https://doi.org/10.1038/s44400-025-00034-y

COVID-19 infection associated with increased risk of new-onset vascular dementia in adults ≥50 years

Dan Shan[1] ✉, Yudi Xu[2], Chuang Yang[3] ✉, Trevor J. Crawford[4,5] & Carol Holland[1,5]

COVID-19 is associated with long-term neurological complications, but its impact on new-onset dementia (NOD), particularly vascular dementia (VaD) and Alzheimer's disease (AD), remains unclear. We observed adults aged 50 years and older from the UK Biobank over a median observational period exceeding two years following COVID-19 infection. Incidences of various types of dementia (including all-cause dementia, AD, and VaD) in these individuals were compared with those in propensity-score-matched controls without COVID-19 and in individuals with non-COVID respiratory illnesses (including both non-communicable respiratory conditions and non-COVID respiratory tract infections). We found that COVID-19 survivors had a higher likelihood of developing NOD compared to uninfected controls. This increased risk was primarily driven by VaD rather than AD; however, the risk did not surpass that observed among individuals with non-COVID respiratory illnesses. Notably, individuals with pre-existing mental health conditions were particularly vulnerable, exhibiting significantly higher risks of VaD following COVID-19 infection.

Although it is evident that COVID-19 infection, particularly when it has been severe during the acute phase, can lead to subsequent cognitive impairments in older adults[1,2], the relationship between COVID-19 and new-onset dementia (NOD) over time remains inconclusive, as prior studies have yielded conflicting results[3–13]. These discrepancies possibly stem from methodological heterogeneity, including variations in baseline demographic and clinical characteristics of included COVID-19 patients, comparator groups (e.g., general non-COVID populations vs. individuals with non-COVID respiratory infections), follow-up durations (ranging from 3 to 24 months), and dementia subtypes (e.g., all-cause dementia vs. Alzheimer's disease)[2]. In an effort to synthesize existing evidence, we previously conducted a systematic review and meta-analysis of 11 original studies, which revealed that older adults aged 60 years and above with prior COVID-19 infection had a 1.84-fold increased risk of developing NOD at 12 months compared with non-COVID counterparts with an otherwise unspecified health status. However, when compared with individuals with non-COVID respiratory infections (e.g., flu), the risk ratio was 1.13 (95% CI: 0.92–1.38), suggesting no significant excess risk of COVID-19 infection[14].

Several critical gaps remain in the literature in this field. First, existing studies have limited follow-up periods (i.e., 3–24 months post-infection), with only one study extending to 24 months[5]. Given the slow and progressive nature of dementia, short-term findings may be confounded by transient cognitive changes, making long-term and continuous monitoring essential. Second, only five prior studies moderately controlled for baseline differences between COVID-19 and comparator groups via using propensity score matching approaches[5,7,8,10,12]. This raises concerns about reverse causality in other studies that did not sufficiently control for certain confounders, as individuals with preexisting cognitive impairment may have been more susceptible to COVID-19 due to difficulties adhering to preventive measures or engaging in post-infection rehabilitation[15]. This could lead to the misattribution of cognitive decline to COVID-19 rather than to underlying cognitive frailty. Third, prior research has largely focused on all-cause dementia or Alzheimer's disease (AD), with no cohort study specifically investigating vascular dementia (VaD). Given converging evidence that COVID-19 could precipitate endothelial dysfunction, vascular inflammation/thromboinflammation and microvascular injury—mechanisms linked to acute cerebrovascular events and downstream cerebral small-vessel disease, blood–brain barrier disruption, and chronic hypoperfusion, which are core substrates of vascular cognitive impairment and dementia—it is biologically plausible that infection may exacerbate VaD risk[16–18];

[1]Centre for Ageing Research, Division of Health Research, Faculty of Health and Medicine, Lancaster University, Health Innovation One, Sir John Fisher Drive, Lancaster, UK. [2]Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China. [3]Medical Faculty, University of Leipzig, Leipzig, Germany. [4]Centre for Ageing Research, Department of Psychology, Faculty of Science and Technology, Fylde College, Lancaster University, Bailrigg, Lancaster, UK. [5]These authors jointly supervised this work: Trevor J. Crawford, Carol Holland. ✉e-mail: d.shan@lancaster.ac.uk; yangchuang_leipzig@outlook.com

accordingly, evaluating VaD as a distinct outcome alongside AD is warranted. Fourth, among the 11 studies included in the meta-analysis, only one accounted for the potential influence of COVID-19 vaccination[5]. This might be a major limitation in this field, as vaccination could not only reduce infection risk but also mitigate severe clinical outcomes by decreasing hospitalisation and ICU admission rates[19], potentially helping to reduce downstream complications resulting from COVID-19, including cognitive impairments.

Given the irreversible nature and profound societal burden of dementia, ongoing surveillance of the association between COVID-19 and NOD is imperative, particularly among older adults. Our primary aim was to explore whether prior COVID-19 infection is associated with an increased risk of NOD over time, thereby contributing further evidence to this field and addressing multiple methodological limitations of prior research (e.g., extended observational window; pre-specification of VaD as a distinct outcome; propensity-score matching on key covariates—including vaccination status—with additional covariate adjustments).

In addition, certain non-communicable respiratory conditions, such as asthma and chronic obstructive pulmonary disease (COPD), may also be associated with increased NOD risks[20,21]. However, no prior studies have directly compared the risk of NOD following COVID-19 infection with that associated with these non-communicable respiratory conditions. Furthermore, our previous meta-analysis revealed no significant excess risk of NOD specifically attributable to COVID-19 infection compared to non-COVID respiratory infections[14]. Hence, our secondary aim was to assess whether certain other respiratory conditions, including both non-COVID respiratory tract infections and certain types of non-communicable respiratory diseases, pose a similar risk of NOD as COVID-19 infection. To achieve these objectives, we aimed to conduct a longitudinal cohort study using secondary data analysis of the UK Biobank (UKBB) public dataset.

Results

A total of 54,757 participants met the inclusion criteria and were eligible for final statistical analysis, including 16,017 participants with COVID-19 and 38,740 non-COVID participants. The median observation period was 24.1 months (interquartile range: 22.1–26.4). The propensity score-matched (PSM) dataset 1 comprised 16,017 participants with COVID-19 matched to 16,017 contemporary non-COVID-19 comparators. The PSM dataset 2 comprised 2150 participants with COVID-19 matched to 2150 non-COVID-19 comparators who had specific respiratory conditions, including non-COVID respiratory tract infections or certain non-communicable respiratory diseases. Table 1 presents the baseline characteristics of matched dataset 1; most covariates achieved SMDs <0.10 and all were <0.20, indicating negligible-to-small residual differences and satisfactory post-match balance. In PSM dataset 2 (Supplementary Table S4), the SMDs for most characteristics were <0.2, except for cardiovascular diseases (SMD = 0.21), cancer (SMD = 0.27), and smoking status (SMD = 0.21), suggesting a minimal imbalance in these characteristics between subgroups. These covariates were additionally adjusted for in the Cox models, yielding estimates consistent with the main analysis.

Main analysis of NOD risk

The Kaplan–Meier survival analysis demonstrated a lower dementia-free probability over time in the COVID-19 group compared to non-COVID-19 group, with significant differences observed for all-cause dementia (log-rank $P = 0.002$, Fig. 1A) and VaD (log-rank $P = 0.014$, Fig. 1C), whereas no significant difference was observed for AD (log-rank $P = 0.659$, Fig. 1B).

As shown in Fig. 1, participants with prior COVID-19 infection had an overall significantly higher risk of new-onset all-cause dementia and VaD, but not AD, compared to matched non-COVID-19 controls. Cox proportional hazards models further supported these results (Table 2). Compared with matched non-COVID-19 controls, prior COVID-19 infection was associated with a 41% increased risk of all-cause dementia (HR: 1.41, 95% CI: 1.13–1.75, $p = 0.002$) and a 77% increased risk of VaD (HR: 1.77, 95% CI: 1.12–2.82, $p = 0.015$), whereas no significant association was found for AD (HR: 1.09, 95% CI: 0.74–1.61, $p = 0.659$). However, when compared with participants diagnosed with non-COVID respiratory tract diseases, COVID-19 was not associated with a statistically significantly elevated risk of all-cause dementia (HR: 0.93, 95% CI: 0.58–1.48, $p = 0.754$), AD (HR: 1.96, 95% CI: 0.69–5.63, $p = 0.209$), or VaD (HR: 0.90, 95% CI: 0.32–2.57, $p = 0.845$). Additional Kaplan–Meier survival analysis in Supplementary Fig. S1 also demonstrated this trend by suggesting overall similar dementia-free probability between the COVID-19 and non-COVID respiratory disease groups, with log-rank tests showing non-significant difference for all-cause dementia (log-rank $P = 0.754$, Supplementary Fig. S1A), AD (log-rank $P = 0.202$, Supplementary Fig. S1B), and VaD (log-rank $P = 0.845$, Supplementary Fig. S1C). As previously defined, all-cause dementia included, but was not limited to, AD and VaD. However, other dementia subtypes could not be analysed due to insufficient data in the UKBB.

Subgroup analysis of NOD risk

Subgroup analyses revealed heterogeneous associations among the COVID-19 group, the contemporary non-COVID group, and the contemporary non-COVID respiratory diseases group in relation to the risk of NOD, with distinct patterns observed for all-cause dementia (Supplementary Table S5, Supplementary Figs. S2, S3), AD (Supplementary Table S6), and VaD (Table 3). To avoid overinterpretation, here we reported statistically significant subgroup findings only when accompanied by significant evidence of effect modification (i.e., $P_{\text{for interaction}} < 0.05$).

Specifically, compared with contemporary non-COVID-19 participants (Supplementary Table S5 and Supplementary Fig. S2), COVID-19 infection was significantly associated with an increased risk of all-cause dementia among men (HR: 1.52, 95% CI: 1.14–2.02, $p = 0.004$), older adults aged ≥65 years (HR: 1.59, 95% CI: 1.27–2.00, $p < 0.001$), unvaccinated participants (HR: 1.46, 95% CI: 1.17–1.82, $p = 0.001$), participants with weekly or more frequent alcohol intake (HR: 1.46, 95% CI: 1.09–1.95, $p = 0.011$), hypertension (HR: 1.60, 95% CI: 1.24–2.07, $p < 0.001$), diabetes mellitus (HR: 1.68, 95% CI: 1.04–2.71, $p = 0.033$), cardiovascular diseases (HR: 1.79, 95% CI: 1.25–2.57, $p = 0.002$), neurological diseases (HR: 1.85, 95% CI: 1.26–2.73, $p = 0.002$), mental illnesses (HR: 2.10, 95% CI: 1.29–3.42, $p = 0.003$), and cancer (HR: 1.70, 95% CI: 1.10–2.63, $p = 0.017$). However, no statistically significant association was observed among individuals aged <65 years (HR: 0.55, 95% CI: 0.23–1.30, $p = 0.173$). Compared with participants diagnosed with contemporary non-COVID respiratory diseases (Supplementary Fig. S3), subgroup analyses revealed no significant differences across sex, age, ethnicity, BMI, lifestyle factors, or pre-existing medical conditions.

As for new-onset AD (Supplementary Table S6), compared with contemporary non-COVID-19 participants, COVID-19 infection was not significantly associated with an increased risk across all subgroups (all $p > 0.05$). Similarly, compared with participants diagnosed with contemporary non-COVID respiratory diseases, no significant associations were observed.

As for new-onset VaD (Table 3), COVID-19 infection was associated with an increased risk compared with the contemporary non-COVID-19 participants among women (HR: 2.80, 95% CI: 1.16–6.75, $p = 0.022$), older adults aged ≥65 years (HR: 1.91, 95% CI: 1.20–3.06, $p = 0.007$), participants with unvaccinated status (HR: 1.91, 95% CI: 1.19–3.05, $p = 0.007$), those with weekly or more frequent alcohol intake (HR: 1.95, 95% CI: 1.06–3.6, $p = 0.033$), hypertension (HR: 2.02, 95% CI: 1.18–3.44, $p = 0.01$), diabetes mellitus (HR: 3.66, 95% CI: 1.35–9.91, $p = 0.011$), neurological diseases (HR: 2.30, 95% CI: 1.05–5.02, $p = 0.037$), mental illnesses (HR: 5.33, 95% CI: 1.68–16.9, $p = 0.004$), cardiovascular diseases (HR: 2.03, 95% CI: 1.04–3.95, $p = 0.038$). When compared to the contemporary non-COVID respiratory diseases group, no significant differences in VaD risk were observed across all subgroups (all $p > 0.05$).

Sensitivity analysis of NOD risk

Sensitivity analyses confirmed the robustness of our findings (Supplementary Tables S7–S15). Excluding participants with <3 months of follow-up

Table 1 | Baseline characteristics of the 1:1 propensity score-matched dataset 1

Characteristics	COVID-19 (*n* = 16,017)	Non-COVID-19 (*n* = 16,017)	SMD
Age	65.62 ± 8.47	65.75 ± 8.27	0.02
Male, *N* (%)	7592 (47.40%)	7515 (46.92%)	0.01
White, *N* (%)	14,341 (89.54%)	14,512 (90.60%)	0.04
Townsend deprivation index	−0.67 ± 3.27	−0.93 ± 3.28	0.08
Body mass index (kg/m^2)	28.36 ± 5.15	28.26 ± 5.30	0.02
Metabolic equivalent task (min)	2703.47 ± 2753.46	2668.76 ± 2760.06	0.01
Diabetes mellitus, *N* (%)	1217 (7.60%)	1192 (7.44%)	0.01
Hypertension, *N* (%)	8146 (50.86%)	8553 (53.40%)	0.05
Cardiovascular diseases, *N* (%)	2245 (14.02%)	2575 (16.08%)	0.06
Neurological diseases, *N* (%)	1294 (8.08%)	1506 (9.40%)	0.05
Mental illnesses, *N* (%)	1360 (8.49%)	1833 (11.44%)	0.10
Cancer, *N* (%)	2504 (15.63%)	3392 (21.18%)	0.14
Vaccinations, *N* (%)			0.03
No	10,744 (67.08%)	10,960 (68.43%)	
1 dose	3297 (20.58%)	3188 (19.90%)	
2 doses	1976 (12.34%)	1869 (11.67%)	
Smoking status, *N* (%)			0.06
Never	6433 (40.16%)	6533 (40.79%)	
Previous	7720 (48.20%)	7335 (45.80%)	
Current	1864 (11.64%)	2149 (13.42%)	
Alcohol intake frequency, *N* (%)			0.08
Never	1640 (10.24%)	1538 (9.60%)	
Special occasions only	2077 (12.97%)	2105 (13.14%)	
One to three times a month	1917 (11.97%)	1900 (11.86%)	
Once or twice a week	4447 (27.76%)	4091 (25.54%)	
Three or four times a week	3308 (20.65%)	3321 (20.73%)	
Daily or almost daily	2628 (16.41%)	3062 (19.12%)	

Cardiovascular diseases were defined as including heart failure, coronary artery disease, and cardiomyopathy. Neurological diseases were defined as including stroke, Parkinson's disease, Huntington's disease, multiple sclerosis, sleep disorders, and intracranial injury. Mental illnesses were defined as including depression, schizophrenia, and bipolar disorder. SMD refers to the standardized mean difference.

yielded consistent results (Supplementary Table S7). COVID-19 infection remained significantly associated with an increased risk of all-cause dementia (HR: 1.52, 95% CI: 1.17–1.98, $p = 0.002$) and VaD (HR: 1.69, 95% CI: 1.01–2.89, $p = 0.048$) when compared with the contemporary non-COVID-19 group. In contrast, no significant excess risk was observed when compared to the contemporary non-COVID respiratory diseases group for either all-cause dementia (HR: 1.02, 95% CI: 0.59–1.78, $p = 0.933$) or VaD (HR: 0.43, 95% CI: 0.11–1.73, $p = 0.235$). Fine-Gray competing risk models further supported these findings (Supplementary Table S8), demonstrating significant associations between COVID-19 and all-cause dementia (sub-distribution Hazard Ratio [sHR]: 1.38, 95% CI: 1.11–1.71, $p = 0.004$) and VaD (sHR: 1.73, 95% CI: 1.08–2.76, $p = 0.022$) compared to the contemporary non-COVID-19 group. Further adjustment for additional covariates after propensity score matching, including cardiometabolic conditions, lifestyle factors, and mental health disorders (Supplementary Table S9), resulted in a stronger association between COVID-19 and all-cause dementia (adjusted HR: 1.58, 95% CI: 1.27–1.97, $p < 0.001$) and VaD (adjusted HR: 2.05, 95% CI: 1.29–3.27, $p = 0.002$), while no significant risk increase was observed for AD (adjusted HR: 1.16, 95% CI: 0.79–1.72, $p = 0.452$). Consistent findings were observed in both partially and fully covariate-adjusted analyses conducted without propensity score matching (Supplementary Tables S10, S11).

Analyses restricted to propensity-score-matched participants with prior COVID-19-related hospitalisation revealed a substantially increased risk of all-cause dementia and VaD, both before and after additional covariate adjustments beyond propensity score matching (adjusted HR: 1.79, 95% CI: 1.26–2.54, $p = 0.001$; and adjusted HR: 2.42, 95% CI: 1.15–5.10, $p = 0.019$, respectively) (Supplementary Tables S12, S13). When comparing previously hospitalised COVID-19 participants with the contemporary non-COVID respiratory disease group, no statistically significant differences were observed for any type of NOD following full covariate adjustment (all $p > 0.05$).

Furthermore, a separate non-matched comparison between the full COVID-19 cohort ($n = 16{,}017$) and a small cohort of non-COVID respiratory infections ($n = 331$) did not indicate a significantly increased risk of all-cause dementia or VaD after adjusting for all covariates (adjusted HR: 1.30, 95% CI: 0.61–2.78, $p = 0.497$; adjusted HR: 2.52, 95% CI: 0.35–18.38, $p = 0.362$, respectively) (Supplementary Table S14).

In an additional sensitivity analysis excluding participants with any recorded major neurological or psychiatric disorders at baseline, fully adjusted estimates were consistent with the main analyses (Supplementary Table S15). Compared with contemporary non-COVID controls, risks remained elevated for all-cause dementia (adjusted HR: 1.45, 95% CI: 1.16–1.82, $p = 0.001$) and VaD (adjusted HR: 2.30, 95% CI: 1.40–3.77, $p = 0.001$), with no association for AD (adjusted HR: 1.14, 95% CI: 0.77–1.68, $p = 0.512$). When compared with the contemporary non-COVID respiratory tract diseases group, no statistically significant excess risk was observed (all $p > 0.05$)

Discussion

This study contributed to the growing body of evidence linking COVID-19 infection to an elevated risk of NOD among individuals aged 50 years and older. Leveraging longitudinal data from the UKBB with a median observation period of 24.1 months, our propensity scores matching analyses, supplemented by additional covariate adjustments, provided evidence supporting that prior COVID-19 infection may be associated with significantly increased risks of all-cause dementia and VaD, but not AD, when compared to non-COVID otherwise unspecified individuals. Specifically, we found that COVID-19 infection was associated with a 58% increased risk of all-cause dementia and a 105% increased risk of VaD after full covariate adjustment. However, when compared to individuals with non-COVID respiratory tract diseases, COVID-19 did not confer a significantly higher risk of dementia (including all-cause dementia, AD, and VaD), suggesting that the observed associations may reflect a broader impact of respiratory conditions on cognitive health rather than a COVID-19-specific effect.

Our findings aligned with two recent meta-analyses that reported similarly heightened risks of all-cause dementia following COVID-19 infection compared to non-COVID otherwise unspecified individuals[2,22]. However, while several previous studies indicated a significantly elevated risk of AD post-infection, our study did not suggest such an association but instead identified a heightened risk of VaD. This distinction is important, as, to our knowledge, VaD has not been specifically explored in a longitudinal setting in prior research on the effects of COVID-19. Although both all-cause dementia and VaD risks were increased in our study, the relative

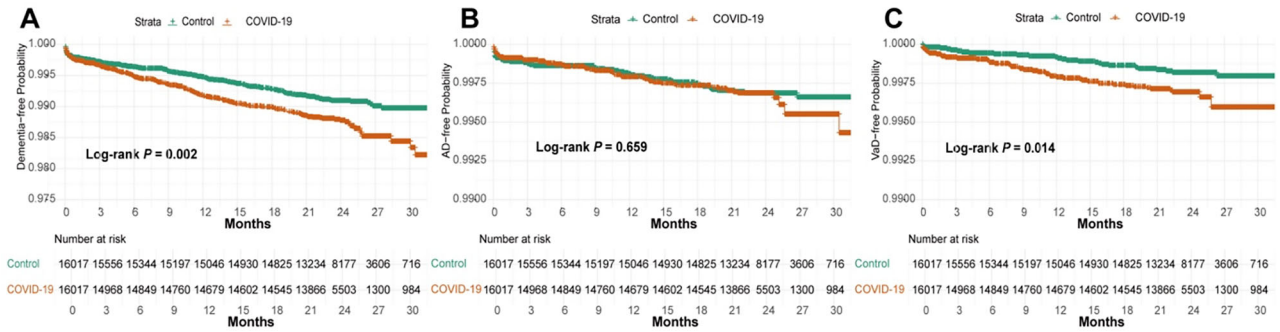

Fig. 1 | Dementia-free probability following COVID-19 infection. Kaplan–Meier survival curves for dementia-free probability among individuals with and without COVID-19 infection, stratified by **A** all-cause dementia, **B** Alzheimer's disease (AD), and **C** Vascular dementia (VaD). In this figure, "control" represents matched contemporary non-COVID-19 participants. In (**A**) and (**C**), dementia-free probability declined more rapidly in the COVID-19 group, with increasing divergence over time, suggesting a potential time-dependent accumulation of risk for all-cause dementia and VaD. In contrast, (**B**) shows no substantial separation between groups throughout most of the observation period; however, a divergence emerged after 24 months, possibly reflecting a delayed effect on AD risk that did not reach overall statistical significance.

Table 2 | Hazard ratios for the risk of NOD at the observational endpoint between the COVID-19 group and the matched contemporary non-COVID-19 group, as well as the contemporary non-COVID respiratory tract diseases group

Dementia types[a]	COVID-19 group (*n* = 16,017) vs. Contemporary non-COVID-19 group (*n* = 16,017)			COVID-19 group (*n* = 2150) vs. Contemporary respiratory tract diseases group (*n* = 2150)		
	Cases	HR (95% CI)	*p*	Cases	HR (95% CI)	*p*
All-cause dementia	336	1.41 (1.13–1.75)	0.002	73	0.93 (0.58–1.48)	0.754
AD	102	1.09 (0.74–1.61)	0.659	16	1.96 (0.69–5.63)	0.209
VaD	77	1.77 (1.12–2.82)	0.015	14	0.9 (0.32–2.57)	0.845

AD Alzheimer's disease, *VaD* Vascular dementia, *HR* Hazard Ratio, *CI* Confidence Interval.
[a]Data on other dementia types were insufficient for analysis. 'Cases' refer to the total number of incident dementia events observed in both the COVID-19 group and the comparator group for each dementia subtype. Hazard ratios with 95% CIs are reported.

contribution of VaD appeared to be the primary driver of the observed increased NOD risk, as the estimated risk increase for VaD was 47 percentage points higher than that for all-cause dementia. These findings might support the assumption that COVID-19 infection is particularly associated with an increased risk of VaD. The underlying pathophysiology likely involves prothrombotic, inflammatory, and microvascular dysfunction mechanisms, contributing to cerebral small vessel disease, blood-brain barrier disruption, and chronic cerebral hypoperfusion, ultimately leading to cognitive impairments and dementia[18]. Since VaD results from persistent cerebral hypoperfusion and vascular injury, the elevated risk observed in COVID-19 survivors may be attributed to direct or indirect cerebrovascular damage induced by SARS-CoV-2, which is known to trigger these pathological mechanisms[16].

It is noteworthy that our study (including findings based on both overall and subgroup analyses) found no statistically significant increase in AD risk following prior COVID-19 infection compared to non-COVID otherwise unspecified individuals, in contrast to earlier retrospective cohort studies that reported a higher risk of AD development post-infection[6,12,13]. This discrepancy may stem from differences in observational duration, as prior studies, which were conducted within a 12-month timeframe, may have overestimated AD risk in COVID-19 survivors. Although it is widely agreed that COVID-19 infection can be linked to long-term cognitive impairments (sometimes referred to as long COVID-related brain fog), especially in individuals of advanced age and with comorbidities[23], AD (which is irreversible compared to mild cognitive impairment) is characterised by a slow and progressive neurodegenerative process. Therefore, shorter observational periods in these studies may not be sufficient to detect clinically meaningful changes, whereas our study, with a median observation period exceeding two years, provided a more robust evaluation of the long-term implications of COVID-19 on NOD risk. Although we did not observe a statistically significant association during the limited study period, neuropathological evidence indicated that SARS-CoV-2 infection may accelerate amyloid-beta accumulation and tau pathology, which are central to AD pathogenesis in susceptible individuals[24–26], underscoring the need for further long-term investigation. Given the slow and progressive nature of AD, the late divergence observed in the Kaplan–Meier curves after 24 months in our study might suggest a delayed effect that warrants confirmation through extended follow-up in future studies. Accordingly, the increasing separation of the survival curves over time likely reflects cumulative hazard and diagnostic latency; vascular pathways (systemic inflammation, endothelial dysfunction, thromboinflammation) may manifest clinically sooner than neurodegenerative processes typical of AD, whereas the latter may require longer follow-up for robust detection. Consistent with this, risks were higher among previously hospitalised cases, and the late—yet non-significant—divergence for AD may suggest limited power within the current timeframe.

The similar dementia risks (including all-cause dementia, AD, and VaD) observed between COVID-19 and non-COVID respiratory tract disease groups underscored the broader impact of respiratory illnesses on cognitive health. The non-COVID respiratory tract disease group included individuals with either non-COVID respiratory tract infections (e.g., influenza A/B) or certain non-communicable respiratory diseases (e.g., asthma, pneumonia, and COPD), conditions that have previously been identified as risk factors for NOD, particularly among older adults. For example, a meta-analysis showed that non-COVID respiratory diseases were associated with a moderately increased all-cause dementia risk (pooled HR: 1.54, 95% CI, 1.30–1.81)[27]. Mechanistically, chronic non-COVID respiratory conditions such as asthma and COPD may plausibly increase the risk of VaD through persistent systemic inflammation, intermittent hypoxaemia/hypercapnia, and endothelial dysfunction, which promote cerebral small-vessel disease, blood–brain barrier disruption, and chronic hypoperfusion; infection- or exacerbation-related thromboinflammatory

Table 3 | Hazard ratios for the risk of new-onset vascular dementia across subgroups, comparing the COVID-19 group with the matched contemporary non-COVID-19 group and the contemporary non-COVID respiratory tract diseases group

Type	COVID-19 group (*n* = 16,017) vs. Contemporary non-COVID-19 group (*n* = 16,017)				COVID-19 group (*n* = 2150) vs. Contemporary respiratory tract diseases group (*n* = 2150)			
Subgroups	**Cases**	**HR (95% CI)**	***p***	***P* for interaction**	**Cases**	**HR (95% CI)**	***p***	***P* for interaction**
Sex				0.003				0.744
Women	25	2.80 (1.16–6.75)	0.022		5	0.61 (0.10–3.65)	0.588	
Men	52	1.45 (0.84–2.52)	0.185		9	1.11 (0.30–4.13)	0.878	
Age				0.001				0.998
<65years	2	0.97 (0.06–15.5)	0.983		0	0 (0-inf)	0.999	
≥65 years	75	1.91 (1.20–3.06)	0.007		14	0.90 (0.31–2.55)	0.836	
Ethnicity				0.992				0.998
Non-White	2	0 (0-inf)	0.999		0	0 (0-inf)	0.999	
White	75	1.72 (1.08–2.75)	0.023		14	0.90 (0.32–2.57)	0.843	
BMI				0.47				0.926
<30 kg/m^2	50	1.40 (0.80–2.45)	0.244		7	0.35 (0.07–1.82)	0.214	
≥30 kg/m^2	27	2.89 (1.22–6.84)	0.016		7	2.31 (0.45–11.9)	0.317	
Alcohol intake frequency				0.017				0.615
Less than weekly	32	1.55 (0.76–3.15)	0.224		6	0.96 (0.19–4.74)	0.957	
Weekly or more	45	1.95 (1.06–3.6)	0.033		8	0.86 (0.22–3.46)	0.837	
Smoking status				0.116				0.336
Never	21	2.60 (0.97–6.69)	0.048		5	1.23 (0.21–7.38)	0.818	
Ever	56	1.55 (0.91–2.65)	0.109		9	0.76 (0.20–2.82)	0.677	
Hypertension				<0.001				0.067
No	18	1.37 (0.53–3.54)	0.511		1	0 (0-inf)	0.999	
Yes	59	2.02 (1.18–3.44)	0.01		13	1.10 (0.37–3.27)	0.864	
Diabetes mellitus				<0.001				0.088
No	55	1.40 (0.82–2.39)	0.219		9	1.10 (0.29–4.10)	0.888	
Yes	22	3.66 (1.35–9.91)	0.011		5	0.70 (0.12–4.22)	0.701	
Cardiovascular diseases				<0.001				0.218
No	39	1.90 (1.00–3.64)	0.052		7	0.32 (0.06–1.67)	0.178	
Yes	38	2.03 (1.04–3.95)	0.038		7	3.49 (0.68–18.0)	0.136	
Neurological diseases				<0.001				<0.001
No	50	1.74 (0.98–3.10)	0.059		8	1.42 (0.34–5.94)	0.632	
Yes	27	2.30 (1.05–5.02)	0.037		6	0.73 (0.13–3.99)	0.716	
Mental illnesses				0.001				0.954
No	61	1.44 (0.86–2.40)	0.162		12	0.85 (0.28–2.65)	0.786	
Yes	16	5.33 (1.68–16.9)	0.004		2	1.71 (0.11–27.5)	0.704	
Cancer				0.549				0.998
No	56	1.54 (0.90–2.64)	0.117		13	inf (0-inf)	0.999	
Yes	21	3.04 (1.22–7.59)	0.017		1	0.68 (0.23–2.03)	0.491	
Vaccination				0.01				0.998
No	76	1.91 (1.19–3.05)	0.007		14	0.90 (0.31–2.56)	0.841	
Yes	1	0 (0-inf)	0.999		0	0 (0-inf)	0.999	

'Cases' refer to the combined total number of new-onset vascular dementia events observed in both the COVID-19 group and the comparator group within each subgroup category.
The subgroup categorized by 'Physical activity' was not analysed due to a high value missing rate (*n* = 13,646, 24.92%).
HR Hazard Ratio, *CI* Confidence Interval, *BMI* body mass index.

activity may further amplify these processes[18,20,21,27–29]. Furthermore, our sensitivity analysis, which compared the COVID-19 group with individuals who had non-COVID respiratory infections, yielded findings consistent with a recent meta-analysis of older adults aged 60 and above, which also suggested a similar risk of new-onset all-cause dementia between COVID-19 survivors and individuals with other respiratory infections[14]. These results highlighted the importance of considering the cognitive consequences of respiratory conditions beyond COVID-19 rather than attributing all observed effects solely to SARS-CoV-2 infection.

Importantly, beyond methodological explanations (e.g., limited statistical power due to small sample size, residual confounding, or differential case ascertainment), an active-comparator effect should also be considered. Non-COVID respiratory infections themselves likely elevated NOD risk, thereby attenuating between-group differences when they were used as

comparators. Large population-based cohorts revealed that hospital-treated infections—including respiratory infections—were associated with long-term increases in incident dementia, with particularly strong links to vascular dementia and dose–response patterns across repeated infections[30,31]. Mechanistically, acute respiratory infections could trigger systemic cytokine surges, endothelial dysfunction, blood–brain barrier disruption, microthromboinflammation, and hypoxaemia, all of which are consistent with pathways to small-vessel disease and vascular cognitive impairment; experimental and human evidence further suggested neurotropic potential for influenza and infection-driven microglial activation[32–34]. Recent multimodal work also connected prior common infections (e.g., influenza and other respiratory infections) to region-specific brain atrophy and immune-proteomic signatures related to neurodegeneration[32]. Taken together, these data support the interpretation that the non-COVID respiratory infection group carries intrinsic, infection-related dementia risk, which would be expected to dilute any excess risk attributable specifically to SARS-CoV-2 in our sensitivity analyses.

Among various subgroup and sensitivity analyses, given the potential masking effect on all-cause dementia risk, here we primarily focused on discussing new-onset VaD. We observed that prior hospitalisation due to COVID-19 infection was associated with an increased risk of VaD development (adjusted HR: 2.42) compared to non-COVID individuals with otherwise unspecified status. This elevated risk exceeded that observed in the overall COVID-19 cohort, which included individuals with varying disease severity, including both those who had been hospitalised and those managed as outpatients, without stratification. Other characteristics associated with an increased risk of new-onset VaD following prior COVID-19 infection included female sex, aged ≥65, weekly or more frequent alcohol intake, hypertension, diabetes mellitus, cardiovascular diseases, neurological diseases, mental illnesses, and lack of COVID-19 vaccination. Among these, age ≥65, hypertension, diabetes mellitus, cardiovascular diseases, neurological diseases, and mental illnesses appeared to be the most prominent risk factors, as supported by more notable interaction effects observed in subgroup analyses, and consistent with prior evidence on established VaD risk factors[28,29,35–38]. Although these factors are traditionally associated with VaD risk, their effects can be exacerbated in the context of COVID-19, potentially due to additive or synergistic mechanisms triggered by SARS-CoV-2. Notably, individuals with pre-existing mental illnesses, including depression, schizophrenia, and bipolar disorder, had the highest risk of developing VaD following COVID-19 infection among these characteristics (HR: 5.33), underscoring their heightened vulnerability and the urgent need for targeted prevention, early intervention, and enhanced neurological monitoring. Importantly, this pattern could not be solely attributed to pre-existing neuropsychiatric morbidity, as the COVID-19–VaD association remained significant even after excluding such conditions at baseline. In addition, while previous research has not identified sex-based differences in cumulative VaD risk generally[39], our findings suggested that women may be disproportionately affected in the post-COVID context (HR: 2.80), warranting further investigation into sex-specific mechanisms and tailored post-infection cognitive care.

Furthermore, our subgroup analyses indicated that unvaccinated individuals were at a substantially higher risk of developing VaD following COVID-19 infection, whereas vaccinated participants did not show such an elevated risk. This pattern may suggest a potential protective role of COVID-19 vaccination, possibly by reducing severe clinical courses, hospitalisation, and related systemic and cerebrovascular complications, which in turn could mitigate downstream pathways to vascular cognitive impairment[40]. Although our study was not designed to directly evaluate vaccine efficacy against dementia, these findings highlight the importance of vaccination not only in preventing acute infection but also in reducing long-term neurological sequelae[40,41].

A major strength of this study was its rigorous methodological approach, including propensity score matching with additional adjustments to minimize baseline confounding, as well as multiple sensitivity analyses to test robustness. Moreover, by comparing COVID-19 with both non-COVID individuals of otherwise unspecified status and with non-COVID respiratory tract diseases, we were able to disentangle the effects of COVID-19 from those of other respiratory illnesses (including non-communicable respiratory conditions and non-COVID respiratory infections). However, several limitations should be acknowledged. First, the median observation period of 24.1 months may not fully capture the long-term dementia risk associated with COVID-19, particularly for conditions with a slow progressive nature, such as AD. Second, although brain MRI data are available for a subset of UKBB participants, these objective imaging findings were not incorporated due to limited coverage and the study's focus on epidemiological associations. Future research could integrate multimodal neuroimaging evidence (e.g., structural MRI, diffusion tensor imaging, or functional MRI) to further elucidate the neuropathological pathways (e.g., cerebral small vessel disease, neuroinflammation, or amyloid and tau pathology) linking COVID-19 with dementia[1]. Third, the proportion of participants with a recorded pre-existing diagnosis of dementia or mild cognitive impairment (MCI) at cohort entry (1.79%) is usually lower than population-based expectations for UK adults aged ≥50, likely reflecting the age distribution of our source population (many in their 50s–60s), the UKBB healthy-volunteer profile (lower burden of multimorbidity), and limited capture—particularly of MCI—in routine hospital/primary-care coding[42–44]. Any resulting non-differential under-ascertainment would be expected to dilute between-group differences (i.e., bias toward the null). Fourth, because dementia was ascertained from routine administrative ICD-10 codes, occasional diagnostic overlap with delirium cannot be fully excluded. Importantly, delirium (e.g., ICD-10, F05.0) was not part of our outcome definition. To further minimise the risk that acute delirium or transient post-infectious cognitive changes were misclassified as dementia, we conducted a sensitivity analysis excluding participants with <3 months of follow-up; results were consistent with the main analysis, indicating limited impact on our findings. Fifth, we did not analyse MCI risk due to the exclusion of individuals with MCI at baseline to avoid potential reverse causality. Given that MCI is a well-established precursor to dementia[42], future studies should examine whether COVID-19 influences its progression to dementia. Sixth, despite the advantages of propensity score matching and additional covariate adjustments, residual confounding cannot be entirely ruled out. Seventh, we did not assess the impact of COVID-19 variants on dementia risk. Prior evidence suggested that cognitive impairment may be more pronounced in individuals infected during earlier pandemic phases than in those infected with later variants, such as Delta and Omicron[45]. Finally, as our study population was predominantly of White British ancestry based on the UKBB, the generalisability of our findings to other racial and ethnic groups may be limited.

From a public health perspective, our findings emphasize the need for heightened cognitive surveillance, especially for older adults recovering from COVID-19 and other vulnerable populations with identified risk factors in this study. Given the global burden of dementia and the challenges of an aging population, early identification and intervention for post-COVID cognitive impairment could have substantial clinical and economic implications. Routine cognitive screening in post-COVID clinics, alongside targeted risk reduction strategies (e.g., vascular health optimization and neuroprotective interventions), may aid in mitigating long-term neurological morbidity. Moreover, since non-COVID respiratory conditions (especially non-COVID respiratory infections such as influenza) have received less public attention than COVID-19[46,47], their potential contribution to dementia risk should be given greater consideration in public health initiatives. Future research should also stratify dementia risk among older adults into more detailed age groups (e.g., 60–70, 71–80, etc.) to better tailor prevention strategies.

Overall, our study contributed to the growing body of evidence linking COVID-19 infection to a potentially increased risk of NOD and particularly VaD, but not AD. However, this excess risk did not appear significantly higher than that observed in individuals with non-COVID respiratory diseases (including non-COVID respiratory tract infections), suggesting a broader impact of respiratory illnesses on cognitive health. Given the substantial societal burden of dementia, continued surveillance and research

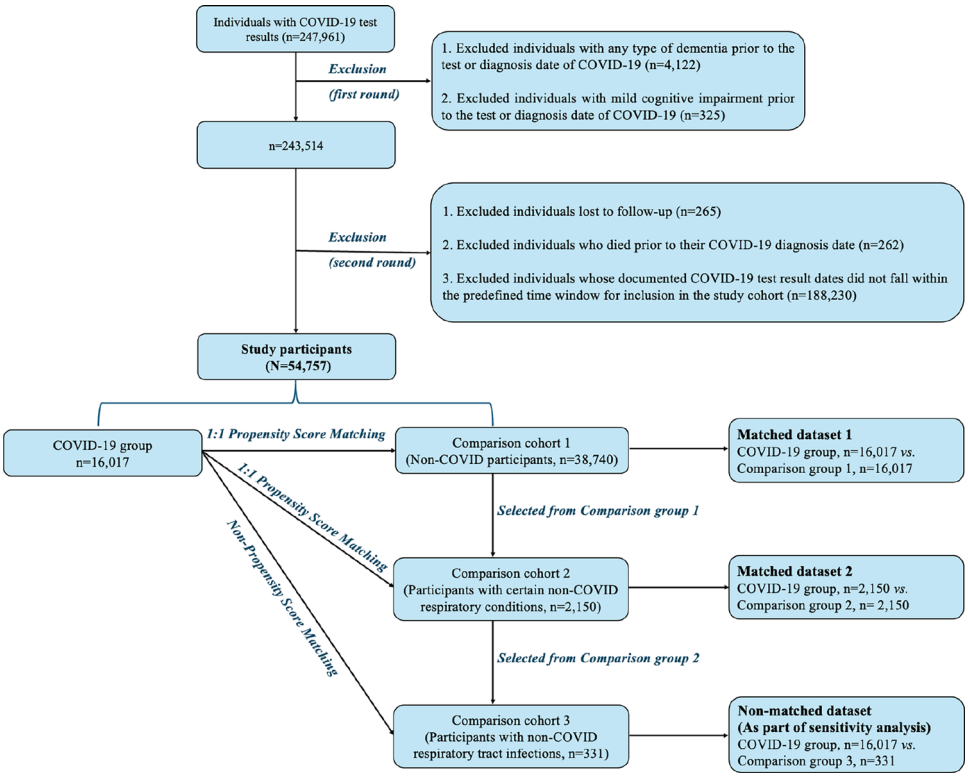

Fig. 2 | Flowchart illustrating the participant selection process. The comparison cohort 2 included participants with certain non-COVID respiratory conditions, selected from the comparison cohort 1 (n = 38,740). These conditions included either non-communicable respiratory tract diseases or non-COVID respiratory tract infections. The comparison cohort 3 included participants with non-COVID respiratory tract infections, selected from the comparison cohort 2 (n = 2150), and was used for sensitivity analysis only.

into the long-term cognitive consequences of COVID-19 are crucial. Further investigation with longer observational periods is needed to clarify the potential differential risks of AD and VaD following COVID-19 infection. As VaD is the second most common form of dementia after AD, policymakers and clinicians should prioritize strategies to mitigate its risk in COVID-19 survivors, particularly among high-risk populations identified in this study, to reduce the long-term healthcare burden of post-COVID neurological complications. Importantly, global evidence suggested that COVID-19's direct and indirect health impacts might have been unevenly distributed, and disadvantaged locations and populations were likely to carry a disproportionate burden[48]. Moreover, inequalities in long COVID vulnerability may exacerbate existing structural health disparities, especially in low- and middle-income settings[49]. These findings may underscore the need for equity-oriented dementia surveillance and preventive strategies to address not only the clinical but also the societal and global health challenges posed by COVID-19–related cognitive decline.

Method

Study design, participants, and data collection

This study utilised data from the UKBB, a large-scale biomedical research initiative designed to investigate risk factors for major health conditions in middle-aged and older adults. Between 2006 and 2010, over 500,000 individuals aged 40–69 years were recruited from across the UK[43,44]. All individuals were registered with the National Health Service (NHS) and resided within 25 miles of one of 22 designated assessment centres. At these centres, these individuals completed touchscreen questionnaires and face-to-face interviews to collect demographic, behavioural, and medical information, including ethnicity, educational attainment, anthropometric measures, and chronic health conditions. Informed electronic consents were obtained from all individuals, facilitating long-term follow-up and linkage to routinely collected NHS health records. Ethical approval for UKBB was granted by the North West Multi-Centre Research Ethics Committee (MREC). This study, as a secondary analysis of de-identified UKBB data, was conducted under approved access protocols and received ethical clearance from the Faculty of Health and Medicine Research Ethics Committee at Lancaster University (reference: FHM-2025-5174-DataOnly-1). Details regarding UKBB design, data linkage, validation, and availability have been described previously and are accessible via the UKBB data showcase (https://biobank.ctsu.ox.ac.uk/crystal/)[50]. In this study, participants' baseline age was determined based on their birth date and the date of their COVID-19 test (mentioned later), allowing us to focus on individuals aged 50 or older.

We initially identified 247,961 individuals with at least one documented COVID-19 test result (i.e., either positive or negative). Exclusion criteria were then applied sequentially: (i) individuals with a prior diagnosis of any type of dementia (n = 4122) or mild cognitive impairment (n = 325) before their COVID-19 test or diagnosis; (ii) those lost to follow-up (n = 265); (iii) those who died before their COVID-19 diagnosis (n = 262); and (iv) those who underwent COVID-19 testing but had only positive and/or negative results outside the predefined time window used to define the COVID-19 and non-COVID-19 groups (with the predefined window described later) (n = 188,230). Here it is important to note that some UKBB participants underwent multiple COVID-19 tests over time. In our study, individuals who did not test or tested negative within the predefined window but subsequently tested positive during the study period were also excluded under criterion (iv), as their only positive results occurred outside the predefined window. Following exclusions, 54,757 participants were eligible for analysis. A flowchart illustrating participant selection and comparator group allocation is presented in Fig. 2.

Participants were then stratified into two groups: the COVID-19 and non-COVID groups. Follow-up began on the date of COVID-19 diagnosis or a negative test and continued until the earliest occurrence of a dementia diagnosis, death, or the observational endpoint (31 October 2022), which marked the latest available dementia diagnosis data from UKBB. The COVID-19 group comprised individuals with a confirmed infection recorded between 31 January 2020 (the date of the first confirmed case in the UK) and 28 February 2021[51], ensuring a minimum observational period of 20 months post-diagnosis, with a maximum of up to 33 months. This index window was chosen a priori both to guarantee adequate latency for incident dementia to manifest and to maximise the available sample size based on the UKBB data, thereby improving statistical power.

The non-COVID group comprised individuals who had a contemporary negative COVID-19 test result between 31 January 2020 and 28 February 2021 (comparison cohort 1), without any documented positive result during the subsequent observational period. This contemporaneous test-negative comparator approach was chosen a priori to harmonise healthcare-seeking/testing behaviour and reduce differential exposure misclassification between groups. We selected participants with certain non-COVID respiratory conditions resembling COVID-19 (comparison cohort 2)[52]. These conditions, encompassing either non-COVID respiratory tract infections or certain non-communicable respiratory diseases, were identified using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes J00–J47, including 'J00-J06 - Acute upper respiratory infections,' 'J09-J18 - Influenzas and pneumonia (e.g., influenza due to identified influenza virus, viral pneumonia, and bacterial pneumonia),' 'J20-J22 - Other acute lower respiratory infections,' 'J30-J39 - Other diseases of upper respiratory tract,' and 'J40-J47 - Chronic lower respiratory diseases (e.g., asthma and COPD).'

Propensity score matching (PSM) was applied to balance potential baseline confounders between groups. The COVID-19 ($n = 16{,}017$) and non-COVID ($n = 38{,}740$) groups were matched 1:1, generating matched dataset 1 (COVID-19 group: $n = 16{,}017$; comparison group 1: $n = 16{,}017$). Participants with certain non-COVID respiratory conditions were extracted from the non-COVID group and 1:1 propensity-score matched to the COVID-19 group, generating matched dataset 2 (COVID-19: $n = 2150$; comparison group 2: $n = 2150$). Covariates included in the propensity score model were age, sex, ethnicity (White vs. non-White), body mass index (BMI), and vaccination status (unvaccinated, one dose, two doses). Other potential confounders were not included in the propensity score model due to limited data availability and were instead adjusted for in further analyses. Age and BMI were treated as continuous variables; sex, ethnicity, and vaccination status were treated as categorical variables. Propensity scores were estimated via logistic regression, followed by 1:1 nearest-neighbour matching[53]. Covariate balance was assessed using absolute standardized mean differences (SMDs). In line with recommended practice, values < 0.10 indicate negligible imbalance and values < 0.20 indicate small differences (i.e., acceptable balance)[54–56]. We then adjusted for any covariates with residual imbalance (particularly those with SMDs between 0.10 and 0.20) in the outcome models. Additionally, a further subset of comparison cohort 2 was defined as comparison cohort 3, comprising only participants with non-COVID respiratory tract infections (e.g., influenza and pneumonia). This cohort was included solely for sensitivity analyses and not in the primary analyses.

Covariates

Baseline demographic characteristics, including age, sex, ethnicity, BMI, COVID-19 vaccination status, Townsend Deprivation Index (TDI), physical activity, smoking status (never, previous, current), and alcohol intake frequency (never, special occasions only, one to three times a month, once or twice a week, three or four times a week, daily or almost daily), were collected at recruitment. Physical activity was measured using metabolic equivalent task (MET) scores, which quantify energy expenditure as multiples of the resting metabolic rate, and TDI was used as a socioeconomic status indicator[57].

All comorbidities were evaluated prior to or on the index date (positive COVID-19 test/ICD-10 code for the exposed group, or the contemporaneous negative test for comparators), and no post-index measurements or diagnoses were used. Baseline comorbidities, including hypertension, diabetes mellitus, cardiovascular diseases, neurological diseases, mental illnesses, and cancer, were ascertained from ICD-10 diagnoses recorded on or before the index date. Hypertension was defined using multiple pre-index criteria: self-reported diagnosis, antihypertensive medication use, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg based on at least two separate blood pressure readings at the baseline assessment, and ICD-10 codes (I10-I15). Diabetes mellitus was defined using self-reported diagnosis, antidiabetic medication use, random blood glucose ≥11.1 mmol/L at baseline, and ICD-10 codes (E10–E14). ICD-10 codes were also used to classify cardiovascular diseases, neurological diseases, mental illnesses, and cancer (Supplementary Table S1).

COVID-19 infection and dementia outcome

COVID-19 infection was defined as a positive polymerase chain reaction (PCR) test from the Public Health England's Second Generation Surveillance System (PHE-SGSS) or hospitalisation with an ICD-10 diagnosis code U07.1 or U07.2. COVID-19 testing data included Pillar 1 (patients with clinical needs and healthcare professionals in PHE laboratories and National Health Service hospitals) and Pillar 2 (wider population testing). Accordingly, a contemporary negative test within the index window did not necessarily indicate symptom-driven testing, because Pillar 2 comprised community screening and other non-symptom-based testing pathways. We therefore adopted a contemporaneous test-negative design to reduce misclassification of prior infection and to align testing access and calendar time across exposure groups.

The primary outcome was NOD, defined as a first recorded diagnosis of dementia occurring only after the index date (the date of a confirmed COVID-19 test for the COVID-19 group or the contemporaneous negative test for comparators). This included AD, VaD, frontotemporal dementia (FD), and other dementia types recorded by UKBB. Diagnoses were determined using ICD-10 codes (Supplementary Table S2).

Statistical analysis

Missing values in baseline covariates, detailed in Supplementary Table S3, were imputed using random forest multiple imputation[58]. Descriptive statistics were stratified by COVID-19 status (COVID-19 vs. non-COVID-19), with continuous variables summarised as mean (SD) and categorical variables as frequency (percentage). To address the primary research objective of evaluating whether COVID-19 infection is associated with an increased risk of NOD, Kaplan–Meier (KM) survival curves were used to estimate dementia-free probability over time, with group differences assessed using log-rank tests[59]. To further quantify this association and address the secondary research objective of evaluating whether non-COVID respiratory conditions pose a comparable risk as COVID-19 infection, Cox proportional hazards models were applied to estimate hazard ratios for NOD across the COVID-19 group and multiple comparator groups, as well as within subgroups[7]. The proportional hazards assumption was verified using Schoenfeld residuals[60].

To identify vulnerable populations at higher risks and investigate whether the association between COVID-19 and dementia varies by individual characteristics, subgroup analyses were stratified by sex, age, ethnicity, BMI, alcohol intake frequency, smoking status, hypertension, diabetes mellitus, cardiovascular diseases, neurological diseases, mental illnesses, cancer, and COVID-19 vaccination status. To facilitate subgroup comparisons, smoking status was categorized as 'ever smoking' for both previous and current smokers. Alcohol intake was grouped into 'less than weekly drinking' (never, special occasions only, or one to three times a month) and 'at least weekly drinking' (once or twice a week, three or four times a week, or daily/almost daily). Physical activity was not analysed due to a high rate of missing values ($n = 13{,}646$, 24.92%). Interaction terms were incorporated as supplementary terms in the Cox models to assess potential effect modification. To test the robustness of the findings and assess the influence of methodological assumptions, multiple sensitivity analyses were conducted, including: (i) exclusion of all participants with <3 months of total follow-up (i.e., <90 days at risk from the index date to censoring), irrespective of outcome status within that period, to mitigate misclassification of delirium or transient cognitive changes as incident dementia[8,61,62]; (ii) adjusting for competing risk of death using Fine-Gray models, which estimate the subdistribution hazard while accounting for the possibility that death may preclude the occurrence of the outcome of interest, namely NOD; (iii) full

adjustment for additional covariates beyond those controlled via the propensity score matching approach; (iv) analysis without PSM, adjusting for PSM covariates; (v) analysis without PSM with full covariate adjustment; (vi) dementia risk in propensity score-matched COVID-19 inpatients vs. contemporary general non-COVID participants as well as a subgroup of non-COVID participants with certain respiratory conditions, with and without additional covariate adjustments; (vii) dementia risk in the non-PSM COVID-19 group vs. the non-COVID respiratory infection group (comparison group 3, $n = 331$), using both partial and fully adjusted covariate models. PSM was not applied in this sensitivity analysis due to limited contemporary data on non-COVID respiratory infections; (viii) excluding participants with any recorded major neurological or psychiatric disorders at baseline (e.g., stroke, Parkinson's disease, multiple sclerosis, depressive disorder, schizophrenia, bipolar disorder).

All statistical analyses were conducted in R (version 4.3.1). A two-sided p-value of less than 0.05 was regarded as indicative of statistical significance.

Ethics

This study, as a secondary analysis, received ethical approval from the Faculty of Health and Medicine Research Ethics Committee at Lancaster University (reference: FHM-2025-5174-DataOnly-1).

Data availability

This research was conducted using the UK Biobank resource under application number 107335. The data are available from the UK Biobank to approved researchers upon application.

Received: 4 June 2025; Accepted: 4 September 2025;
Published online: 01 October 2025

References

1. Shan, D. et al. Post-COVID-19 human memory impairment: a PRISMA-based systematic review of evidence from brain imaging studies. *Front. Aging Neurosci.* **14**, 1077384 (2022).
2. Shan, D., Wang, C., Crawford, T. & Holland, C. Association between COVID-19 infection and new-onset dementia in older adults: a systematic review and meta-analysis. *BMC Geriatr.* **24**, 940 (2024).
3. Liu, Y. H. et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol. Neurodegener.* **16**, 48 (2021).
4. Liu, Y. H. et al. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. *JAMA Neurol.* **79**, 509–517 (2022).
5. Taquet, M. et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry* **9**, 815–827 (2022).
6. Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. *Nat. Med.* **28**, 2406–2415 (2022).
7. Cohen, K. et al. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* **376**, e068414 (2022).
8. Gollop, C. et al. Incidence of newly-diagnosed dementia after COVID-19 infection versus acute upper respiratory infection: a retrospective cohort study. *J. Alzheimers Dis.* **93**, 1033–1040 (2023).
9. Park, H. Y., Song, I. A. & Oh, T. K. Dementia risk among coronavirus disease survivors: a nationwide cohort study in South Korea. *J. Pers. Med.* **11**, 1015 (2021).
10. Qureshi, A. I., Baskett, W. I., Huang, W., Naqvi, S. H. & Shyu, C. R. New-onset dementia among survivors of pneumonia associated with severe acute respiratory syndrome coronavirus 2 infection. *Open Forum Infect. Dis.* **9**, ofac115 (2022).
11. Taquet, M., Luciano, S., Geddes, J. R. & Harrison, P. J. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry* **8**, 130–140 (2021).
12. Wang, L. et al. Association of COVID-19 with new-onset Alzheimer's disease. *J. Alzheimers Dis.* **89**, 411–414 (2022).
13. Zarifkar, P., Peinkhofer, C., Benros, M. E. & Kondziella, D. Frequency of neurological diseases after COVID-19, influenza A/B and bacterial pneumonia. *Front. Neurol.* **13**, 904796 (2022).
14. Shan, D., Wang, C., Crawford, T. & Holland, C. Temporal association between COVID-19 infection and subsequent new-onset dementia in older adults (aged 60 years and above): a systematic review and meta-analysis. *Lancet* **404**, S73 (2024).
15. Zeng, Q. & Shan, D. Advocating for rigorous and multifactorial analyses in post-COVID cognitive research. *Lancet Reg. Health West Pac.* **49**, 101166 (2024).
16. Dhamoon, M. S. et al. Acute cerebrovascular events with COVID-19 infection. *Stroke* **52**, 48–56 (2021).
17. Altable, M. & de la Serna, J. M. Cerebrovascular disease in COVID-19: Is there a higher risk of stroke?. *Brain Behav. Immun. Health* **6**, 100092 (2020).
18. Rajeev, V. et al. Pathophysiology of blood brain barrier dysfunction during chronic cerebral hypoperfusion in vascular cognitive impairment. *Theranostics* **12**, 1639–1658 (2022).
19. Nascimento, T. et al. Vaccination status and long COVID symptoms in patients discharged from hospital. *Sci. Rep.* **13**, 2481 (2023).
20. Wang, J. et al. Risk of dementia or cognitive impairment in COPD patients: a meta-analysis of cohort studies. *Front. Aging Neurosci.* **14**, 962562 (2022).
21. Peng, Y. H. et al. Adult asthma increases dementia risk: a nationwide cohort study. *J. Epidemiol. Community Health* **69**, 123–128 (2015).
22. Rahmati, M. et al. New-onset neurodegenerative diseases as long-term sequelae of SARS-CoV-2 infection: a systematic review and meta-analysis. *J. Med. Virol.* **95**, e28909 (2023).
23. Zhao, S. et al. Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study. *EClinicalMedicine* **68**, 102434 (2024).
24. Duff, E. P. et al. Plasma proteomic evidence for increased β-amyloid pathology after SARS-CoV-2 infection. *Nat. Med.* **31**, 797–806 (2025).
25. Qi, X. et al. Emerging signs of Alzheimer-like tau hyperphosphorylation and neuroinflammation in the brain post recovery from COVID-19. *Aging Cell* **23**, e14352 (2024).
26. Imai, M. et al. SARS-CoV-2 propagation to the TPH2-positive neurons in the ventral tegmental area induces cell death via GSK3β-dependent accumulation of phosphorylated tau. *PLoS One* **19**, e0312834 (2024).
27. Russ, T. C., Kivimäki, M. & Batty, G. D. Respiratory disease and lower pulmonary function as risk factors for dementia: a systematic review with meta-analysis. *Chest* **157**, 1538–1558 (2020).
28. Takeda, S., Rakugi, H. & Morishita, R. Roles of vascular risk factors in the pathogenesis of dementia. *Hypertens. Res.* **43**, 162–167 (2020).
29. Kalaria, R. N., Akinyemi, R. & Ihara, M. Stroke injury, cognitive impairment and vascular dementia. *Biochim. Biophys. Acta* **1862**, 915–925 (2016).
30. Sipilä, P. N. et al. Hospital-treated infectious diseases and the risk of dementia: a large, multicohort, observational study with a replication cohort. *Lancet Infect. Dis.* **21**, 1557–1567 (2021).
31. Janbek, J. et al. Hospital-diagnosed infections, autoimmune diseases, and subsequent dementia incidence. *JAMA Netw. Open* **6**, e2332635 (2023).
32. Duggan, M. R. et al. Proteomics identifies potential immunological drivers of postinfection brain atrophy and cognitive decline. *Nat. Aging* **4**, 1263–1278 (2024).
33. Damiano, R. F. et al. Cognitive decline following acute viral infections: literature review and projections for post-COVID-19. *Eur. Arch. Psychiatry Clin. Neurosci.* **272**, 139–154 (2022).
34. Łuc, M., Woźniak, M. & Rymaszewska, J. Neuroinflammation in dementia-therapeutic directions in a COVID-19 pandemic setting. *Cells* **11**, 2959 (2022).

35. Livingston, G. et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet* **404**, 572–628 (2024).
36. van der Flier, W. M. & Scheltens, P. Epidemiology and risk factors of dementia. *J. Neurol. Neurosurg. Psychiatry* **76**, v2–v7 (2005).
37. Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A. & Reynolds, C. F. 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br. J. Psychiatry* **202**, 329–335 (2013).
38. Ballard, C. et al. Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *J. Affect Disord.* **59**, 97–106 (2000).
39. Andersen, K. et al. Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. *EURODEM Incid. Res. Group. Neurol.* **53**, 1992–1997 (1999).
40. Watanabe, A., Iwagami, M., Yasuhara, J., Takagi, H. & Kuno, T. Protective effect of COVID-19 vaccination against long COVID syndrome: a systematic review and meta-analysis. *Vaccine* **41**, 1783–1790 (2023).
41. Lam, I. C. H. et al. Persistence in risk and effect of COVID-19 vaccination on long-term health consequences after SARS-CoV-2 infection. *Nat. Commun.* **15**, 1716 (2024).
42. Knopman, D. S. & Petersen, R. C. Mild cognitive impairment and mild dementia: a clinical perspective. *Mayo Clin. Proc.* **89**, 1452–1459 (2014).
43. Fry, A. et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am. J. Epidemiol.* **186**, 1026–1034 (2017).
44. Schoeler, T., Pingault, J. B. & Kutalik, Z. The impact of self-report inaccuracy in the UK Biobank and its interplay with selective participation. *Nat. Hum. Behav.* **9**, 584–594 (2024).
45. Hampshire, A. et al. Cognition and memory after Covid-19 in a large community sample. *N. Engl. J. Med.* **390**, 806–818 (2024).
46. Bager, P. et al. The hospital and mortality burden of COVID-19 compared with influenza in Denmark: a national observational cohort study, 2022-24. *Lancet Infect Dis.* **25**, 616–624 (2025).
47. Han, Y., Guo, J., Li, X. & Zhong, Z. Differences in clinical characteristics between coronavirus disease 2019 (COVID-19) and influenza: a systematic review and meta-analysis. *NPJ Prim. Care Respir. Med.* **35**, 8 (2025).
48. Shan, D., Jin, W., Li, F., Zeng, Y., Xie, R., Yang, C. et al. Global, Regional, National, and Local Burden of COVID-19 With Inequality Analysis Across 920 Locations,2020–2021. *Med Res*. (2025). https://doi.org/10.1002/mdr2.70013. Online ahead of print.
49. Shan, D., Jin, W., Li, F., Yang, C., Zeng, Y., Xie, R. et al. Identifying Potential Vulnerability to Long COVID Through Global-to-Local Inequalities in Years Lived With Disability Attributed to COVID-19, 2020-2021, Across 920 Locations. *Med Res*. (2025). https://doi.org/10.1002/mdr2.70023. Online ahead of print.
50. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
51. Elliott, J. et al. COVID-19 mortality in the UK Biobank cohort: revisiting and evaluating risk factors. *Eur. J. Epidemiol.* **36**, 299–309 (2021).
52. Hu, B., Guo, H., Zhou, P. & Shi, Z. L. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* **19**, 141–154 (2021).
53. Haukoos, J. S. & Lewis, R. J. The propensity score. *JAMA* **314**, 1637–1638 (2015).
54. Austin, P. C. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat. Med.* **28**, 3083–3107 (2009).
55. Stuart, E. A. Matching methods for causal inference: a review and a look forward. *Stat. Sci. Rev. J. Inst. Math. Stat.* **25**, 1 (2010).
56. Cohen, J. *Statistical power analysis for the behavioral sciences* (Routledge; 2013).
57. Ye, X. et al. Associations of socioeconomic status with infectious diseases mediated by lifestyle, environmental pollution and chronic comorbidities: a comprehensive evaluation based on UK Biobank. *Infect. Dis. Poverty* **12**, 5 (2023).
58. Hong, S. & Lynn, H. S. Accuracy of random-forest-based imputation of missing data in the presence of non-normality, non-linearity, and interaction. *BMC Med. Res. Methodol.* **20**, 199 (2020).
59. Edmonds, E. C. et al. Data-driven classification of cognitively normal and mild cognitive impairment subtypes predicts progression in the NACC dataset. *Alzheimers Dement* **20**, 3442–3454 (2024).
60. In, J. & Lee, D. K. Survival analysis: part II - applied clinical data analysis. *Korean J. Anesthesiol.* **72**, 441–457 (2019).
61. Muzambi, R. et al. Assessment of common infections and incident dementia using UK primary and secondary care data: a historical cohort study. *Lancet Healthy Longev.* **2**, e426–e435 (2021).
62. Muzambi, R. et al. Common bacterial infections and risk of dementia or cognitive decline: a systematic review. *J. Alzheimers Dis.* **76**, 1609–1626 (2020).

Acknowledgements

The authors received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors. In addition, the authors are grateful to the participants of the UK Biobank Study.

Author contributions

D.S., T.C. and C.H. designed the study, with useful suggestions from Y.X. and C.Y. C.Y. curated and analysed the data, incorporating suggestions from D.S. D.S. independently drafted the manuscript, and all authors contributed to its revision. T.C. and C.H. supervised the study.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44400-025-00034-y.

Correspondence and requests for materials should be addressed to Dan Shan or Chuang Yang.