dementia mechanisms (Pyne & Brickman, 2021). In populations with an elevated baseline dementia risk, particularly older adults with cardiovascular risk factors, COVID-19 not only augments cognitive decline risks but also synergistically interacts with pre-existing dementia risk factors, leading to a disproportionate escalation in dementia risk (Pyne & Brickman, 2021).

Despite these explorations, the literature examining the link between COVID-19 and dementia new-onset remains fragmented, characterized by diverse methodologies and nuanced outcomes. These variabilities span research approaches, baseline clinical characteristics of COVID-19-afflicted patients, comparator groups, follow-up durations,

dementia types, ethnic demographics and so on. While a previous meta-analysis has examined this link across patients of all ages (Rahmati et al., 2023), no clear association among older adults (≥60) has been established. Consequently, there is a notable void in the systematically exploration and in quantifying COVID-19's association with Alzheimer's disease and other dementia in older adults over time following acute COVID-19 infection. The elusive nature of these associations is compounded by the scarcity of definitive original studies and the absence of quantitative reviews synthesizing individual findings. This understanding is critical, particularly as evidence indicated elevated mortality risks in COVID-19-infected older adults patients diagnosed with dementia (e.g., Saragih et al., 2021). Furthermore, the ongoing pandemic, potential for multiple infections in vulnerable older adults, and the projected tripling of the global dementia burden by 2050 (unless countries take actions to address relevant risk factors) (GBD 2019 Dementia Forecasting Collaborators, 2022), underscore the urgency of this inquiry.

This review endeavours to bridge these research gaps by rigorously analysing extant original investigation studies, thereby offering a more definitive comprehension of these associations. This effort is geared towards enhancing the long-term cognitive care and management of COVID-19-infected older adults, fostering early intervention strategies in the waning, yet still unpredictable pandemic era. The primary goal was to ascertain the extent to which the COVID-19 infection impacts the risk of subsequent NOD development over time in older adults.

2. Methods & Materials

In this systematic review and meta-analysis, we adhered to the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. Its checklist is detailed in Supplementary File 1 (sTable 1) (Page et al., 2021). Furthermore, this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; reference number CRD42023491714) prior to its official commencement.

2.1 Search strategy and selection criteria

Two researchers, D.S. and C.X.Y.W., independently conducted comprehensive electronic searches across five major databases: MEDLINE/PubMed, APA PsycINFO, Scopus, medRxiv preprint server, and ProQuest Dissertations and Theses Global (PQDT Global), targeting English-language publications from January 2020 to December 2023. The objective was to identify potentially eligible articles, including original empirical articles, short communications, and research letters. However, some review studies that were retrieved were manually screened to identify additional eligible empirical research discussed in these reviews but not found in our initial search. Our systematic review and meta-analysis adhered to predefined inclusion criteria focused on participants' characteristics (P), interventions (I), and outcomes (O). A list of keywords associated with COVID-19 and its neurological impacts was used, simplifying the search algorithm to ("COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "pandemic" OR "post-COVID syndrome" OR "long COVID" OR "chronic COVID") AND ("Alzheimer's Disease" OR "dementia" OR "neurodegenerative disorder" OR "neurodegeneration" OR "neurological sequelae" OR "brain health") AND ("older adult" OR "elderly" OR “geriatric” OR "senior population" OR "aging" OR “ageing”). For comprehensive details of our search algorithm in the searched databases, see sTable 2.

Manual searches of the reference lists from retrieved articles in addition to reviews were also performed to uncover additional relevant studies. However, all animal studies were excluded from this review.

Our study included research evaluating the long-term impact of COVID-19 infection on the new-onset of any type of dementia in COVID-19 survivors aged 60 years and older (i.e., older adults) (Singh et al., 2023), observed over time. We considered both prospective and retrospective observational studies involving targeted patients who had recovered from COVID-19 (forming the experimental groups) and underwent dementia assessments at certain stages post-recovery. In our evaluation of comparison groups within potentially eligible studies, the scope extended beyond merely healthy controls. It encompassed all non-COVID status age-matched individuals, regardless of whether they had other respiratory infections or were unremarkable in their respiratory tracts (i.e., healthy controls). EndNote 21 software (Clarivate Analytics) was used for literature management.

2.2 Data extraction, planned subgroup analysis, and research quality assessment

The following data were extracted from the eligible studies: author and year, country, type of research, experimental and control groups, age of participants, method of COVID-19 diagnosis, method of dementia determination, examined type of dementia, post-COVID-19 follow-up period. As we only explored aged ≥ 60, when original studies which explored all age groups, we carefully extracted data of participants aged ≥ 60 from their datasets. The counts of events (i.e., outcomes) and non-events in both the COVID and non-COVID groups were directly recorded or calculated from the data presented in the original articles or their

accompanying supplementary files. When a study investigated multiple follow-up periods post-COVID-19, the longest follow-up duration was retained for the overall pooled meta-analysis.

To perform subgroup analyses assessing the impact of demographical [i.e., age group (such as 60-69, 70-79, 80-89, ≥ 90) and sex (male vs. female)] and clinical characteristics [e.g., type of newly developed dementia (all-cause dementia, Alzheimer's Disease, vascular dementia, Lewy Body dementia, and others), type of respiratory infection (COVID-19, influenza A/B, and bacterial infection), co-morbidities, COVID-19 severity status (severe vs. non-severe), indication of statistically significant cognitive impairment (but not necessarily dementia), and follow-up duration (3, 6, 12, 24 months)], we also extracted relevant data in both COVID-19 and controls groups (where available). The quality of the included studies was assessed by evaluating the risk of bias in each study using the Newcastle–Ottawa Scale (NOS). Two assessors (D.S. and C.X.Y.W.) independently carried out data extraction and quality assessment. Any disagreements were resolved through discussions with two additional reviewers (C.H. and T.C.) before proceeding to the meta-analysis.

2.3 Statistical analyses

Binary outcome comparisons between two groups were pooled and analysed, presenting the results as risk ratio (RR) with 95% confidence intervals (CI). The reported log RRs were converted back to RRs through exponentiation. To estimate pooled effect sizes, random-effects models employing the Restricted Maximum Likelihood (REML) method were used for more accurate variance component estimation across studies, therefore enhancing

the generalizability of the model's findings (Lee, 2022). The potential presence of heterogeneity beyond sampling error was examined using Cochran's Q statistics and I^2 statistics. The I^2 values were categorized as low (<25%), low to moderate (25%–50%), moderate to substantial (50%–75%), or substantial (>75%) (Lee, 2022). Visual analysis of between-study variance was supported by L'Abbé and Galbraith plots. A random-effects meta-regression model was utilized to identify variables potentially causing significant between-study variance. The robustness of summary estimates and the influence of individual studies on heterogeneity were assessed using a leave-one-out sensitivity analysis (Rahmati et al., 2022). Publication bias was evaluated through a contour-enhanced funnel plot, combined with Egger's regression test, and Begg's rank correlation test (for the number of included studies exceeding ten). We used the Trim-and-fill method to provide the adjusted effect sizes including imputed studies. All meta-analyses were conducted in Stata 18.0, considering a two-sided p-value of less than 0.05 as statistically significant.

3. Results

3.1 Study screening, general characteristics and quality assessment

Our systematic review and meta-analysis initiated with the process of literature search and screening. The PRISMA flow diagram of the included studies is presented in Figure 1, with the PRISMA 2020 Checklist accessible in sTable 1. sTable 3 lists the studies that investigated the associations of our interests from certain perspectives yet were excluded due to their deviation from our review's precise scope, including the reasons for their exclusion.

This procedure consequently resulted in the inclusion of data from 939,824 post-COVID-19 cases and 6,765,117 controls across 11 studies, as detailed in Table 1, where data specific

to older adults (≥ 60) were extracted either from the original articles directly or their corresponding supplementary files. The included studies, primarily retrospective cohort studies along with a cross-sectional study (Liu et al., 2021), spanned across the USA, Germany, China Mainland, South Korea, and Denmark. All these studies investigated the risk of NOD in older adults post-COVID-19 over varying follow-up periods. In our review, 5 studies employed Propensity Score Matching (PSM) to establish 1:1 matched cohorts of older adults without COVID-19 (meanwhile, they feature an identical number of participants in both the COVID group and the non-COVID group), therefore ensuring comparability of baseline characteristics in control groups (Cohen et al., 2022; Gollop et al., 2023; Qureshi et al., 2022; Taquet et al., 2022; Wang et al., 2022). The dementia risk in these populations was compared to two types of control groups: non-COVID cohorts with other respiratory infections [control group (C1)] in 5 studies, and non-COVID cohorts with otherwise unspecified health statuses [control group (C2)] in 7 studies. Zarifkar et al. (2022) compared COVID-19 patients to both C1 and C2 control groups within the same study. RT-PCR was consistently utilized for COVID-19 diagnosis, with all participants being 60 years or older.

For dementia assessment, most studies used the International Classification of Diseases 10th Revision (ICD-10), except for two employing the Chinese version of the Telephone Interview of Cognitive Status-40 (TICS-40) (Liu et al., 2021; Liu et al., 2022). The focus was on all-cause dementia (primarily including AD, vascular dementia, and unspecified dementia) in 8 studies, while the remaining 3 specifically examined AD (Wang et al., 2022; Xu et al., 2022; Zarifkar et al., 2022). In studies addressing all-cause dementia, AD was the most prevalent type (if they reported the proportions of each dementia subtype), followed by vascular

dementia (Park et al., 2021; Taquet et al., 2021). The 11 included studies, considering follow-up periods of 3, 6, 12, and 24 months, either explicitly excluded patients with a prior dementia diagnosis at enrolment, or, in cases where patients' prior dementia status was not considered for recruitment, the incidence of NOD was calculated in their original investigations exclusively from cohorts without a previous dementia diagnosis at the time of enrolment. Hence, all cases of dementia diagnosed among the 939,824 post-COVID-19 patients and the 6,765,117 controls over time represent new instances of the condition. It is worth noting that, while 9 studies recorded definitive dementia diagnoses using ICD-10, the TICS-40 used in Liu et al.'s studies could only indicate, rather than confirm, dementia (Liu et al., 2021; Liu et al., 2022). Every study included in our review was rated as good quality (≥7) based on the NOS quality assessment criteria (Wells et al., 2000), as the details shown in sTable 4a for 10 cohort studies and sTable 4b for a cross-sectional study. The studies by Park et al and Qureshi et al. each lost one point for NOS comparability items, as they only controlled for demographical features, but not for known dementia risk factors such as the body mass index, alcohol consumption, smoking history and physical activity (Park et al., 2021; Qureshi et al., 2022).

3.2 Overall pooled meta-analysis results from all 11 included studies

Regarding the overall pooled meta-analysis results as shown in Figure 2, a random-effects REML model was used due to substantial heterogeneity. Among them, 9 out of 11 studies reported an increased risk for developing NOD in COVID-19 infected older adults, in comparison to their non-infected counterparts (Cohen et al., 2022; Liu et al., 2021; Liu et al., 2022; Qureshi et al., 2022; Taquet et al., 2021; Taquet et al., 2022; Wang et al., 2022; Xu et

al., 2022; Zarifka et al., 2022). Notably, compared to 8 studies indicating a RR from 1.28 to 4.87, one study showed that COVID-19 infection led to a likelihood of developing NOD that was more than 20 times that of those uninfected (RR = 20.92, 95% CI 1.29-340.63), albeit contributing minimally to the overall weight (0.87%). Contrarily, one study suggested no significant difference in NOD risk between COVID-19 infected and non-infected groups (RR = 1.03, 95% CI 0.83-1.30) (Gollop et al., 2023), and another study suggested a protective effect of COVID-19 infection against NOD risk (RR = 0.64, 95% CI 0.48-0.86) (Park et al., 2021).

The overall pooled analysis revealed a significant link between COVID-19 infection and increased risk for all-cause dementia (RR = 1.58, 95% CI 1.21–2.08, $p<0.001$; $I^2 = 98.57\%$, $p<0.001$) in COVID-19 older adult survivors.

3.3 Subgroup analyses

Figures 3 and 4, along with Supplementary Figures S1 to S4, display the results of subgroup analyses, examining: (i). NOD risk based on COVID-19 infection status (infected vs. uninfected vs. other respiratory infections), as shown in Figure 3 and Figure 4; (ii). the risk of developing cognitive impairment in COVID-19 infected individuals compared to those not infected (regardless of other respiratory infections) with cognitive impairment as the measured outcome, as shown in sFigure 1; (iii). NOD risk across groups - those testing positive for COVID-19, those with other respiratory infections, those testing negative for COVID-19 otherwise unspecified, specifically analysing sex differences (male vs. female), as shown in sFigure 2; and (iv). NOD risk among COVID-19 patients, categorized by illness severity, as depicted in sFigure 3 and sFigure 4. All subgroup meta-analyses applied random-effects REML

models due to substantial heterogeneity, except for the analysis concerning COVID-19 severity in sFigure 4, which utilized a fixed-effects Mantel-Haenszel model.

3.31 Newly developed dementia risk among COVID-19 Infected, non-COVID-19 infected otherwise unspecified, and non-COVID-infected with other respiratory infections groups across follow-up periods

No significant difference was observed in terms of NOD risk between the COVID-19 infected group and the non-COVID cohorts with other respiratory infections [C1 group] (overall RR = 1.13, 95% CI 0.92–1.38, p=0.23; I^2 = 95.58%, p<0.001) (refer to Figure 3). However, a significantly increased risk for NOD was noted in the COVID-19 group compared to the non-COVID cohorts with otherwise unspecified health statuses [C2 group] at 12 months post-diagnosis (RR = 1.84, 95% CI 1.41–2.38). This increased risk was not evident at 3 months (RR = 0.87, 95% CI 0.46–1.65) or 6 months (RR = 1.73, 95% CI 0.72–4.14). The overall effect size of the comparison between the COVID-19 infected group and the C2 group also indicated a heightened risk of developing NOD (RR = 1.67, 95% CI 1.15–2.42, p<0.05; I^2 = 97.95%, p<0.001) (refer to Figure 4).

3.32 Comparison of newly developed cognitive impairment risk between COVID-19 infected and non-COVID-19 infected groups

Among the 3 studies which explored the risk of developing new-onset cognitive impairments between the COVID-Infected group and the non-COVID-19 infected group (Cohen et al., 2022; Liu et al., 2021; Liu et al., 2022), a significant increased risk for NOD was

observed in the COVID-infected group (overall RR = 1.93, 95% CI 1.52–2.43, p<0.001; I^2 = 79.04%, p<0.001). More details refer to sFigure 1.

3.33 Newly developed dementia risk based on sex in COVID-positive, other respiratory infection, and COVID-negative otherwise unspecified groups, separately

Female was found to have a higher risk for NOD among the COVID-positive patients (RR = 1.65, 95% CI 1.53–1.78, p<0.001; I^2 = 0.00%, p>0.05) as well as the COVID-negative otherwise unspecified controls (RR = 1.33, 95% CI 1.22–1.44, p<0.001; I^2 = 0.00%, p>0.05). An overall effect size also suggested a significant increased risk for female to develop NOD (RR = 1.41, 95% CI 1.24–1.60, p<0.001; I^2 = 62.72%, p<0.001). However, no significant difference in terms of such risks between male and female was found in the other respiratory infection-positive group (RR = 1.15, 95% CI 0.84–1.57, p>0.05; I2 = 0.00%, p>0.05). More details refer to sFigure 2.

3.34 Newly developed dementia risk in COVID-19 infected patients, based on COVID severity

All the 3 studies in this subgroup meta-analysis suggested that COVID-infection with a severe status could significantly lead to a higher risk for NOD (overall RR = 7.19, 95% CI 1.29–39.97, p<0.05; I2 = 94.51%, p<0.001). Of note, two studies by Liu et al. 2021 (RR = 15.18, 95% CI 7.18–32.12) and Liu et al. 2022 (RR = 19.63, 95% CI 9.63–40.02) reported a more than 10 times of risk ratio in comparison to that found by Zarifka et al (RR = 1.28, 95% CI 0.68–2.41). After excluding the study by Zarifka et al (2020), a significantly elevated risk was observed in

patients with severe COVID-19 (RR = 17.58, 95% CI 10.48–29.49). More details refer to sFigure 3 and 4.

3.4 Overall heterogeneity and sensitivity analyses

We observed substantial heterogeneity among the 11 included studies in the main overall pooled meta-analysis in Figure 2 (I^2 = 98.57%, p<0.001). Also, L'Abbé and Galbraith plots, as shown in sFigure 5 and sFigure 6, visually indicated the discrepancies among the studies included in our review. Contrary to expectations, the meta-regression results, as shown in sFigure 7, revealed that variables such as follow-up durations (3, 6, 12, 24 months), types of control groups (non-COVID cohorts otherwise unspecified vs. non-COVID cohorts with other types of respiratory infections), and dementia types assessed (all-cause dementia vs. AD) did not contribute to the variability between studies within the 11 studies considered. The sensitivity analysis, as shown in sFigure 8, suggested that the overall results remained consistent despite the removal of individual studies (with acceptable changes in effect size ranging from 0.09 to 0.12), indicating that the conclusions of the meta-analysis we carried out in Figure 2 were robust and not overly dependent on any single study.

3.5 Publication bias

The contour-enhanced funnel plot, illustrated in sFigure 9, visually indicated potential asymmetry, hinting at publication bias. Two imputed studies were strategically placed to mirror the asymmetrical gaps. However, the regression-based Egger's test (p=0.052) and the nonparametric rank correlation Begg's test (p=0.978) did not provide strong evidence of

significant publication bias in our main overall pooled meta-analysis. Meanwhile, incorporating the two imputed studies into the analysis yields a revised pooled effect size for a total of 13 studies (RR = 1.48, 95% CI 1.12-1.96), which did not markedly differ from the initial analysis (RR = 1.58, 95% CI 1.21-2.08). In addition, the average NOS score of 8.5 [standard deviation (SD) = 0.66] was suggestive of a good methodological quality of included studies. All included studies properly represented the target population, investigating the impact of COVID-19 on the NOD risk in older adults, with satisfactory sample sizes throughout.

4. Discussion

In this systematic review with meta-analysis, we explored the association between COVID-19 infection and the risk of developing in new-onset dementia (NOD) in older adults ≥ 60. We further explored impacts on subgroups from multiple aspects, such as different control groups (COVID-negative with other respiratory infections vs. COVID-negative otherwise unspecified), across various follow-up periods (at 3, 6, 12, 24 months), and examined new-onset cognitive impairments (not necessarily progressing to dementia), sex differences (male vs. female) in NOD risk, and the influence of COVID-19 severity (severe vs. non-severe). The overall pooled meta-analysis indicated a heightened risk of developing NOD post-COVID-19 infection among older adults (RR=1.58, 95% CI 1.21-2.08), consistent with a prior meta-analysis which investigated all age groups (Rahmati et al., 2023). We assume that non-COVID-infected status may act as a protective factor against the development of dementia over time.

In subgroup meta-analyses, we found that at 12 months follow-up, the COVID-infected

group exhibited a significantly higher risk of developing NOD compared to the C2 group (RR=1.84, 95% CI 1.41-2.38), a risk elevation not present at the 3 and 6 months marks, indicating that NOD is a long-term consequence of COVID-19 infection (Xu et al., 2022). When controlling for baseline characteristics, COVID-infection and other types of reparatory infections showed a similar risk for leading to NOD (overall RR=1.13, 95% CI 0.92-1.38). This aligned with the findings of Gollop et al. (2023), but contradicted these by Taquet et al (2021), which suggested increased risk of cognitive deficits and dementia persisting for at least two years post-COVID-19 diagnosis compared to other respiratory infections. However, Taquet et al. considered populations across all age groups, not specifically older adults. Furthermore, Taquet et al. noted that some dementia diagnoses in their study may represent misdiagnoses of patients exhibiting transient and reversible dementia-like symptoms (Gollop et al., 2023; Varatharaj et al., 2020), also known as post-COVID 'brain fog' (Asadi-Pooya et al., 2023). In their analysis, Taquet et al. considered instances of dementia from day 15 to day 90 within the 3-month follow-up period (Taquet et al, 2021). This approach might lead to an overestimation of the incidence of NOD in COVID-infected patients, given the progressive and irreversible nature of neurocognitive and behavioural changes associated with dementia (Gollop et al., 2023). On the other hand, the similar risks associated with COVID-19 and other respiratory infections may be attributed to the vulnerability of older adults. Indeed, a previous study found that older adult patients hospitalized for flu, with or without pneumonia, were 2-7 times more likely to develop AD, all-cause dementia, and vascular dementia (Levine et al., 2023). Moreover, Influenza and pneumonia vaccinations were observed to reduce the risk of AD (Bukhbinder et al., 2022). These studies provided evidence that respiratory infections

caused by microorganisms may significantly influence the NOD risk in vulnerable populations.

Regarding the impact of sex on NOD risk, females were consistently identified as having a higher risk for NOD in both COVID-positive and COVID-negative groups. This aligned with the prevailing consensus that females are more susceptible to developing AD and all-cause dementia (Gong et al., 2023; Oveisgharan et al., 2018). When examining cognitive impairment (without necessary progression to dementia), COVID-infected patients were found nearly twice as likely to develop NOD compared to uninfected individuals, corroborating earlier findings (Liu et al., 2021; Quan et al., 2023). Concerning the impact of COVID-19 severity on NOD risk, our initial findings indicated that older adults with severe COVID-19 were more prone to develop NOD, with an effect size of 7.19 (refer to Figure 6), which increased to 17.58 after excluding the study by Zarifka et al. (2020). The definitions of 'severe COVID' varied, with Liu et al. (2021), and Liu et al. (2022) characterizing it based on the American Thoracic Society guidelines (i.e., COVID-infected patients plus one of the following conditions: respiratory rate higher than 30 breaths per minute, severe respiratory distress, or oxygen saturation less than 90% on room air), whereas we subjectively defined it in the study by Zarifka et al. (2022) based on patient care setting (inpatient vs. outpatient). The discrepancy in effect size suggested that classifying patients as having severe cases based solely on inpatient status was not appropriate and could lead to an overestimation of the true severity. Additionally, the difference in effect size could also stem from the distinct dementia types investigated, with Liu et al. focusing on all-cause dementia and Zarifka et al. on AD specifically. It is critical to pay close attention to severe COVID-19 cases in older adult patients, as they are significantly more likely (i.e., with a likelihood more than 15 times greater) to develop NOD compared to non-

severe cases, though further research is necessary for additional evidence.

There might be additional reasons why patients with severe COVID-19 had a markedly higher risk of developing NOD (refer to sFigure 3 and sFigure 4). While most studies utilized ICD-10 codes for indication of dementia diagnosis, Liu et al. (2021), and Liu et al. (2022) used the TICS-40. Previous reports indicated that ICD-10 codes exhibit a sensitivity of 92.7% and a specificity of 98.9% for diagnosing dementia (Quan et al., 2008). In contrast, although Liu et al. (2021) mentioned that the Chinese version of the TICS-40 was validated by an earlier study, that study actually emphasized that its purpose was not to assess the TICS-40's validity as a screening tool but to suggest it as a viable alternative to the Mini-Mental State Examination (MMSE) (Fong et al., 2009). Beyond cognitive assessments, considerations for age, education level, and further neuroimaging and laboratory tests may be necessary (Crum et al., 1993; Ziso, B., & Larner, 2019). Consequently, the efficacy of the Chinese version of TICS-40 in screening for dementia among those ≥ 60 remains uncertain, warranting additional research for validation. Furthermore, the initial strain of COVID-19 might have been more detrimental than subsequent variants, given the situation of very limited effective measures available to safeguard cognitive functions at the early pandemic era (Zhao et al., 2023; Zhou et al., 2021). These factors could also play a role in the significantly elevated NOD risk observed in these particular patients (Liu et al., 2021; Liu et al., 2022).

In one of the 11 included studies, the COVID-19 cohort was propensity score matched based on critical variables including the vaccination status, with a follow-up period of 24 months. This cohort exhibited a reduced risk of NOD compared to the overall risk (Taquet et al., 2022) (refer to Figure 2). Although there is no scientific evidence to date suggesting that

coronavirus vaccines directly influence NOD risk, it has been noted that common vaccines, such as those for influenza, were significantly associated with a reduced risk of dementia. Moreover, more vaccinations correlated with a stronger protective effect against the development of dementia (Wu et al., 2022). Also, Wu et al. indicated that while studies directly assessing the impact of COVID-19 vaccines on dementia risk are yet to be conducted, the array of neurological complications linked to SARS-CoV-2 suggests that vaccination against COVID-19 could potentially aid in mitigating cognitive decline, thereby offering some degree of protection against NOD (Wu et al., 2022). Nonetheless, this field remains speculative and warrants further investigation, particularly concerning older adults who are more susceptible due to their predisposed condition.

The present study offers multiple advantages. Firstly, we believe it is among the first studies to explore the impact of COVID-19 infection on NOD risk in older adults aged 60 and above. It also proposes the protective benefits of being free from COVID-19 and other types of respiratory infections in reducing the risk of NOD. Secondly, we divided controlled groups into a non-COVID otherwise unspecified group and a non-COVID with other respiratory infection group, conducting comparative analyses across varying follow-up durations (i.e., at 3, 6, 12 and 24 months). Thirdly, we also performed subgroup analyses based on sex differences, COVID-19 severity, and cognitive impairments as an outcome. Fourthly, we employed multiple heterogeneity and sensitivity tests to confirm the robustness of the findings, indicating they are not excessively reliant on any single study. Meanwhile, the Trim-and-Fill method was used to address potential publication bias, suggesting it did not significantly alter the main results. Unlike previous meta-analyses that encompassed all age

groups and contained inaccuracies in data from original studies regarding the number of COVID-19 cases and control participants, this review addressed this issue. For instance, from the Cohen et al. study (2022), only 87,337 of the 133,366 COVID-19 patients and an identical number of controls from a total of 2,762,557 should have been incorporated into the Rahmati et al. study (2023). This is because the original research by Cohen et al. (2022) utilized data from exactly 87,337 COVID-19 patients and the number-matched controls for calculating the cumulative incidence of NOD.

5. Limitation and future directions

Our systematic review with meta-analysis is not without limitations. First, substantial statistical heterogeneity among the 11 studies was observed in the analytic results, potentially attributed to variations in the age groups of older adults explored, types of dementia examined, characteristics of the non-COVID control groups, baseline time points for follow-up, duration of follow-up, diagnostic criteria for dementia, participant sample sizes, and specific viral variants of COVID-19 in the experimental groups. Second, the included studies were either retrospective or cross-sectional, hindering our ability to infer causality or prospectively observe temporal changes. Such studies are susceptible to biases like recall and selection bias due to their reliance on existing records and participant memory. Third, the duration of follow-up varied across cohorts from 3 to 24 months. A longer follow-up period may be necessary to fully understand COVID-19's long-term neurological impacts. Fourth, the results of the current meta-analysis only provide evidence regarding the association between COVID-19 infection and NOD in our targeted population, and cannot be utilized to establish cause-and-effect relationships. Fifth, our analyses were limited to evaluating the effects of

different control groups, sex differences, and the severity of COVID-19 on the risk of NOD after a COVID infection. Data on other potential moderators influencing this relationship was not accessible. For example, constraints in accessing comprehensive data on the cumulative incidence of NOD across various age groups (i.e., 60-69, 70-79, 80-89 and ≥ 90 years) restricted our ability to perform a meta-analysis assessing the impact of COVID-19 on NOD risk among different age cohorts when comparing COVID-19 infected older adults with those uninfected. Sixth, most included studies used ICD-10 codes to identify NOD, potentially introducing variations in diagnosis due to differing institutional criteria and coding practices (Qureshi et al., 2022). Lastly, due to inconsistencies in NOD incidence data at 6 months between Liu et al. (2021) and Liu et al. (2022), we included both studies to preserve data originality, choosing to use the 6-month data from Liu et al. 2021 and the 12-month data from Liu et al. 2022, albeit acknowledging potential biases. We assume that there might be a partially different (if not entirely different) sample of patients in separate studies, or that Liu et al. in 2022 excluded some data due to participants being lost to follow-up at 12 months when conducting the statistical analysis for the 6-month period. However, considering that more dementia cases in control and severe COVID-19 groups were reported in Liu et al 2022 at 6-month post-follow-up mark, compared to those reported in 2021, it is more likely that at least some of the samples differed between these two studies, highlighting the necessity to include both studies in our review.

These limitations in our review emphasize areas for future directions, when addressable. In addition, potentially various risks of different types of dementia related to COVID-infection, the effects of multiple COVID infections and vaccination status, and the development of

prevention and rehabilitation strategies may also hold value for future research.

6. CONCLUSIONS

In the current review of 11 studies comparing 939,824 post-COVID-19 cases with 6,765,117 controls, it was found that, relative to all non-COVID controls, COVID-19 infection significantly increased the risk of new-onset dementia at subacute and chronic stages in recovered COVID-19 older adult patients aged 60 years and above. When control groups were categorized, COVID-19 positive patients exhibited a higher risk of NOD compared to non-COVID cohorts with otherwise unspecified health status. This risk level was similar to that observed in non-COVID patients with other respiratory infections. Future studies are encouraged to provide more evidence in these findings, and specify the risks associated with different dementia types, assess the impacts of multiple COVID-19 infections and vaccination statuses, and explore strategies for better rehabilitation of affected patients.

Conflicts of interest and financial disclosures

All authors declare no financial or non-financial conflicts of interest.

Author contributions

DS, TC, and CH conceived the idea of the study and developed the protocol. DS accessed and verified the data, and analysed and interpreted the data. DS undertook the literature search, selected studies, and extracted the data with help from CXYW. DS wrote the first draft of the manuscript with input from CXYW, TC, and CH. All authors read and commented critically on drafts of the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication. TC and CH supervised the entire work and is the guarantor.

Data availability statement

All data relevant to the current study are included in this manuscript or available from the supplementary files uploaded.

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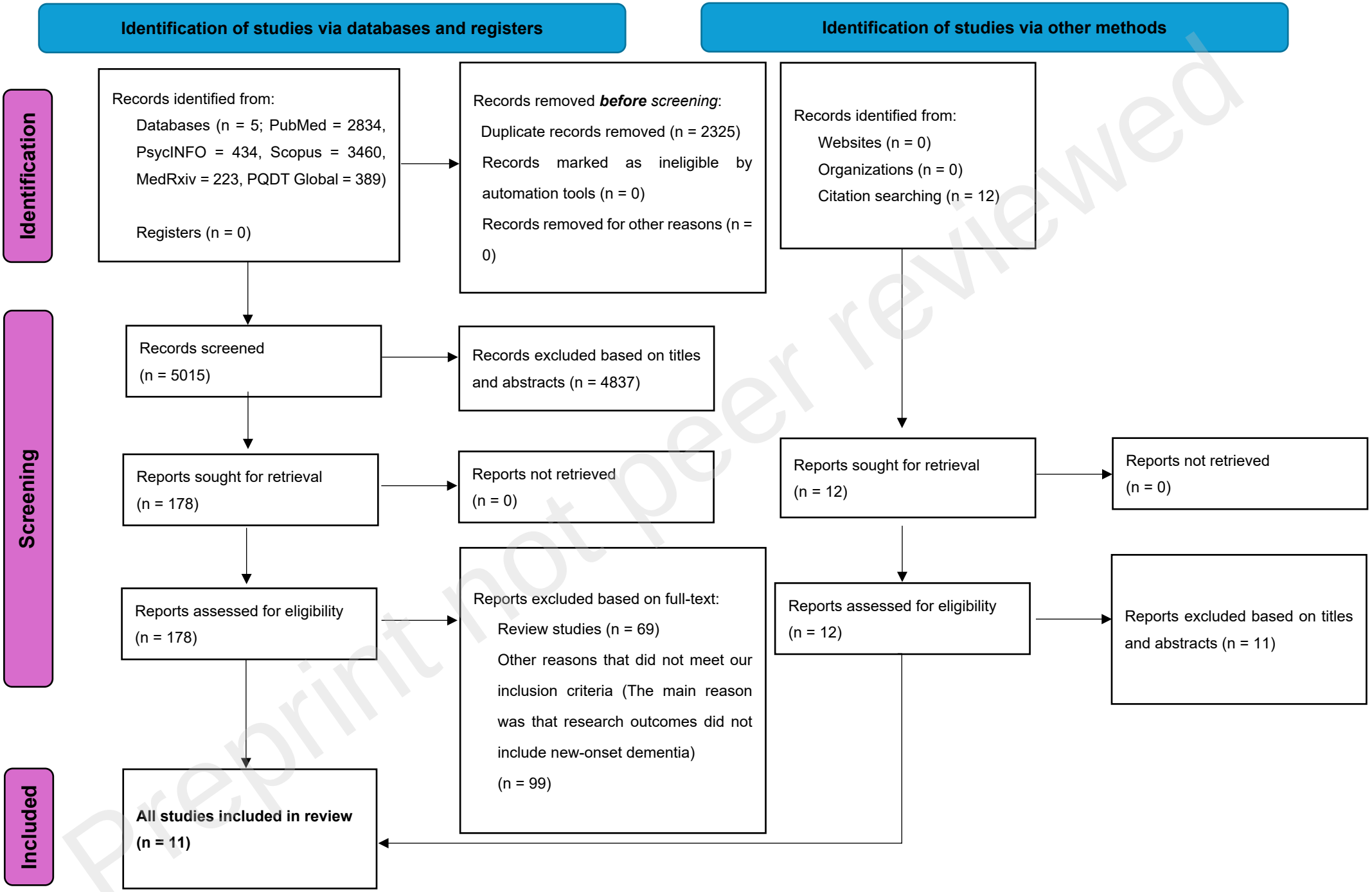


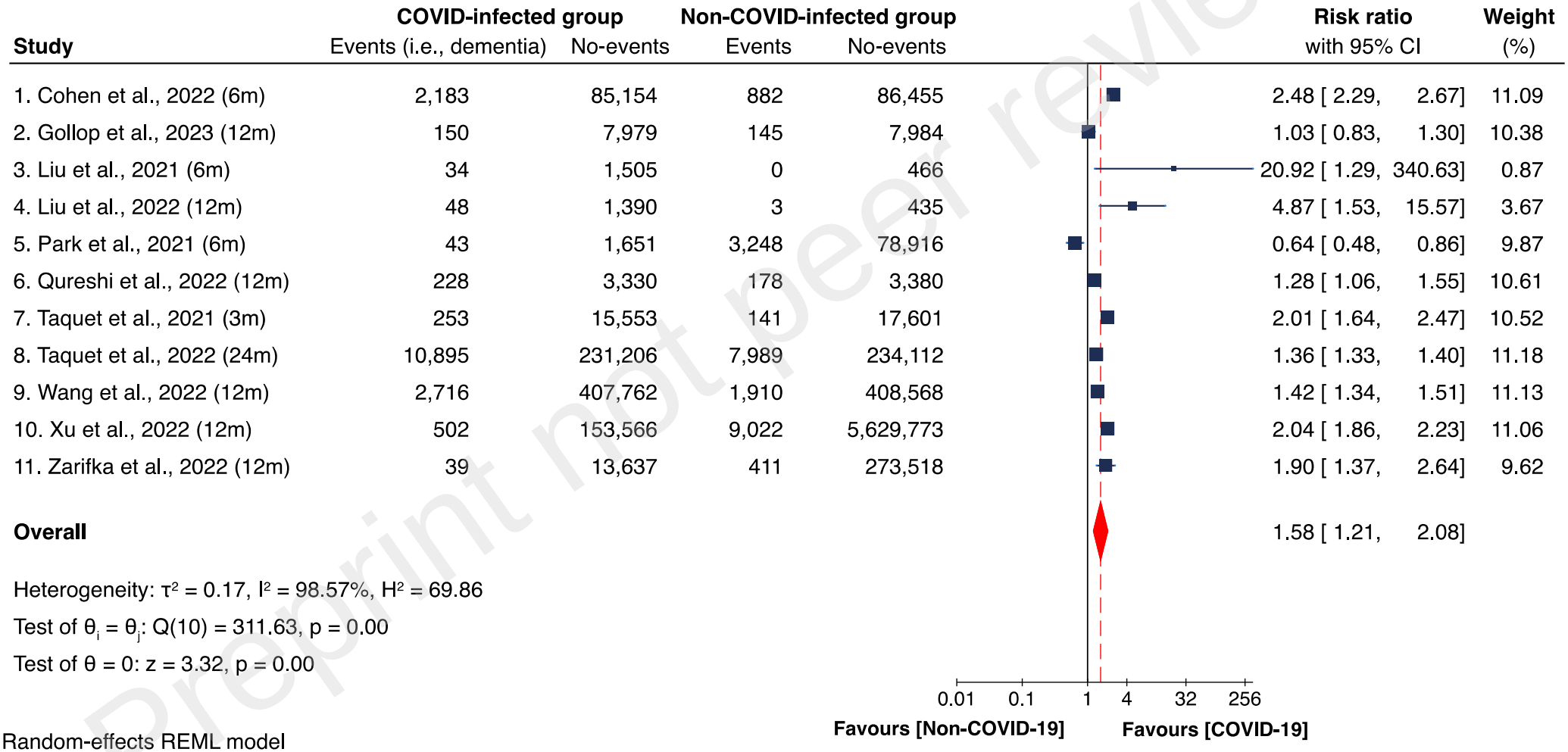
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram demonstrating search strategy.

Table 1. A summary of the general characteristics of the 11 studies included in this review.

Study	Country	Type of research	Groups	Older adults age group	COVID-19 diagnosis	Dementia assessment	Examined type of dementia	Post-COVID follow-up
Cohen et al. (2022)	USA	Retrospective cohort	COVID +: 87337 Matched COVID -: 87337	≥65 years	RT-PCR	ICD-10	All-cause Dementia	6 months
Gollop et al. (2023)	Germany	Retrospective cohort	COVID+: 8129 Matched AURI: 8129	≥65 years	RT-PCR	ICD-10	All-cause Dementia	3, 6, and 12 months
Liu et al. (2021)	China Mainland	Cross-sectional	COVID +: 1539 COVID -: 466	≥60 years	RT-PCR	TICS-40	All-cause Dementia	6 months
Liu et al. (2022)	China Mainland	Prospective cohort	COVID +: 1438 COVID -: 438	≥60 years	RT-PCR	TICS-40	All-cause Dementia	12 months
Park et al. (2021)	South Korea	Retrospective cohort	COVID +: 1694 COVID -: 82164	≥60 years	RT-PCR	ICD-10	All-cause Dementia	6 months
Qureshi et al. (2022)	USA	Retrospective cohort	COVID + pneumonia: 3558 Matched COVID - pneumonia: 3538	>70 years	RT-PCR	ICD-10	All-cause Dementia	12 months
Taquet et al. (2021)	USA	Retrospective cohort	COVID +: 15806 Matched Influenza: 4416 Matched other respiratory tract infection: 13326	≥65 years	RT-PCR	ICD-10	All-cause Dementia	3 months
Taquet et al. (2022)	USA, Australia, the UK, Spain, Bulgaria, India, Malaysia, and Taiwan	Retrospective cohort	COVID+: 242,101 Matched another respiratory infection: 242,101	≥65 years	RT-PCR	ICD-10	All-cause Dementia	6 and 24 months
Wang et al. (2022)	USA	Retrospective cohort	COVID+: 410,478 Matched COVID-: 410,478	≥65 years	RT-PCR	ICD-10	AD	12 months
Xu et al. (2022)	USA	Retrospective cohort	COVID+: 154,068 Contemporary COVID-: 5,638,795	≥60 years	RT-PCR	ICD-10	AD	12 months

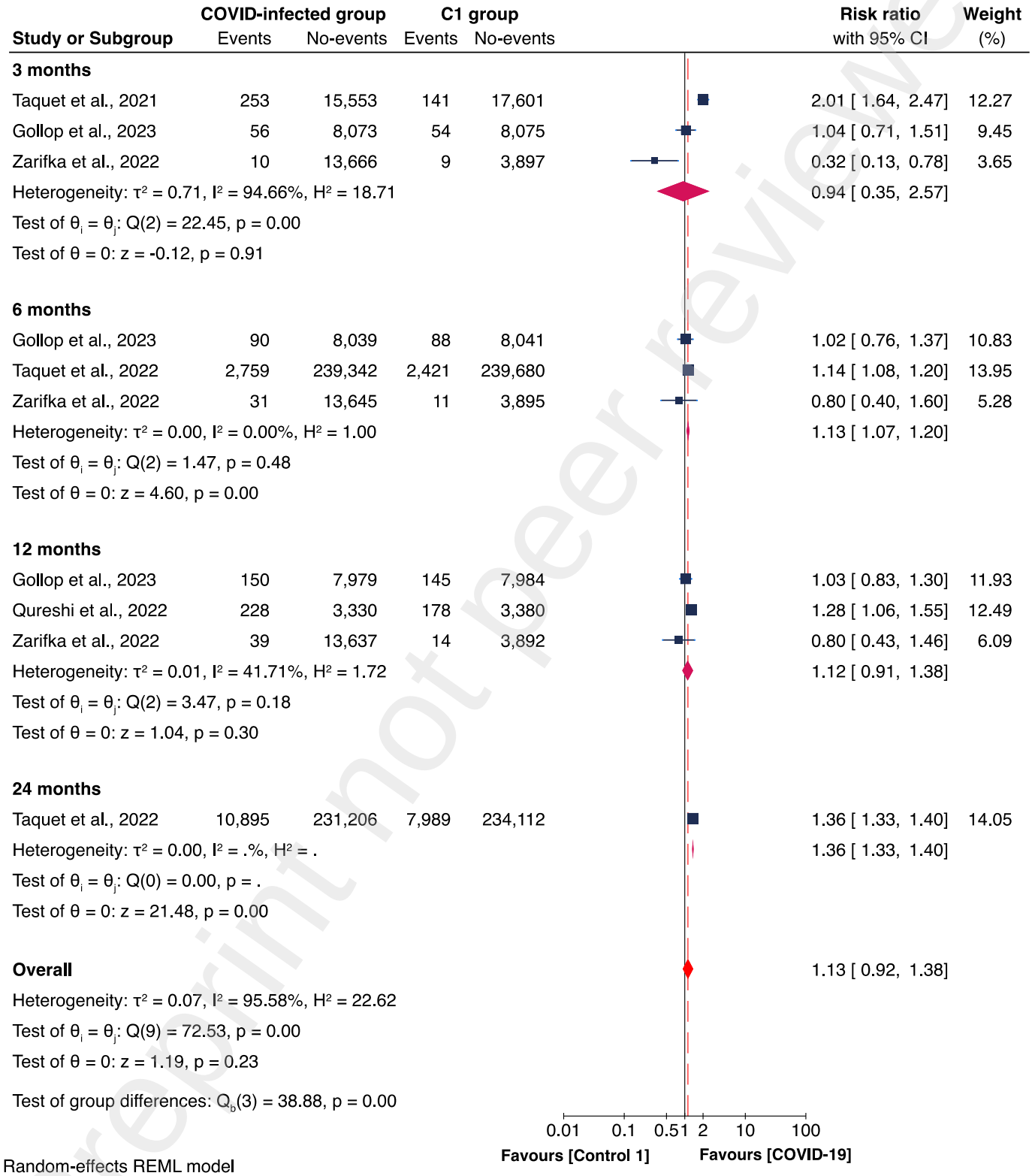
Zarifkar et al. (2022)	Denmark	Retrospective cohort	COVID+: 13676 COVID-: 270,023 Influenza A/B: 3906	≥60 years	RT-PCR	ICD-10	AD	3, 6 and 12 months

Figure 2. Forest plot of overall pooled meta-analysis of NOD risk between COVID-infected group and non-COVID-infected group across all 11 studies.



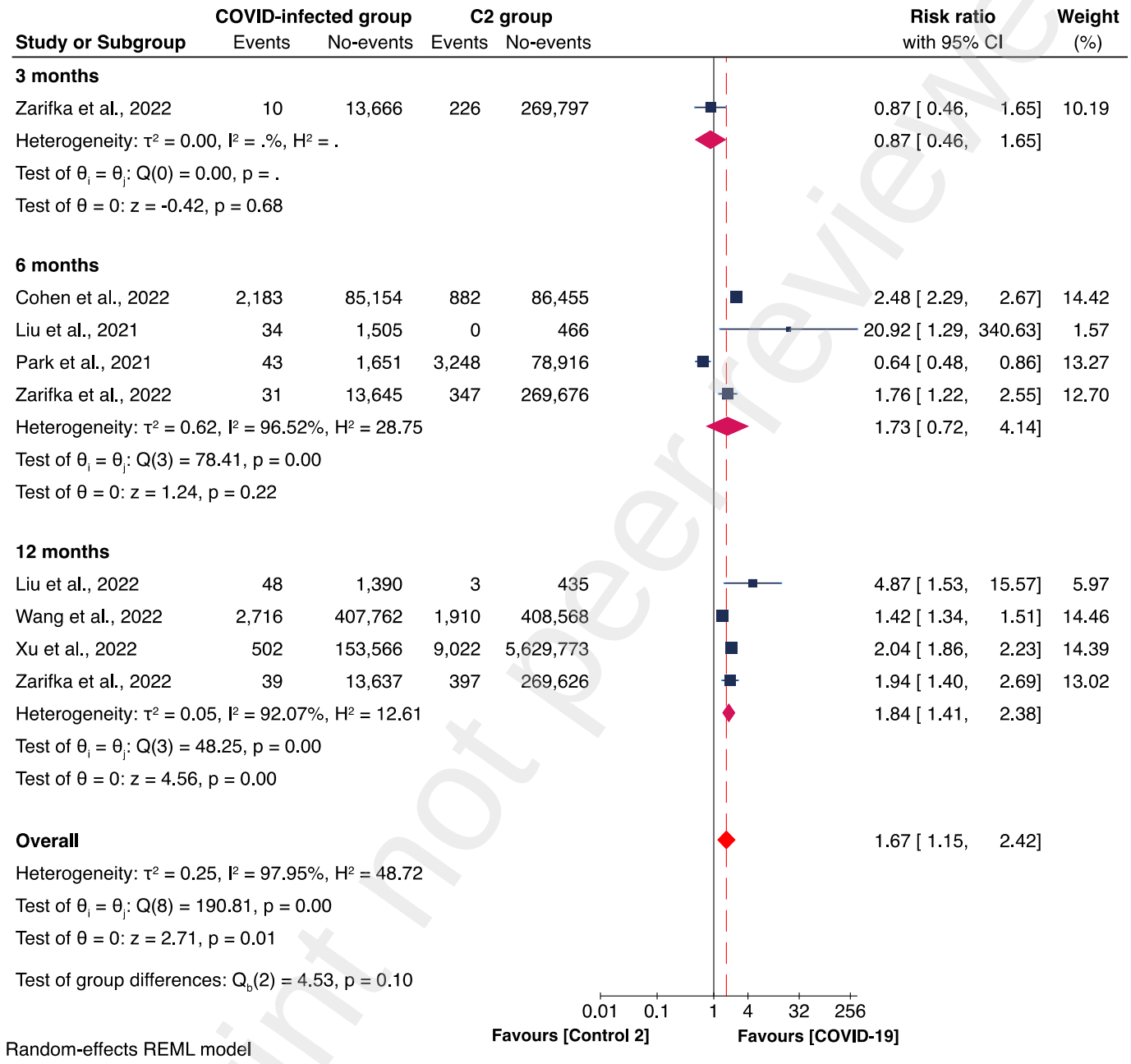
Abbreviation: m, months. NOD, new-onset dementia.

Figure 3. Forest plot of the meta-analysis of NOD risk between COVID-infected group and C1 group at 3, 6, 12, 24 months.



Abbreviation: C1, non-COVID cohorts with other types of respiratory infections. NOD, new-onset dementia.

Figure 4. Forest plot of the meta-analysis of NOD risk between COVID-infected group and C2 group at 3, 6, 12, 24 months.



Abbreviation: C2, non-COVID cohorts with otherwise unspecified health status. NOD, new-onset dementia.