SARS-CoV-2 susceptibility and COVID-19 illness course and outcome in people with pre-existing neurodegenerative disorders: systematic review with frequentist and Bayesian meta-analyses

Smadi, M.; Kaburis, M.; Schnapper, Y.; Reina, G.; Molero, P.; Molendijk, M.L.

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Review

SARS-CoV-2 susceptibility and COVID-19 illness course and outcome in people with pre-existing neurodegenerative disorders: systematic review with frequentist and Bayesian meta-analyses

Muhannad Smadi, Melina Kaburis, Youval Schnapper, Gabriel Reina, Patricio Molero and Marc L. Molendijk

Background

People with neurodegenerative disease and mild cognitive impairment (MCI) may have an elevated risk of acquiring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and may be disproportionally affected by coronavirus disease 2019 (COVID-19) once infected.

Aims

To review all eligible studies and quantify the strength of associations between various pre-existing neurodegenerative disorders and both SARS-CoV-2 susceptibility and COVID-19 illness course and outcome.

Method

Pre-registered systematic review with frequentist and Bayesian meta-analyses. Systematic searches were executed in PubMed, Web of Science and preprint servers. The final search date was 9 January 2023. Odds ratios (ORs) were used as measures of effect.

Results

In total, 136 primary studies (total sample size $n = 97\,643\,494$), reporting on 268 effect-size estimates, met the inclusion criteria. The odds for a positive SARS-CoV-2 test result were increased for people with pre-existing dementia (OR = 1.83, 95% CI 1.16–2.87), Alzheimer's disease (OR = 2.86, 95% CI 1.44–5.66) and Parkinson's disease (OR = 1.65, 95% CI 1.34–2.04). People with pre-existing dementia were more likely to experience a relatively severe COVID-19 course, once infected (OR = 1.43, 95% CI 1.00–2.03). People with pre-existing dementia or Alzheimer's disease were at increased risk for COVID-19-related hospital admission (pooled OR range: 1.60–3.72). Intensive care unit admission rates were relatively low for people with dementia (OR = 0.54, 95% CI 0.40–0.74). All neurodegenerative disorders, including MCI, were at higher risk for COVID-19-related mortality (pooled OR range: 1.56–2.27).

Conclusions

Our findings confirm that, in general, people with neurodegenerative disease and MCI are at a disproportionally high risk of contracting COVID-19 and have a poor outcome once infected.

Keywords:

Alzheimer's disease; coronavirus disease 2019; dementia; mild cognitive impairment; Parkinson's disease.

The novel 'coronavirus disease 2019' (COVID-19) is a widespread public health threat that is caused by a highly transmissible respiratory pathogen, 'severe acute respiratory syndrome (SARS-CoV-2)'.[1,2] Although much has returned to normal in our everyday lives, the virus continues to spread and infect millions and to be lethal to thousands of people on a daily basis, across the globe.[3] Early in the pandemic, it became clear that there are individual differences in COVID-19 infection susceptibility and severity.[4] More than half of all COVID-19 casualties and intensive care unit (ICU) admissions were older adults.[5]

Both age and age-related comorbidities are known to be strong risk factors for the development of dementia.[6–10] The dementias (i.e. Alzheimer's disease; Parkinson's disease with dementia; and mild cognitive impairment (MCI)) are a leading cause of impairment, dependence and mortality, especially among the elderly.[10,11] People with dementia, including MCI, are more likely to have comorbid conditions that confer a vulnerability for other medical conditions, including COVID-19.[12] In addition, studies have suggested that individuals who have comorbid conditions are more likely to experience severe illness and require hospital admission due to COVID-19 infection.[9,13] Previous data suggest that a dysregulated immune response in people with dementia can put them at further risk for COVID-19, leading to poor outcome, including death.[14–16] Furthermore, people with dementia have been particularly susceptible to the stressors brought on by the pandemic and the social restrictions to help deter the spread of the virus.[17] In particular, social distancing may worsen stress in people with dementia owing to a disruption in routines developed to compensate for their memory loss.[1]

Age-related comorbidities, immune dysregulation and exposure to stressors, as well as a reduced ability to comprehend the risks of infection and follow strict protocols to mitigate the spread of the virus, have all been related to infection risk and disease course.[1,17–19] Consequently, people with dementia may be more susceptible to SARS-CoV-2 infection and a relatively poor course and outcome of this disease once infected.[20] A meta-analysis conducted early in the pandemic found a higher risk of death due to COVID-19 in those with dementia compared with those without dementia.[2] However, the authors reported substantial heterogeneity which remained unexplained, and there was evidence of publication bias. A later meta-analysis showed that the risk for mortality was higher in people with pre-existing dementia.[21] A limitation of both meta-analyses is the small number of studies synthesised and the likelihood of duplicate data, as both included nationwide data from Italy and Korea multiple times, which may invalidate results.[22–25] Therefore, we considered conducting an updated meta-analysis. Another reason for such an update is the rapidly evolving situation and recent influx of publications. In addition, past meta-analyses focused solely on dementia and not its precursor, MCI.

The current meta-analysis aims to quantify all eligible cohort studies reporting on infection risk for COVID-19 and course of

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disease due to COVID-19 as a function of dementia status. We hypothesise that individuals with pre-existing dementia or MCI are more likely to become infected with SARS-CoV-2 and to experience worse COVID-19 severity and outcome (i.e. COVID-19-related hospital admission, ICU admission or mortality).

Method

The searches and methodology of this systematic review and meta-analysis are reported in accordance with the guidelines set out by Meta-analyses of Observational Studies in Epidemiology (MOOSE)[26] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[27] A review protocol was drafted and pre-registered with the PROSPERO database (registration number CRD42022299941) and with the Open Science Framework (OSF).

Search and selection strategy

Systematic searches were executed in PubMed and Web of Science. These were supplemented with a non-systematic search in Google Scholar. A grey literature search on the preprint servers PsyArXiv and MedArXiv was also executed. The final search date was 9 January 2023. The search string and terms used per database are presented in the supplementary material available online at https://dx.doi.org/10.1192/bjp.2023.43. Eligibility of article inclusion was assessed independently by four members of the research team masked to each other's assessments, based on (a) title and abstract of potential papers, followed by (b) full-text assessment. A final decision on eligibility was made by four members of the review team (M.S., M.L.M., Y.S. and M.K.) based on the set eligibility criteria.

Eligibility criteria

Articles were included when they (a) reported SARS-CoV-2 infection rates (determined by any of the diagnostic methods, including blood, saliva analysis, polymerase chain reaction (PCR) and antibody testing) and the effect of infection on illness course of COVID-19, including mortality in people with pre-existing dementia (any type, including MCI) compared with controls; and (b) were written in English, Dutch, Spanish, Arabic, Hebrew, German, Italian or French. Articles were excluded if (a) no relevant outcome data could be extracted, (b) no original data were reported (e.g. reviews) or (c) they were case studies. When articles used data that we suspected might be overlapping, we included the article that was most informative for our purposes (see Article selection and overlapping data-sets in the supplementary material).

Exposure and outcome variables

Exposure variables were pre-existing dementias, including the precursor condition MCI, as defined by DSM-IV, DSM-5,[28,29] ICD-10[30] or other validated assessment tools, compared with reference groups of people without a dementia. Outcome variables of interest included (a) SARS-CoV-2 infection risk (risk of getting infected with COVID-19), presented as the percentage of SARS-CoV-2 positive tests in the populations under study and (b) the course of COVID-19, further specified as (i) indicators of severity of the disease (e.g. symptomatic versus non-symptomatic, requiring respiratory assistance or not), (ii) hospital admission rates, (iii) ICU admission rates and (iv) COVID-19-related mortality rates.

Data extraction

The following data were extracted from eligible articles: average age (as mean or median in years), gender distribution at follow-up, country in which the study was performed; clinical data (i.e. method of diagnostic assessment, type of disorder), validity of assessment, the covariates that were used in statistical analyses, differences in outcome in covariate adjusted and unadjusted models, whether time-varying covariates were used, the analytical strategy that was used; and raw numbers or effect-size estimates and corresponding 95% confidence intervals (95% CIs) on outcome data. Data extraction was performed independently and masked, by at least two members of the review team (M.S., M.L.M., Y.S. and/or M.K.).

Measures of effect

We extracted ORs and corresponding 95% CIs as measures of effect. Where reported, we extracted data from analyses that controlled for the largest number of potential confounders or that came from (propensity-) matched samples. When results were reported as hazard ratios or risk ratios and raw data were not available, we interpreted these as an OR when the incidence of the reported outcome was <20%. Hazard ratios and risk ratios based on data reporting on an incidence of outcome >20% were transformed.[31–33]

Assessment of methodological quality

The methodological quality of input studies was scored by three members of the review team (M.S., M.L.M. and Y.S.), who were masked to each other's assessment, using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies recommended by the US National Institutes of Health.[34]

Statistical analysis

All analyses were performed in JASP version 0.17.1 for Apple Silicon (JASP Team, University of Amsterdam, Netherlands; https://jasp-stats.org/download). To check the robustness of results, analyses were also performed in IBM SPSS Statistics version 28 for Macintosh and STATA version 17 for Macintosh. Random-effects frequentist meta-analyses were used to pool the data on SARS-CoV-2 infection risk, COVID-19 course, hospital admissions, ICU admissions and mortality rates in relation to the types of pre-existing dementia. Statistical significance was set at $P < 0.05$. Heterogeneity among studies was quantified using the I^2 measure and assessed for statistical significance using the Q^2 statistic.[35] Meta-analyses were repeated using a Bayesian approach to verify robustness of results over different analytical approaches. When heterogeneity in outcome was present, subgroup and meta-regression analyses were performed with the aim of identifying study or population characteristics that might explain the heterogeneity. Potential moderators included the percentage of females, average age and methodological quality scores per sample. Subgroup analysis by geographical region was also performed if heterogeneity in outcome was present. Publication bias was assessed by means of Kendall's tau.[35]

Results

Of the 5548 candidate articles that we retrieved, 136 met the eligibility criteria (Fig. 1). Supplementary Tables 1 and 2 list all the articles that were included for full-text assessment as well as reasons for final inclusion and exclusion.

Tables 1 and 2 provide demographic and clinical information on the samples in the studies included, stratified by SARS-CoV-2 susceptibility and COVID-19 course and outcome, respectively. The median age was 70.1 years (range 35–89.5 years), the percentage

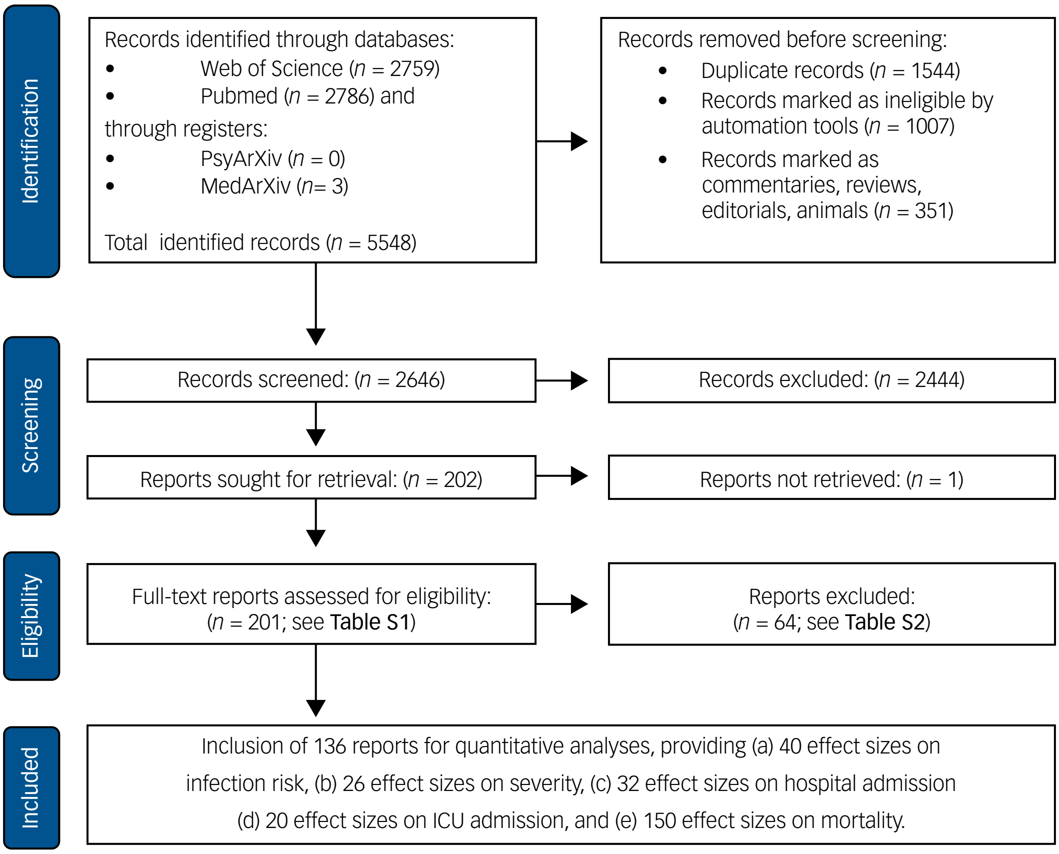

Fig. 1 Flowchart on identification, screening and inclusion of eligible publications. ICU, intensive care unit.

of females was 53% (range 31–82%) and the median sample size per analysis was 94 624 (range 46–62 250 998). The methodological quality of the majority of input studies was high (Supplementary Tables 16 and 17). Supplementary Box 2 lists studies in which data-sets were (suspected to be) used more than once and the choices that we subsequently made to ensure that data on which we performed our analyses were independent. Supplementary Tables 3(a) and 3(b) provide further information on potential overlap and actions taken per analysis. It should be noted that when nationwide data were available for analysis alongside data gathered more locally, we ran analyses once with the nationwide data included and the local data excluded and once with the local data included and the nationwide data excluded. Therefore, we occasionally reported on fewer data-sets per analysis relative to the numbers provided in the flowchart.

SARS-CoV-2 infection risk

The odds for a SARS-CoV-2 positive test result were increased for people with documented pre-existing dementia (OR = 1.83, 95% CI 1.16–2.87; Table 3). These results were evident in multivariable analyses controlling for potential confounding factors such as age, gender and other comorbidities, but not in crude analyses (Supplementary Table 5). Alzheimer's disease, Parkinson's disease and mixed dementia were all associated with an increase in SARS-CoV-2 susceptibility (Fig. 2). When replacing nationwide data with local data, an increase in SARS-CoV-2 susceptibility remained evident in people with Alzheimer's disease, but not in those with the other disorders (Supplementary Table 4). Between-study heterogeneity in outcome was evident in all analyses (Table 3 and Supplementary Table 5). A small positive association between percentage of females and odds for infection was found in people with dementia (Supplementary Table 7). Methodological quality was not associated with between-study heterogeneity (Supplementary Table 6). The odds for infection risk for all categories of neurodegenerative disorder were not evident in the data gathered in Asia, except for dementia (Supplementary Table 9).

COVID-19 course and outcome

People with pre-existing dementia were more likely to experience a severe COVID-19 course, once infected, relative to people in control conditions (OR = 2.66, 95% CI 1.16–6.12; Supplementary Table 5). This was also evident, although with attenuated effect size, in studies utilising multivariable analyses (OR = 1.43, 95% CI 1.00–2.03; Table 4). People with pre-existing dementia were at lower risk for ICU admission (OR = 0.54, 95% CI 0.40–0.74), but at higher risk for COVID-19-related hospital admission (OR = 1.60, 95% CI 1.09–2.35) and mortality (OR = 1.58, 95% CI 1.39–1.79; Fig. 3) in studies utilising multivariable analyses (Table 4). People with Alzheimer's disease were at higher risk for COVID-19-related hospital admission (OR = 3.72, 95% CI 2.35–5.90), but people with MCI, Parkinson's disease or mixed dementia were not. Based on a single study, it was found that people with Alzheimer's disease or Parkinson's disease were at higher risk for COVID-19-related ICU admissions (pooled OR range: 1.55–1.65; Table 4). All patient groups were at higher risk for COVID-19-related mortality (pooled OR range: 1.56–2.27; Table 4). When replacing nationwide data with local data, higher odds for COVID-19-related mortality remained evident for people with dementia or Parkinson's disease (Supplementary Table 4). Between-study heterogeneity in outcome was observed in most analyses (see Table 4 for two exceptions). Average age was positively associated with odds for COVID-19-related hospital admission in people with Parkinson's disease

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Table 1. Characteristics of the studies included and samples reporting on SARS-CoV-2 infection risk.

Study	*N*	Age	Female (%)	Predictor	Country
Ajayi et al. 2020[36]	657	55 AVG.	40	Dem	UK
Beobide Telleria et al. 2022[37]	436	87 MED.	72	Dem	Spain
Castilla et al. 2021[38]	643 757	44 MED.	37	Dem	Spain
de Malherbe et al. 2022[39]	881	89 AVG.	79	AD	France
Del Ser et al. 2021[40]	913	82 AVG.	65	AD	Spain
Emmerson et al. 2022[41]	9571	82 AVG.	68	Dem	Wales
Karapetyan et al. 2021[42]	99 811	44 AVG.	60	Dem	Germany
Kim et al. 2022b.[43]	129 120	45 MED.	36	Dem	Korea
Orlando et al. 2021[44]	3497	48 AVG.	54	Mix, PD	Italy
Pan et al. 2021[45]	12 384	78 AVG.	57	CI	USA
Profili et al. 2020[46]	1840	65 MED.	48	Dem	Italy
Scherbaum et al. 2021[47]	30 872	78 MED.	58	PD	Germany
Smith et al. 2021[48]	124 167	n.a.	n.a.	Dem	USA
Seon et al. 2021[49]	123 480	53 MED.	61	Dem	Korea
Soldevila et al. 2022[50]	8021	86 AVG.	74	Dem	Spain
Tahira et al. 2021[51]	12 863	75 MED.	49	AD, PD, Dem	UK
Wang et al. 2021a[52]	61 916 260	47 MED.	54	Dem	USA
Wang et al. 2021b[53]	446	65 MED.	66	AD, Dem	Korea
Wang et al. 2021c[54]	60 446	67 AVG.	67	Dem, AD, PD, Mix	UK
Wong & Lovier 2022[55]	3257	74 AVG.	58	Dem	USA
Worcel et al. 2021[56]	173	80 AVG.	61	AD, Dem	France
Yu et al. 2021[57]	13 338	70 AVG.	51	AD, PD	UK
Zenesini et al. 2022[58]	10 172	76 AVG.	41	PD	Italy
Zhou et al. 2021a[59]	3884	57 AVG.	55	AD, Dem	UK

a. Studies are divided by outcome: 'infection risk' and 'course and outcome'. The latter includes only participants with positive COVID-19 infection.
AVG., average (mean); MED., median; AD, Alzheimer's disease; n.a., not applicable; CI, cognitive impairment; Dem, dementia; Mix, mixed dementia; PD, Parkinson's disease.

(Supplementary Table 8). In crude analyses, average age was positively associated with odds for mortality in people with dementia or Alzheimer's disease (Supplementary Table 7). The percentage of females was positively associated with odds for mortality in people with Alzheimer's disease in studies utilising crude analyses (Supplementary Table 7) and in people with MCI in studies utilising multivariable analyses (Supplementary Table 8). Methodological quality was not associated with any of the outcomes (Supplementary Tables 7 and 8). The odds of experiencing severe COVID-19, hospital admission, ICU admission and mortality for all categories of neurodegenerative disorders differed by continent (Supplementary Tables 9 and 10).

Bayesian meta-analysis

Supplementary Tables 11–14 present the odds ratios and 95% confidence intervals based on Bayesian analysis. For ease of comparison, frequentist results are also reported in these tables. Overall, the Bayesian analyses yielded largely similar results to the frequentist approach across all neurodegenerative disorders and the evidence for the alternative hypotheses, in case of significant findings, ranges from moderately strong (Bayes factor between 3 and 10) to extremely strong (Bayes factor >100).

Discussion

This systematic review with meta-analysis, which synthesised 136 primary studies, corroborates that individuals with pre-existing neurodegenerative disorders (i.e. dementia, Alzheimer's disease, Parkinson's disease, MCI or mixed dementia) have an increased susceptibility for SARS-CoV-2 infection and, in general, have higher morbidity and mortality rates for COVID-19. A notable observation is the lower risk for ICU admission in people with dementia. Large sample sizes and convergence of findings using both the frequentist and the Bayesian methods suggest robustness of the findings.

Susceptibility for SARS-CoV-2 infection and neurodegenerative disorders

The odds of infection with SARS-CoV-2 are about 1.5 to 3.0 times higher in individuals with pre-existing neurodegenerative disorders. Age and gender are known risk factors for various chronic diseases.[172] In fact, older individuals are more susceptible to SARS-CoV-2[173] because of age-related changes in the immune system, which deteriorate immune response and efficiency.[18,174] The living conditions of individuals with a neurodegenerative disorder may be a risk factor, since long-term care facilities (e.g. nursing homes) are predominantly tenanted by the elderly, 48–50.4% of whom have Alzheimer's disease or other dementias.[10,175] The combination of age and age-related comorbidities (e.g. neurodegenerative disorders) with proximity and exposure of vulnerable individuals in communal housing, through shared (overcrowded) spaces, may translate to increased susceptibility to COVID-19.[17] Nevertheless, associations that were controlled for age also yielded significant findings. Additionally, factors such as poor health behaviour (e.g. decreased physical activity) and non-adherence to public health measures may play a significant role in explaining the increased risk for infection with SARS-CoV-2 in individuals with neurodegenerative disorders. This may be attributed to the inability to comprehend the severity of contracting the virus and thus the necessity of complying with the protocols, owing to memory loss and cognitive impairment in individuals with dementia or MCI.[2,17] A further explanation may be an unwillingness to adhere to the measures owing to apathy,[2] which is evident in individuals with dementia.[176] There were no data on whether there was preferential testing among people with dementia that might have led to an increased likelihood of having a diagnosis.

In some instances, we were unable to run subgroup analyses for some of the disorder types by continent (e.g. Asia) owing to the lack of data. Nevertheless, there were some differences in SARS-CoV-2 susceptibility among the geographic continents (i.e. Asia, America, Europe). This might be explained by the financial opportunities of each country to implement safety measures. In addition,

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Table 2. Characteristics of the studies included and samples reporting on COVID-19 course and outcome.

Study	*N*	Age	% Female	Predictor	Outcome	Country
Ajayi et al. 2020[36]	39	73 AVG.	44%	Dem	[5]	UK
Ajayi et al. 2021[60]	75	55 AVG.	47%	Dem	[5]	UK
Alqahtani et al. 2021[61]	101	75 AVG.	58%	Dem	[5]	KSA
An et al. 2021[62]	5596	59 AVG.	53%	Dem	[2], [5]	Korea
Atkins et al. 2020[63]	507	73 AVG.	39%	Dem	[4], [5]	UK
Bae et al. 2021[64]	1232	61 AVG.	39%	Dem	[5]	Korea
Baker et al. 2021[65]	100	67 AVG.	45%	Dem	[2], [3], [5]	USA
Banoei et al. 2021[66]	250	69 MED.	56%	Dem	[5]	USA
Becerra-Muñoz et al. 2021[67]	1520	76 MED.	40%	Dem, PD	[5]	Multiple
Bennett et al. 2021[68]	1 926 526	47 AVG.	55%	Dem	[2]	USA
Beobide Telleria et al. 2022[37]	173	87 MED.	72%	Dem	[5]	Spain
Bhargava et al. 2021[69]	656	64 AVG.	48%	Dem	[5]	USA
Bianchetti et al. 2020[70]	627	76 AVG.	53%	Dem	[5]	Italy
Bielza et al. 2021[71]	630	87 MED.	65%	Dem	[5], [2]	Spain
Booij et al. 2022[72]	134	85 AVG.	60%	Dem	[5]	Netherlands
Boye et al. 2021[73]	4298	70 AVG.	50%	Dem	[4], [5]	USA
Bucholc et al. 2022[74]	6036	72 MED.	47%	Dem	[5]	N. Ireland
Busetto et al. 2020[75]	92	71 AVG.	62%	Dem	[3], [5]	Italy
Caliskan and Saylan, 2020[76]	565	50 AVG.	n.a.	Dem	[3], [5]	Turkey
Carrillo-Garcia et al. 2021[77]	165	89 MED.	69%	Dem	[5]	Spain
Castilla et al. 2021[38]	35 387	44 MED.	37%	Dem	[4], [5]	Spain
Chang et al. 2020[78]	710 980	71 MED.	50%	Mix	[4]	USA
Chatterjee et al. 2021[79]	2337	65 MED.	80%	Dem	[5]	Netherlands
Chen et al. 2022[80]	1 271 033	53 AVG.	60%	Dem	[5]	USA
Choi et al. 2021[81]	7590	40 MED.	60%	Dem	[3], [5]	Korea
Chojnicki et al. 2021[82]	322	78 AVG.	62%	CI	[5]	Poland
Cisterna-García et al. 2022[83]	86 867	54 MED.	53%	Dem	[3], [4], [5]	Spain
COVIDSurg, 2021[84]	1063	90 MED.	66%	Dem	[5]	Multiple
Covino et al. 2020[85]	69	84 MED.	46%	Dem	[2], [5]	Italy
Covino et al. 2021a[86]	729	85 MED.	53%	Dem	[5]	Italy
Covino et al. 2021b[87]	729	85 MED.	53%	Dem	[5]	Italy
Cummins et al. 2021[88]	1781	35 MED.	45%	Dem	[3], [4], [5]	UK
de Marcaida et al. 2020[89]	36	75 MED.	36%	PD	[5]	USA
De Smet et al. 2020[90]	81	85 MED.	59%	Dem	[5]	Belgium
Del Ser et al. 2021[40]	62	82 AVG.	39%	AD	[2]	Spain
Descamps et al. 2022[91]	90 950	85 MED.	55%	Dem	[3], [5]	France
Ellis et al. 2022[92]	1071	84 MED.	52%	Dem, MCI	[4], [5]	Australia
Escribà-Salvans et al. 2022[93]	78	85 AVG.	76%	CI	[2]	Spain
Esme et al. 2021a[94]	16 942	71 AVG.	51%	Dem	[5]	Turkey
Esme et al. 2021b[94]	3172	71 AVG.	51%	Dem	[5]	Turkey
España et al. 2021a[95]	9121	84 AVG.	70%	Dem	[5]	Spain
España et al. 2021b[95]	2140	84 AVG.	70%	Dem	[5]	Spain
Esteban et al. 2021[96]	113	87 MED.	82%	Dem	[2]	Argentina
Fasano et al. 2020[97]	1486	71 AVG.	48%	PD	[4], [5]	Italy
Fathi et al. 2021[98]	3732	78 AVG.	74%	AD, PD	[5]	Iran
Filardo et al. 2020[99]	337	58 MED.	33%	Dem	[5]	USA
Filipe et al. 2021[100]	3550	68 MED.	41%	Dem	[3], [5]	Switzerland
Fumagalli et al. 2021[101]	221	82 AVG.	39%	Dem	[5]	Italy
Gale and Boland, 2021[102]	1181	59 AVG.	40%	Dem	[5]	UK
Ge et al. 2021[103]	167 500	43 MED.	52%	Dem	[2], [5]	Canada
Genet et al. 2020[104]	201	86 AVG.	67%	Dem	[5]	France
Geriatric et al. 2021[105]	5711	74 MED.	45%	Dem	[3], [5]	Multiple
Ghaffari et al. 2021[106]	361	62 AVG.	41%	Dem	[2]	Iran
Gómez Antúnez et al. 2020[107]	746	69 MED.	43%	Dem, Mix	[5]	Spain
Harrison et al. 2020[108]	31 461	50 MED.	55%	Dem	[5]	USA
Hasani Azad et al. 2021[109]	2351	47 AVG.	48%	Dem	[3]	Iran
Hatamabadi et al. 2022[110]	5318	60 MED.	43%	AD, PD	[5]	Iran
Hippisley-Cox et al. 2021[111]	6 952 440	53 AVG.	52%	Dem, PD	[4], [5]	UK
Hwang et al. 2020[112]	103	68 AVG.	50%	AD	[5]	Korea
Izurieta et al. 2021[113]	24 367 476	75 MED.	56%	CI, PD	[4], [5]	USA
Kang and Kong, 2021[114]	4141	50 MED.	58%	Dem	[2], [5]	Korea
Karapetyan et al. 2021[42]	46 071	44 AVG.	61%	Dem	[2]	Germany
Ken-Dror et al. 2020[115]	429	70 AVG.	44%	Dem	[5]	UK
Kim et al. 2020[116]	2959	40 MED.	39%	Dem	[2]	Korea
Kim et al. 2021[117]	2254	58 MED.	64%	Dem	[5]	Korea
Kim et al. 2022a. (65-74)[118]	17 890	69 MED.	51%	Dem	[2], [4], [5]	USA
Kim et al. 2022a. (75-84)[118]	9500	79 MED.	53%	Dem	[2], [4], [5]	USA
Kim et al. 2022a. (85+)[118]	4380	89 MED.	59%	Dem	[2], [4], [5]	USA
Kim et al. 2022b.[43]	19 912	45 MED.	36%	Dem	[2]	Korea
Kong et al. 2021[119]	5307	50 AVG.	59%	Dem	[2], [5]	Korea
Kostev et al. 2022[120]	28 311	73 AVG.	49%	Dem, VD, AD	[5]	Germany
Kyoung et al. 2021[121]	1697	47 MED.	58%	Dem	[5]	Korea
Lazcano et al. 2021[122]	91 629	55 AVG.	58%	Dem	[5]	Spain
Li et al. 2020[123]	42	75 MED.	68%	AD	[5]	China
Livingston et al. 2020[124]	131	75 AVG.	52%	Dem	[5]	UK

(*Continued*)

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Table 2. (*Continued*)

Study	*N*	Age	% Female	Predictor	Outcome	Country
Lozano-Montoya et al. 2021[125]	300	86 AVG.	63%	Dem	[5]	Spain
Lu et al. 2021[126]	608 251	74MED.	56%	PD, CI	[4], [5]	USA
Lucijanić et al. 2022[127]	2586	70 MED.	44%	Dem	[5]	Croatia
Magallon-Botaya et al. 2021[128]	6286	61 MED.	56%	Dem	[3], [4], [5]	Spain
Maguire et al. 2020[129]	224	n.a.	45%	CI	[5]	UK
Mahmoud et al. 2021[130]	126	83 AVG.	43%	Dem	[5]	Italy
Maniero et al. 2022[131]	102	83 MED.	45%	Dem, PD	[5]	UK
Martinot et al. 2021[132]	600	71 MED.	42%	Dem	[3], [5]	France
Meis-Pinheiro et al. 2021[133]	249	87AVG.	73%	Dem	[5]	Spain
Menditto et al. 2021[134]	283	57 AVG.	49%	CI	[4]	Italy
Miyashita et al. 2020a[135]	1557	70 MED.	47%	Dem	[3], [4], [5]	USA
Miyashita et al. 2020b[135]	514	70 MED.	47%	Dem	[3], [4], [5]	USA
Molani et al. 2022[136]	4943	60 AVG.	44%	Dem	[2]	USA
Moon et al. 2021[137]	5626	35 MED.	58%	Dem	[5]	Korea
Munblit et al. 2021[138]	3382	56 MED.	50%	Dem	[5]	Russia
Nojiri et al. 2022[139]	5980	79 MED.	42%	Dem, PD	[2], [5]	Japan
Oh et al. 2022[140]	5077	n.a.	59%	Dem	[2], [5]	Korea
Ouattara et al. 2021a[141]	25 765	66 MED.	46%	Dem	[5]	France
Ouattara et al. 2021b[141]	72 601	66 MED.	46%	CI	[5]	France
Pan et al. 2021[45]	13 874	78 AVG.	57%	CI	[5]	USA
Panagiotou et al. 2021a[142]	3202	79 MED.	61%	Dem	[5]	USA
Panagiotou et al. 2021b[142]	3570	79 MED.	61%	Dem	[5]	USA
Panagiotou et al. 2021c[142]	2486	79 MED.	61%	Dem	[5]	USA
Patel et al. 2022[143]	264	78 AVG.	59%	Dem, PD, AD, VD	[5]	USA
Pisaturo et al. 2021[144]	69	63 MED.	39%	Dem, PD	[2], [5]	Italy
Raheja et al. 2021[145]	355	84 AVG.	46%	Dem	[5]	USA
Ramos-Rincón et al. 2021a[146]	2772	86 MED.	51%	Dem	[5]	Spain
Ramos-Rincon et al. 2021b[147]	6189	86 MED.	51%	Dem	[5]	Spain
Rebora et al. 2021[148]	516	78 MED.	38%	Dem	[5]	Italy
Roig-Marín & Roig-Rico 2021[149]	300	82 AVG.	49%	Dem	[5]	Spain
Romagnolo et al. 2021a[150]	344	62 AVG.	41%	Mix	[2], [3], [4], [5]	Italy
Romagnolo et al. 2021b[151]	46	62 AVG.	40%	Mix	[2]	Italy
Rossi et al. 2020[152]	2653	63 AVG.	50%	Dem	[4], [5]	Italy
Russo et al. 2021a[153]	19 854	72 AVG.	45%	AD/Dem, PD	[5]	Italy
Russo et al. 2021b[153]	11 118	83 AVG.	53%	PD	[5]	Italy
Rutten et al. 2021[154]	1294	84 AVG.	64%	Dem, PD	[5]	Netherlands
Salari et al. 2021c[155]	12 909	77 AVG.	n.a.	PD	[5]	Iran
Samuels et al. 2021[156]	1692	57 AVG.	53%	Dem	[3]	USA
Scherbaum et al. 2021[47]	30 872	78 MED.	58%	PD	[5]	Germany
Secnik et al. 2023 (≤70)[157]	359	66 AVG.	n.a.	Dem	[5]	Sweden
Secnik et al. 2023 (71–80)[157]	1521	75 AVG.	n.a.	Dem	[5]	Sweden
Secnik et al. 2023 (81–90)[157]	2091	85 AVG.	n.a.	Dem	[5]	Sweden
Secnik et al. 2023 (>90)[157]	1151	93 AVG.	n.a.	Dem	[5]	Sweden
Seon et al. 2021[49]	7713	53 MED.	61%	Dem	[5]	Korea
Shin et al. 2021[158]	5771	62MED.	59%	Dem	[2], [5]	Korea
Soldevila et al. 2022[50]	2225	86 AVG.	27%	Dem	[5]	Spain
Song et al. 2021[159]	5621	45MED.	59%	Dem	[5]	Korea
Stawinski et al. 2021[160]	186	67 AVG.	47%	Dem	[5]	USA
Tahira et al. 2021[51]	12 863	75 MED.	49%	AD, PD, Dem	[4], [5]	UK
Tsai et al. 2020[161]	627	47 AVG.	53%	Dem	[5]	USA
Tyson et al. 2021[162]	150	78 AVG.	50%	Dem, PD	[5]	USA
Vekaria et al. 2022[163]	10 473	79 MED.	50%	Dem	[3], [5]	Finland
Venturini et al. 2021[164]	175	75 MED.	44%	Dem	[3], [5]	Italy
Vignatelli et al. 2021[165]	9470	77 AVG.	55%	Dem	[4], [5]	Italy
Wan et al. 2020[166]	30	64 AVG.	67%	Dem	[5]	China
Wang et al. 2021c[54]	14 874	65 AVG.	53%	Dem, AD, VD	[5]	UK
Worcel et al. 2021[56]	63	85 AVG.	61%	AD, Dem	[5]	France
Yakar et al. 2021[167]	1626	68AVG.	48%	AD, PD, VD, FTD, Dem	[5]	UK
Yu et al. 2021[57]	249	71 MED.	31%	PD, Dem	[5]	Turkey
Zakaria et al. 2021[168]	1064	65 AVG.	51%	Dem	[3], [4], [5]	USA
Zenesini et al. 2022a[58]	736	78 AVG.	33%	Dem, PD	[4]	Italy
Zenesini et al. 2022b[58]	331	81AVG.	41%	Dem, PD	[5]	Italy
Zerbo et al. 2021[169]	219 001	45 MED.	51%	AD, PD	[5]	USA
Zhang et al. 2021[170]	387 841	51 MED.	55%	Mix	[5]	USA
Zhou et al. 2021b[171]	4442	45 MED.	49%	Mix	[2]	China

a. Studies are divided by outcome: 'infection risk' and 'course and outcome'. The latter includes only participants with positive COVID-19 infection.
AVG., average (mean); MED., median; AD, Alzheimer's disease; n.a., not applicable; CI, cognitive impairment; Dem, dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; Mix, mixed dementia; PD, Parkinson's disease; VD, vascular dementia; KSA, Kingdom of Saudi Arabia; N. Ireland, Northern Ireland; 1, infection risk; 2, severity; 3, intensive care unit admission; 4, hospital admission; 5, mortality.

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Table 3 Neurodegenerative disorders and SARS-CoV-2 infection risk from multivariable analyses

Disorder	OR (95% CI)	Studies, *k*	Participants, *n*	I^2	Egger's *t*
Dementia	1.83 (1.16–2.87)**	7	62 859 255	99.3***	−0.078
Alzheimer's disease[a]	2.86 (1.44–5.66)**	4	61 978 500	98.1***	−0.518
Parkinson's disease	1.65 (1.34–2.04)***	6	278 245	86.8***	0.397
Mild cognitive impairment	1.51 (1.35–1.70)***	1	12 384	n.a.	n.a.
Mixed dementia	2.48 (1.17–5.27)*	3	76 327	93.5***	3.745

n.a., not applicable.
a. Estimates come from analyses including nationwide data, at the expense of local data, hence the number of studies (*k*) is relatively low.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

owing to better financial resources and advanced medical technology, such as laboratories, (self-) diagnostic kits, and public and private funded testing stations in high-income countries, more cases have been detected in high-income countries compared with low-income countries.[177] Similarly, nursing homes, more common in high-income countries, tend to have a larger elderly population than in low-income countries, which may also explain differences among continents.[18]

Severity, course and outcome of SARs-CoV-2 and neurodegenerative disorders

Individuals with most types of pre-existing neurodegenerative disorder are disproportionally affected by COVID-19 once infected. These effects were evident over disease types and outcome, suggesting an approximately twofold increase in risk of more severe illness, and a relatively poor course and outcome, for people with pre-existing dementia, and about a fourfold increase in risk of hospital admission in people with Alzheimer's disease. It has conclusively been shown that age is a risk factor for severe COVID-19.[178] However, analyses controlled for age yielded similar findings. A possible explanation for the observed findings may be deleterious interactions between COVID-19 and some specific clinical presentations and comorbidities inherent in neurodegenerative disorders. The atypical manifestation of COVID-19 symptoms in the elderly may lead to a delay in detection and diagnosis of the virus, accelerating the risk of developing severe complications and therefore resulting in a higher risk of hospital admission and ICU admission.[179,180] In addition, dementia is associated with oropharyngeal dysphagia,[181] a serious comorbidity or complication that independently increases the risk of pneumonia, malnutrition and mortality.[182] Furthermore, Parkinson's disease, dementia and dysphagia are well-known independent and substantial risk factors for pneumonia,[183] which is a common cause of death in advanced dementia.[184] A notable exception that was observed is that people with pre-existing dementia are less likely to be admitted to an ICU because of COVID-19. We are not aware of any studies showing that widespread vaccination altered this association. This finding might best be explained by the triage criteria (e.g. age, frailty and likelihood of benefit) commonly used in disaster situations to maximise the number of survivors.[185,186] In countries such as Belgium and the UK, it is advised against admitting to an ICU individuals aged 65 years or older presenting a Clinical Frailty Scale (CFS) score ≥5, who have been diagnosed with COVID-19 or are suspected of having contracted the virus.[90,187] Another significant finding is that individuals with pre-existing neurodegenerative disorders are at higher risk for mortality. This finding is in line with previous studies, demonstrating that in 2020, recorded deaths from Alzheimer's disease and from dementia were respectively 13% and 17% higher than expected, compared with 5 years earlier.[10,188] It should be noted that we conducted separate meta-analyses focused on unadjusted effect estimates and on adjusted effect estimates, and all associations yielded significant findings when adjusted for age and gender.

The results of these meta-analyses raise the question of whether the increased susceptibility of people with neurodegenerative

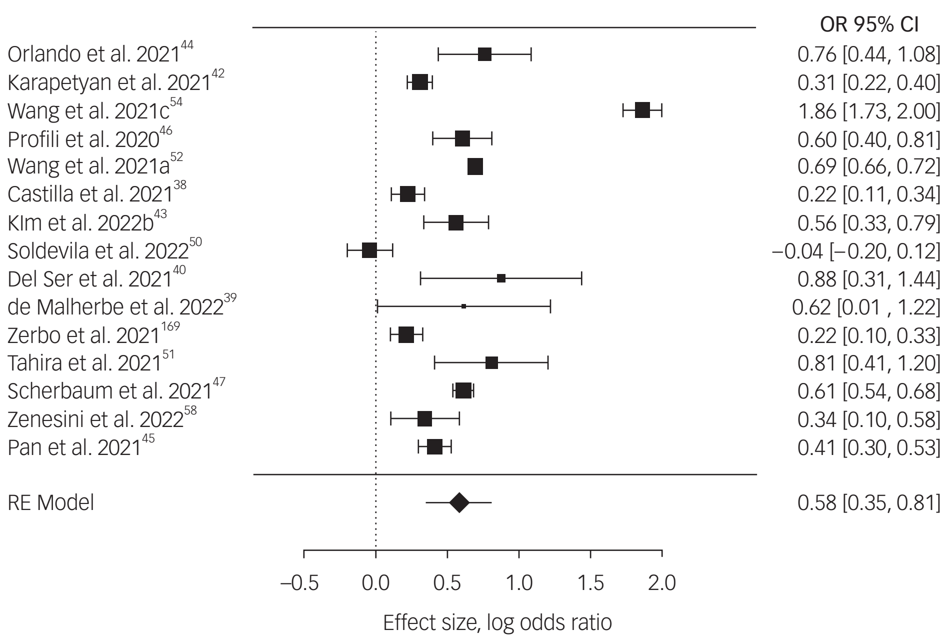

Fig. 2 Forest plot of pooled effect estimates for SARS-CoV-2 infection risk across all disorders.

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Table 4 Neurodegenerative disorders and COVID-19 severity, hospital admission, intenrtsive care unit admission and mortality from multivariable analyses

Disorder	OR (95% CI)	Studies, *k*	Participants, *n*	I^2	Egger's *t*
COVID-19 severity					
Dementia[a]	1.43 (1.00–2.03)*	6	2 058 163	94.2***	1.504
Alzheimer's disease	0.73 (0.20–2.67)	1	913	n.a.	n.a.
Mild cognitive impairment	0.95 (0.59–1.53)	1	78	n.a.	n.a.
Mixed dementia	1.40 (1.12–1.76)**	4	182 781	18.5	1.189
COVID-19 hospital admission					
Dementia[a]	1.60 (1.09–2.35)*	6	94 624	95.2***	1.002
Alzheimer's disease	3.72 (2.35–5.90)***	2	231 864	58.6	n.a.
Parkinson's disease[a]	1.06 (0.67–1.70)	4	24 382 561	88.4*	−1.069
Mild cognitive impairment	1.64 (0.82–3.28)	2	24 368 547	87.1**	n.a.
Mixed dementia	1.01 (0.99–1.03)	1	670 496	n.a.	n.a.
COVID-19 intensive care unit admission					
Dementia[a]	0.54 (0.40–0.74)***	12	47 015	80.4**	−2.020
Alzheimer's disease	1.65 (1.13–2.42)**	1	219 001	n.a.	n.a.
Parkinson's disease	1.55 (1.01–2.38)*	1	219 001	n.a.	n.a.
COVID-19 mortality					
Dementia[a]	1.58 (1.39–1.79)***	29	756 194	86.9***	3.625***
Alzheimer's disease	1.96 (1.34–2.86)***	7	673 716	93.8***	1.405
Parkinson's disease[a]	1.56 (1.25–1.94)***	9	7 942 537	81.9***	0.133
Mild cognitive impairment[a]	1.68 (1.11–2.54)**	5	10 651	89.4***	−1.117
Mixed dementia	2.27 (1.49–3.46)***	6	432 426	73.8**	3.608*

n.a., not applicable.
a. Estimates come from analyses including nationwide data, at the expense of local data, hence the number of studies (*k*) is relatively low.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

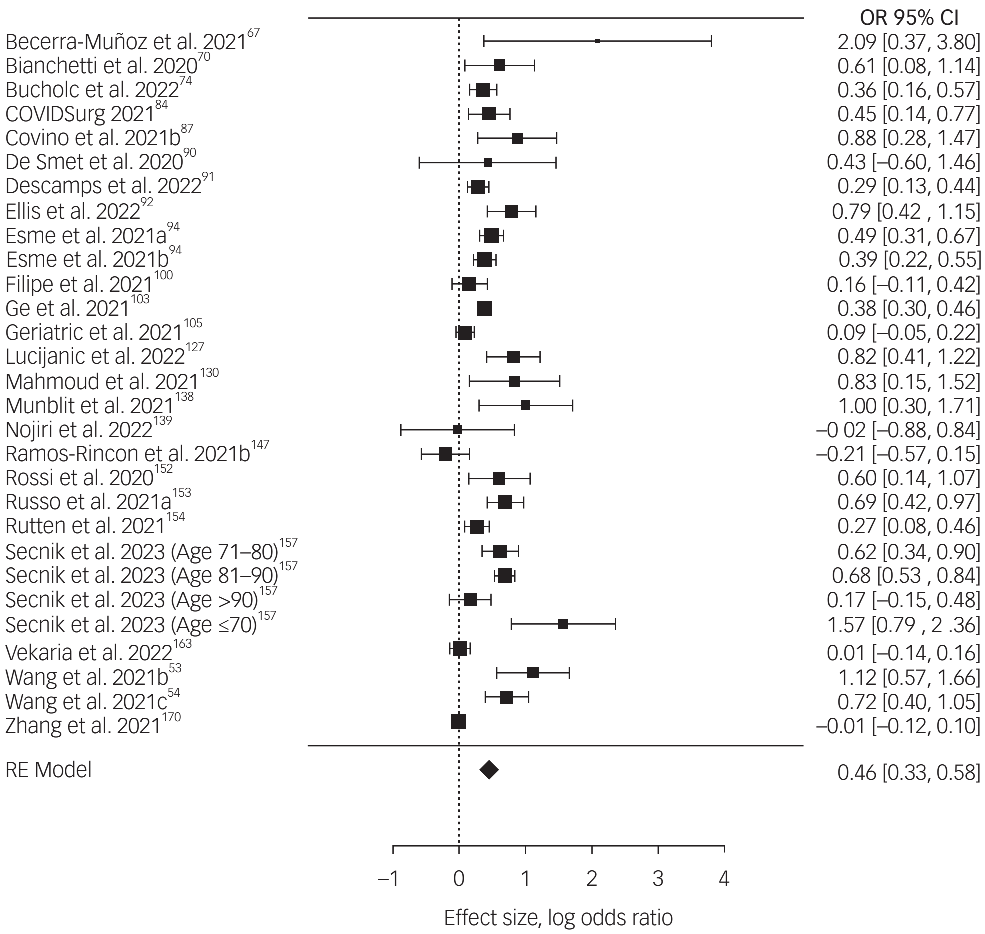

Fig. 3 Forest plot of pooled effect estimates for COVID-19 mortality in people with dementia.

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diseases to COVID-19 and poorer outcome may be attributable (at least partly) to biological factors and support a research agenda on this topic. We propose two main putative pathophysiological underpinnings that deserve further investigation: (a) a dysfunction of first barrier mucosal defences, leading to a higher infection rate and (b) a deteriorated, slower immune response to SARS-CoV-2, particularly an impaired T-cell immunity, essential to reduce the severity of the infection and facilitate the recovery of infected individuals. The first hypothesis may be approached by the investigation of the possible role in SARS-CoV-2 infection rates of oropharyngeal dysphagia, common in dementia,[181] and the effect of reduced salivary lactoferrin levels in Alzheimer's disease, which will reduce the defence mechanisms against SARS-CoV-2 and increase COVID-19 susceptibility.[189] The second one would require an investigation of the clinical significance of some changes in peripheral blood cell profiles involved at least in Alzheimer's disease and related to inflammation and immune dysfunction, such as the CD4/CD8 ratio,[190] which in turn may contribute to severe COVID-19.[191] In addition, individuals homozygous for apolipoprotein E (APOE) ε4 have shown a higher risk of COVID-19-related hospital admission, which could be explained by the changes associated with APOE ε4 that lead to extensive central nervous system inflammation, neurodegeneration and aggressive inflammatory response due to increased blood–brain barrier permeability, exacerbated microglia-mediated neuroinflammation and increased cytokine production in response to inflammatory stimuli.[192]

Strength and limitations

This meta-analysis followed MOOSE[26] and PRISMA[27] guidelines. In addition, a review protocol was pre-registered with the PROSPERO database. In support of the open science movement to promote transparency, expand access and broaden the range of research output, all the extracted data are openly available at the Open Science Framework (OSF). A further key strength of the study is the inclusion of independent data, which is a crucial assumption in meta-analysis.[193] Given that most of the conducted research on the topic of interest is based on freely accessible electronic data-sets, overlapping data-sets were anticipated. Hence, we carefully followed an inclusion protocol, ensuring that no duplicate data were used in each meta-analysis. To achieve this, we ran analyses for both local and nationwide data, and reported similarities or differences among the analyses. An additional strength of the study is the composition of the data-sets. We reported on several outcomes stratified by type of neurodegenerative disease. Last, our study makes use of both frequentist and Bayesian methods. Using this enhanced methodology in our meta-analysis enabled the collection of more exhaustive and reliable data regarding the association between various types of pre-existing neurodegenerative disease and SARS-CoV-2 susceptibility, course and outcome. In this meta-analysis both the frequentist and the Bayesian method showed comparable results, which suggests consistency and overall robustness of the findings.

Aside from these strengths, several limitations need to be considered. First, most of the meta-analyses revealed high between-study heterogeneity which remained unexplained, and publication bias was found in associations between dementia and COVID-19 severity and mortality. Three of the analyses had a small number of studies (fewer than 10) and were difficult to interpret and thought to be unreliable. Accounting for this by means of trim-and-fill methods did not result in different estimates. For the analyses on the associations between dementia and mortality and between mixed dementia and mortality, the trim-and-fill yielded slightly smaller yet significant effect-size estimates (funnel plots and trim-and-fill analyses can be found in the supplementary material). The number of studies for certain outcomes and disease types was relatively small, which may have resulted in high levels of between-study heterogeneity.[194] However, this could also be attributed to the scarce reporting on potential sources of heterogeneity (such as diagnostic criteria, time frame of diagnostic assessment, type of analysis used) in the majority of studies. Consequently, inadequate reporting limited the ability to examine the effect of these sources by running subgroup analyses, sensitivity analyses or meta-regression. Moreover, primary studies that specified subgroups of neurodegenerative disorders reported effect estimates for each category using the entire sample, rather than by subsample. We were therefore unable to pool all effect estimates for some disease types. The Cochrane handbook advises that results derived from meta-regression should be interpreted only when there are >10 studies available per analysis.[195] Sometimes we reported results based on fewer studies. Last, we cannot attribute causality to the relationships we reported on as all studies were observational and most retrospective.

Implications

Our findings underline the importance of vaccine priority and health surveillance in people with pre-existing neurodegenerative disease, in the current and possibly a next pandemic.

Muhannad Smadi, Institute of Psychology, Department of Clinical Psychology, Leiden University, Leiden, The Netherlands; **Melina Kaburis**, Institute of Psychology, Department of Clinical Psychology, Leiden University, Leiden, The Netherlands; **Youval Schnapper**, Institute of Psychology, Department of Clinical Psychology, Leiden University, Leiden, The Netherlands; **Gabriel Reina**, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain; and Clínica Universidad de Navarra, Department of Microbiology, Pamplona, Spain; **Patricio Molero**, Navarra Institute for Health Research (IdiSNA), Pamplona, Spain; and Clínica Universidad de Navarra, Department of Psychiatry and Medical Psychology, Pamplona, Spain; **Marc L. Molendijk**, Institute of Psychology, Department of Clinical Psychology, Leiden University, Leiden, The Netherlands; and Leiden Institute for Brain and Cognition, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence: Marc L. Molendijk. Email: m.l.molendijk@fsw.leidenuniv.nl

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Supplementary material

Supplementary material for this article is available at https://doi.org/10.1192/bjp.2023.43.

Data availability

The data that support the findings of this study are openly available on the Open Science Framework (OSF) at https://osf.io/fz5j4/?view_only=95054452816442eaa1e05d5d42be4b2e

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Author contributions

M.S. and M.L.M. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analyses. All authors were responsible for the study concept and design. M.S., Y.S., M.K. and M.L.M. contributed to the collecting and processing of the data. M.S. and M.L.M. ran all statistical analyses. M.S., M.K., G.R., P.M. and M.L.M. drafted the manuscript. All authors interpreted and discussed the findings. All authors critically revised the manuscript. All authors agreed on the final manuscript and the decision to submit it for publication.

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Declaration of interest

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