

The Effects of COVID-19 lockdown on neuropsychiatric symptoms in patients with dementia or mild cognitive impairment: A systematic review and meta-analysis

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ABSTRACT (283/300)

The COVID-19 pandemic may have a disproportionate impact on people with dementia/Mild cognitive impairment (MCI) due to isolation and loss of services. The aim of this systematic review was to investigate the effects of COVID-19 lockdown on neuropsychiatric symptoms (NPS) in people living with dementia/MCI. Two authors searched major electronic databases from inception to June 2021 for observational studies investigating COVID-19 and NPS in people with dementia/MCI. Summary estimates of mean differences in NPS scores pre-versus post COVID-19 were calculated using a random-effects model was conducted, weighting cases using the inverse variance. Study quality and risk of bias were assessed by the Newcastle–Ottawa Scale. From 2730 citations, 21 studies including 7139 patients (4.0% MCI), with dementia were evaluated in the review: (60.0% female mean age 75.6 ± 7.9 years). Five studies found no changes in NPS, but in all other studies, an increase in at least one NPS or Neuropsychiatric Inventory (NPI) score was found compared to pre-pandemic. The most common aggravated NPS were depression, anxiety, agitation, irritability, and apathy during lockdown, but 66.7% of the studies had a high bias. Seven studies including 420 patients (22.1% MCI) yielded enough data to be included in the meta-analysis. The mean follow-up time was 5.9 ± 1.5 weeks. The pooled increase in NPI score before compared to during COVID-19 was 3.85 (95% CI: 0.43 to 7.27; $p=0.03$; $I^2=82.4\%$). All the studies had high risk of bias. These results were characterized by high heterogeneity, but there was no presence of publication bias. There is an increase in the worsening of NPS in people living with dementia/MCI during lockdown in COVID pandemic. Future comparative studies are needed to elucidate whether a similar deterioration might occur in people without dementia/MCI.

Keywords: COVID-19, dementia, mild cognitive impairment neuropsychiatric symptoms

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The COVID-19 pandemic has had negative physical and psychological effects, among those who contracted the virus SARS-CoV-2 and subsequently COVID-19, as well as those who simply lived through the pandemic (1). People with dementia had high rates of hospitalisations and mortality when infected with SARS-COV2, but they were also impacted by COVID-19 in other ways (2,3).

People living with dementia might be more vulnerable to exposure to COVID-19 infection due to their advancing age, comorbidities, reduced cognitive and physical reserve capacities, difficulties in following and maintaining physical distance recommendations, and difficulties in understanding, following and remembering other COVID-19 prevention measures (4,5). During “lockdowns” implemented by governments to achieve a reduction in social contact, lasting approximately two years, physical activity and social interaction, which are considered as modifiable risk factors in the development and progression of dementia, were limited (6,7). Moreover, it may be difficult for people living with dementia compared to those who are dementia-free to use telecommunications to maintain social connections, or participate in home-based physical activity programmes (8). In addition, since similar limitations are experienced in terms of caregivers, the caregiver burden has increased during the lockdown (9). Moreover, all the negative situations experienced in this COVID-19 pandemic were not only valid for patients with living dementia, but also for patients with Mild cognitive impairment (MCI) (4,10,11).

Given the aforementioned factors, it may be hypothesized that COVID-19 restrictions could have worsened NPS (12,13). However, there are inconsistent results regarding this issue in the literature (14,15). Therefore, the aim of this review is to examine the effect of the COVID-19 pandemic on NPS in people living with dementia or MCI.

Methods

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria (16), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement (17). The review followed a predetermined, but unpublished protocol that can be requested by contacting the corresponding author.

Search strategy

Four electronic databases, MEDLINE, Scopus, EMBASE, and Cochrane Central were searched, targeting reports published from database inception to 2 June 2021 with no language restrictions. The search terms used were (dement*) Alzheimer* OR Lewy OR “Posterior cortical atrophy” OR “Binswanger” OR “Progressive supranuclear palsy” OR Frontotemporal disorder* OR Frontotemporal degeneration OR Corticobasal degeneration OR Corticobasal syndrome) OR Mild cognitive impairment AND (COVID-19 OR Novel Coronavirus–Infected Pneumonia OR 2019 novel coronavirus OR 2019-nCoV OR SARS-CoV-2).

The included studies were published as observational quantitative studies of a cross-sectional or longitudinal design. Inclusion criteria were (1) Study conducted during the COVID-19 pandemic (2) Patients had prior diagnosis of dementia or MCI (3) The prevalence or incidence value of one or more NPS was reported. Studies were excluded if they were qualitative or thematic studies.

Data extraction and statistical analyses

The literature search, assessment of inclusion and exclusion criteria, quality of studies, and extraction of data were independently undertaken and verified by two authors (PS, LS). The results were then compared, and, in case of inconsistency, consensus was reached with the participation of a third author (NV). Conference abstracts and minutes of relevant conferences relating to dementia or geriatric medicine, included in the databases were also searched. The following information was extracted: 1) characteristics of the study population (e.g., sample size, demographics, country in which the study was performed); 2) setting in which the study was performed; 3) presence of MCI or dementia, 4) dementia type, 5) type of NPS and method of evaluation; 6) the mean time between the assessment prior the outbreak of the pandemic and the assessment that took place during the COVID-19 crisis.

Data regarding the incidence or prevalence of NPS were reported descriptively. Studies in which NPS were evaluated using the Neuropsychiatric Inventory (NPI) before and after the pandemic were summarized using a meta-analytic approach.

Meta-analysis method

Studies reporting NPI values before and during COVID-19 lockdown were included in the meta-analysis. Due to the anticipated heterogeneity, a random-effects model was applied, weighting cases using inverse variance, calculating mean differences in NPI scores pre versus

post COVID-19 with 95% confidence intervals (CIs) using STATA 14.0. Statistical heterogeneity was assessed with the I^2 statistic for all analyses, with 0-50% being classified as low, 50-75% moderate, and >75% high heterogeneity (18). In case of high heterogeneity, meta-regression analyses were performed on available data, including mean age, percentage of females, stage of minor and major neurocognitive disorder, percentage of people having MCI, and lockdown duration. Publication bias was assessed with a visual inspection of the funnel plot and the Egger bias test (19). Finally, to test the robustness of results, a sensitivity analysis using the one-study removed method was conducted.

Assessment of study quality/Risk of bias

Study quality was assessed independently by two investigators using the Newcastle–Ottawa Scale (NOS) (MT, PS). This scale has been adapted from the Newcastle–Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies and cohort studies for the systematic review. A third reviewer was available for mediation (SGT). The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome (20). NOS scores were categorized into three groups: very high risk of bias (0 to 3 NOS points), high risk of bias (4 to 6), and low risk of bias (≥ 7) (21). Data of the meta-analysis were evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) that ranked the evidence from very low to high (22).

Results

Four electronic databases, MEDLINE (n=2090), Scopus (n=777), EMBASE (n=417), and Cochrane Central (n=0) were searched, targeting reports published from database inception to 2 June 2021 with no language restrictions. The search identified 2730 non-duplicated potentially eligible studies. The duplicates were removed both automatically and was this done manually. Following a detailed review of title and abstracts, a total of 64 full text articles were reviewed. (**Figure 1**) with 21 articles meeting the inclusion criteria: N= 7139, range 18-4913, 4.0 % MCI, mean age 75.6 ± 7.9 years, 60.0% female). The majority of the studies were conducted (n=16) (13–15,23–35) in the European continent, and (n=15) in the Americas (5,12,36–38). 8 of these studies were cohort studies, 13 were cross-sectional studies (**Table 1**).

3 studies did not specify the type of dementia (5,15,32). According to data of the remaining studies, the prevalence of Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and mixed type dementia were 64.7%, 12.9%, 6.4%, 7.5%, and 1.2%, respectively. NPS were most commonly evaluated by NPI (11 of the 22 included

studies) (23–30,35,36,38). 4 studies used validated scales such as Geriatric depression scale, Generalized Anxiety Disorder Scale, - Hospital Anxiety and Depression Scale (13–15,32) and other studies used non-validated questionnaires. Almost all of the evaluations were made with a caregiver-based telephone interview or online questionnaire (**Table 1**).

Prevalence/incidence of NPS during the COVID-19 crisis:

Narrative synthesis

Cross-Sectional Studies

In cross-sectional studies, caregivers were asked about NPS changes in patients', comparing to the period before the pandemic, and evaluated accordingly. Out of 13 studies, only 1 evaluating depressive symptoms before and after the outbreak of the COVID-19 crisis found no change (15). Based on the results of 12 other studies, the most common aggravated reported NPS were depression, anxiety, agitation, irritability, and apathy during lockdown (5,12–15,30–34,36–38). The rate of incidence was not specified in 3 studies, only pre- and post-COVID-19 crisis outbreak values were compared (13,30,33). The 2 studies including different populations and conducted by El Haj et al. determined that higher levels of depression and anxiety were recorded during compared to before the pandemic (13,33). Baschi et al. demonstrated that depression, anxiety, apathy, irritability and changes in sleep behaviours revealed the most significant difference before and after lockdown (30). Anxiety was one of the most frequent aggravated NPS in eight studies, and rate of increase in the prevalence of anxiety varied 22.4%-48% (5,12,14,31,34,36–38). Seven studies showed that incidence of depression was very common during lockdown (23.3%-61.5%) (12,14,31,32,34,36,38). Four studies showed an increase in agitation and aggression (20.7%-36.4%) and showed an increase in irritability (20.7%-49.4%) (5,31,36,38) and the other four studies revealed that apathy increased (24.1%-48.1%) compared to pre-lockdown (31,34,36,38). Unlike the aforementioned studies, Cagnin et al. examined the frequency of new onset NPS with aggravated NPS and showed that aggravated and new-onset NPS were similar, but sleep disorder was one of the most commonly new onset NPS (31). Most of the studies (46.1%) had a high level of bias. The reasons for this might be due to the absence of those without cognitive impairment (i.e. control group), the fact that NPS were evaluated with a caregiver-based telephone interview instead of a validated scale, and the effect of residual confounding (**Supplementary table 1**).

Cohort Studies

In two of the 8 cohort studies, the follow-up period was not reported, while the follow-up period in the others ranged from 4 to 12 weeks. In contrast to cross-sectional studies, NPI was used in cohort studies rather than individual evaluation of NPS. In 4 of 8 studies, there was no change in NPI scores compared to pre-lockdown (23,24,26,29). However, Mannin et al. showed that agitation, aggression, depression, apathy, and irritability were among the most increased NPS (26). In 2 of the 4 studies showing an increase in NPI scores, a statistical change for each of the NPS was shown without specifying the rate of increase, and how much proportional change there was in one study (25,35). While agitation was the common NPS found to be increased in 3 studies, depression, apathy, and anxiety were the NPS found to be increased in 2 studies. Manini et al evaluated new onset NPS and worsening of pre-existing NPS separately, and in this study, sleep disorders were determined to be one of the most incipient NPS (26). However, there is a high risk of bias in all cohort studies (**Table 1**). The reasons for this are the absence of a control group in the study that were not exposed to the pandemic, the short follow-up time, and the initial NPI values are usually based on retrospective medical records (**Supplementary table 1**).

Meta-analysis results

Seven studies including 420 participants (22.1% MCI) yielded enough data to be included in the meta-analysis (24–29,35), i.e. studies reporting NPI values before and during COVID-19 lockdown. The mean follow-up time was 5.9 ± 1.5 weeks. The pooled increase in NPI score before compared to during COVID-19 was 3.85 (95% CI 0.43 to 7.27; $p=0.03$; $I^2=82.4\%$) (**Figure 2**). This evidence was supported by a very low certainty of evidence according to the GRADE since all included studies had a high risk of bias, small sample size included, and high heterogeneity were present. In the sensitivity analysis, the significance and magnitude of the results did not change with the removal of any one study. The removal of van Maurik et al (2020) reduced the heterogeneity to 70%. The visual inspection of the funnel plot indicated no publication bias and the Egger's test p -value was 0.54, suggesting no presence of publication bias (**Supplementary Figure 1**).

In the meta regression analyses, bivariate analyses did not moderate the associations between mean age, gender distribution (percentage female), follow-up duration or percentage of people with mild dementia, percentage of people with MCI and changes in NPS scores (mean age coefficient= -0.58 95% CI -1.17 to 0.01; $p=0.05$; $r^2=0.62$; gender distribution coefficient =-0.09

95%CI -0.43 to 0.24; $p=0.50$; $r^2=0.00$; follow-up duration: coefficient= 0.43; 95%CI: -2.13 to 2.99; $p=0.63$; $r^2=0.00$; percentage of people with mild dementia: coefficient=-0.05; 95%CI: -0.30 to 0.22; $p=0.69$; $r^2=0.00$; percentage of people with MCI: coefficient=0.04; 95%CI: -0.26 to 0.34; $p=0.75$; $r^2=0.00$).

DISCUSSION

In this systematic review and meta-analysis of 21 studies including more than 7,000 people living with dementia or MCI, NPS tended to increase during the pandemic, with aggravated NPS being most commonly depression, anxiety, agitation, irritability, and apathy. Moreover, according to the meta-analysis results of seven studies with NPI scores before and after lockdown, a significant worsening in NPI was found. Studies had high heterogeneity and high risk of bias, i.e. low quality.

NPS, very common in patients with dementia, affects more than 97% of patients during the course of their disease (39). It may cause cognitive and functional deterioration, long-term hospitalization, mortality, and decreased quality of life for caregivers and patients (7). Given these outcomes, it is clear that NPS can negatively affect both people living with dementia and their caregivers. However, while coping with NPS is difficult for both healthcare professionals and families, the COVID-19 pandemic is making this more complex. In this systematic review, an increase in NPS was determined in most of the 21 studies. Although a 3-point change from baseline in NPI scores is considered a clinically meaningful difference, no clinical score is available in the changes of NPI between two evaluations. Therefore, we could only analyse changes in NPI scores and a statistically significant worsening in NPI was found in this meta-analysis over a mean of ~ 5 weeks. Possible reasons for this may be as follows: First, the inability to maintain physical activity and social interactions, which are non-pharmacological approaches recommended for NPS prevention, due to forced lockdown at home, and the closure of outpatient rehabilitation centres that provide services such as cognitive training, occupational therapy, and group activities, may have increased the risk for development of NPS (37). Loneliness, social isolation and loss of routine activities are an important cause of increased depression and anxiety (33,40). For example, according to one study, during, covid-19 pandemic, two out of three older adults experienced a moderate sense of loneliness, and individuals who displayed a higher level of loneliness also had a higher severity of anxiety level depressive symptoms and irritability (41). However, the lockdown exaggerated feelings of hopelessness, sadness, and loneliness, not only among older people, but also in the general population, leading to widespread depression and anxiety. A study comparing older people with

and without dementia showed that people living with dementia mostly suffered from depressive symptoms, while cognitively normal older adults experienced more anxiety (32). Dementia patients may show more depressive symptoms due to their inability to adapt to performing activities such as physical activity or leisure time activities. On the other hand, those who are cognitively normal may experience more anxiety because they are aware of adverse COVID-related situations, such as health problems. Although the covid-19 lockdown has increased NPS in the entire general population, it should be considered as a separate entity as the course of NPS in dementia patients may be different.

Second, caregiver distress itself may have increased NPS in people living with dementia, or may have affected the reporting of features of NPS by the caregiver, which was the method of data collection from the majority of studies (9). Caregivers may have been concerned about losing paid caregivers (37), the ability of the patient with dementia to comply with infection control precautions (42), and less contact with their wider family to reduce the risk of virus transmission, as well as the challenges of using virtual telecommunications technology (37,42). Previous studies have shown that distressed caregivers tend to use emotion-focused rather than problem-focused coping strategies, which appear to increase the patient's NPS (9). A prolonged proximity between the caregiver and his/her relative can promote tensions and mirror reactions (34). Irritation, anger or impatience of the caregiver may cause more aggression/irritability in people living with dementia (9,34). Third, the rapid cognitive deterioration in people living with dementia during the pandemic, the inability of these patients to adapt to new living conditions and the inability of patients to continue their usual daily activities may have led to the development of apathy and triggered depression (4,32). Finally, distress factors such as loneliness and anxiety, as well as the NPS itself, such as aggravating depression and anxiety, may also result in sleep disorders due to the covid-19 lockdown in patients (43).

It was observed that the worsening in NPS (especially anxiety) during quarantine was much greater in patients with mild dementia than in those with advanced dementia (44). One possible explanation for this may be that subjects with relatively mild dementia may have undergone more radical changes in their lifestyle habits during quarantine than those with severe dementia, who are generally more home-bound and less active (12). It is possible that people with mild dementia during quarantine have a greater awareness of the pandemic and the risks of getting sick, and that this information is likely to cause more concern (12,32). Indeed, it is considered that awareness of the COVID-19 outbreak and “patients understanding the reason for wearing a mask” was more than 3 times greater in mild AD than in moderate-severe AD, and that due

to this less awareness, the depressive symptoms associated with the COVID-19 pandemic were less common in moderate and severe dementia (44). However, comparing neuropsychiatric symptoms one by one according to the severity of dementia, Azevedo et al. determined that anxiety, psychotic symptoms, and appetite changes were more common in moderate dementia than in mild and severe dementia (5). It is important to note that the interviews may have been influenced by the emotional state of each caregiver on the day of the survey.

According to the meta-analysis, seven studies found that NPI scores increase in COVID-19 lockdown (24–29,35). However, on the contrary to MA results, interestingly, there was some studies resulting in no change in NPS in the literature. One possible reason for this could be the short lockdown duration to re-evaluate the NPI. For example, in a study in which the mean lockdown duration was 27.4 days, it was shown that a very small percentage of AD patients had a change in NPS, but there was a positive correlation between lockdown duration and both NPS severity and caregiver distress (23). Re-evaluation after 5 weeks (35 days) of lockdown in one of the 7 studies and a mean of 32 days in the other (not clear in the others) suggests that the change in NPS may occur over a longer period of time (25,29). Furthermore, although caregiving is a stressful situation that imposes physical, mental and social constraints, it may be that the lockdown to stem the COVID-19 pandemic had little or no additional impact on the caregivers' routines. For example, the fact that some societies, such as Italy, have supported and trained their caregivers by a formal health care network, at least until the onset of the pandemic, suggests that these caregivers have less difficulty coping with the day-to-day care of people with dementia and the way they perceive NPS has changed or they do not report their own reluctance to manage NPS (24,45). The lack of significant changes in NPI in two studies conducted in Italy also supports this (24,26). Finally, depending on the proportion of moderate and severe dementia in the studies, it may be that risk to health of the COVID-19 pandemic is not perceived by patients and the NPS does not change accordingly (44). However, our meta-analysis' results did not change after adjusting for severity of dementia.

Our study has some limitations: most of the studies included in the review (especially the meta-analysis) have small sample sizes and are of a cross-sectional design; thus, there is no clear information about pre-pandemic evaluation. Second, lockdown duration was short, and many studies don't report time from first to second assessment. Third, although NPS is seen with different severity and frequency in different dementia subtypes, analysis by dementia subtypes was not performed, except in one study (31). Fourth, it has not been clearly determined how each of the NPS, such as depression, anxiety, and apathy, is affected separately. Fifth, no

separate evaluation was made for MCI patients, as pre- and post-lockdown NPI scores were given only for the total sample size in the studies. Last, the studies were clinically and statistically heterogeneous; this may be partly due to different time periods between assessments, differences in not only dementia type or severity, but also evaluation of NPS. Additionally, the variation in impact of COVID and restrictions may be different in different countries, which might be the cause of high heterogeneity and high risk of bias. The strength of our study is that it is the first compilation of results of studies conducted under difficult pandemic conditions.

In conclusion, there is an increase in the worsening of NPS, frequency of depression, anxiety, agitation, irritability and apathy in people living with cognitive impairment during lockdown in the COVID pandemic. There is a clear need to explore the causes of NPS and how people living with dementia and their caregivers can be supported in any future pandemic and lockdown or where usual support services are not available and face-to-face contact is limited. Therefore, it is of substantial importance to develop appropriate strategies for preventing and coping with NPS in people living dementia. A few examples of these strategies can be listed as follows: Developing and disseminating telehealth applications in order to maintain coordination with doctors and other health professionals during the closure, educating caregivers on how to manage NPS, with or without a pandemic, arranging the necessary technological infrastructure for the continuation of socialization during the lockdown.

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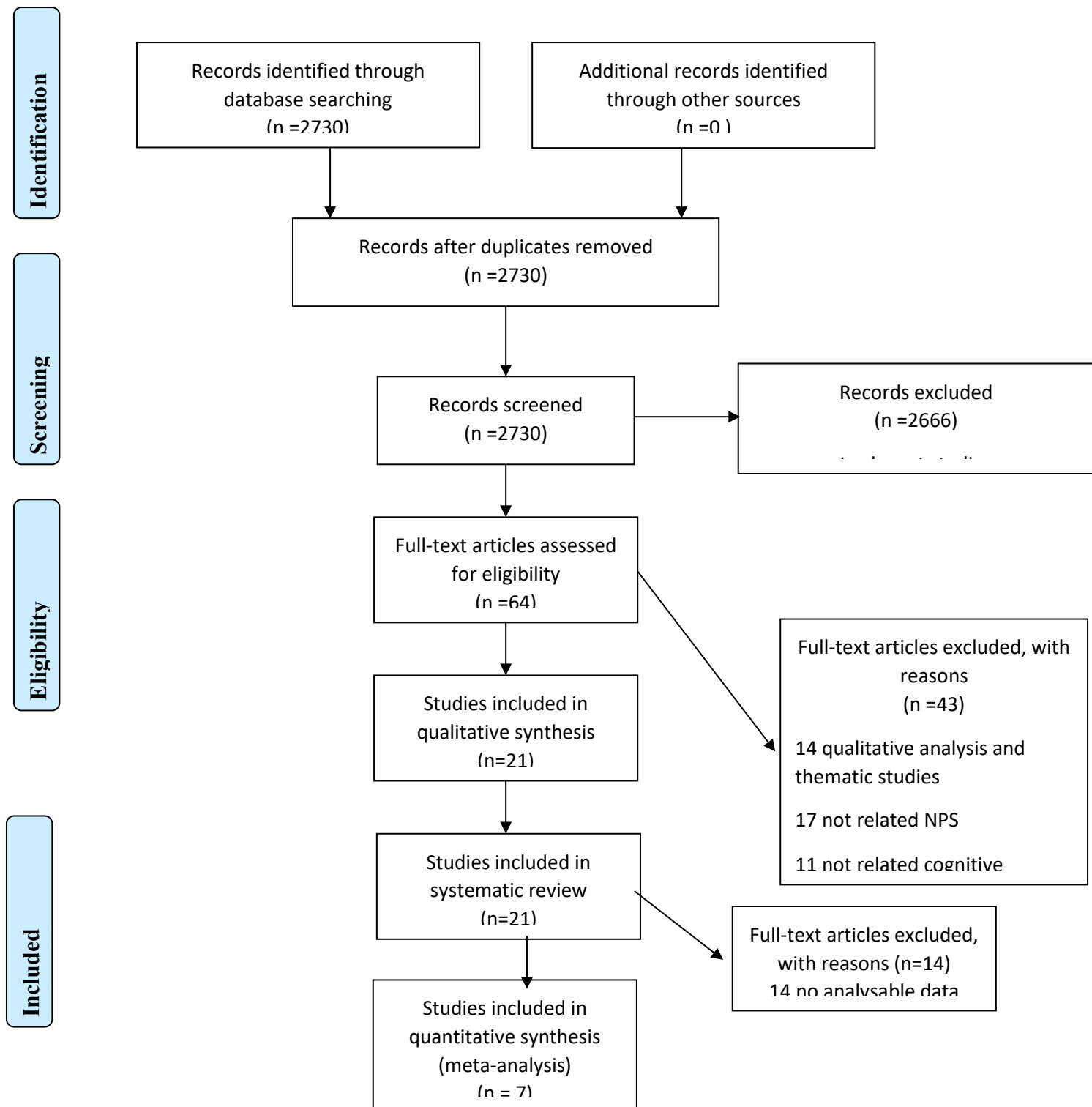
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Tables and Figures

Figure 1. PRISMA Flow Diagram



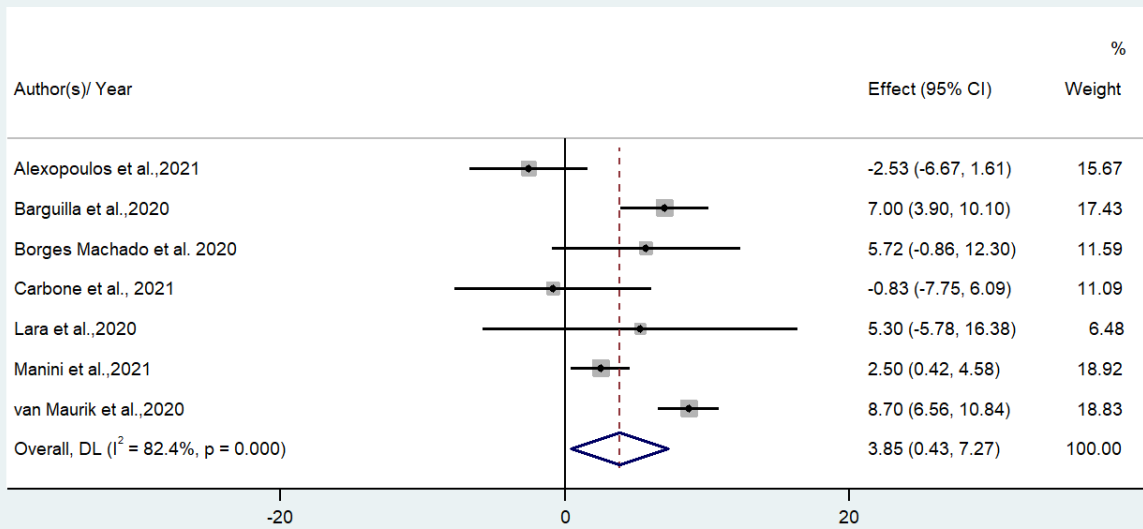


Table 1. The included studies investigating neuropsychiatric symptoms in people living with dementia or mild cognitive impairment.

Year	Country/ Assessment/ Confinement tme	Mean Age/Female Gender (n)	Sample Size	Dementia Type /Features of patients with dementia	From first assessment to second assessment	Depressi on	Anxiety	Agitati on	Apathy	Irritability	Aggression	Psychoti c Sympto ms	Sleep/nighttime behavior disorder	Appetite/ eating problems	NPI/NPS	RoB
CROSS-SECTIONAL STUDIES																
Azevedo et al. 2021 ⁵	Argantina Brazil Chile - caregiver-based telephone interview	77.2±9.3 / 183	321	-Mild 50.1% -Moderate 23.1% -Severe 26.8%	NA	NA	37.4 %	23.1 %	NA	37.1%	16.8 %	19.0%	23.1%	35.2 %	↑	High
Baschi et al. 2020 ³⁰	Italy -patients or caregiver based telephone interview	68.3±11.5/ 35	62	MCI-PD: 31 MCI-noPD: 31	10 weeks	↑	↑	-	↑	↑	-	↑	↑	↑	↑	Low

COHORT STUDIES																
Alexopoulos et al. 2021 ¹²	Greece	80.21±7.70 / 47	67	AD: 45	4.6 weeks	NA	NA	NA	NA	NA	NA	NA	NA	NA	→	High
	-caregiver-based telephone interview			VAD: 9 FTD :2 Mixed dementia: 11												
Barguilla et al. 2020 ²⁶	Spain	75.4± 5.2/ 32	60	AD: 25	4 weeks	↑	↑	↑						↑	↑	High
	- caregiver-based telephone interview			MCI: 15 FTD: 6 VAD: 3 DLB: 2 Others: 9					NA	NA	NA	NA	NA			
Borges Machado et al. 2020 ³²	Portugal	74.28 + 6.76/ 24	36	AD: 17	12 weeks	NA	NA	NA	NA	NA	NA	NA	NA	NA		High
	-caregiver-based telephone interview			Multiple Etiologies: 6 Unspecified: 4 VAD: 2 FTD: 1 Korsakoff Syndrome: 1 MCI: 5										↑ / %44.4		

van Maurik et al. 2020 ³¹	Netherlands -a self reported corona survey	69±6/ 40	121	AD : 43 DLB : 34 MCI: 35 Others: 9	NA	20-40%	20-40%	30%	40%	NA	NA	NA	37.0%	NA	↑	High
21 studies	16 European countries 5 American countries	75.6 ± 7.9/ 4270	7139	AD : 4312 VAD: 868 DLB: 425 FTD: 501 MCI: 293 Mixed dementia: 80 Others : 660 Cohort : 8 Cross-sectional :13	12 studies: 6.2 week, 9 studies: NA data										Not increased changes in NPS/NPI scores: 5 Increased in NPI/NPS: 16	7 studies: Low RoB 14 studies: High RoB

Abbreviations: ↑ : statistically significant increased in neuropsychiatric symptoms, → : insignificant changes in neuropsychiatric symptoms

AD: Alzheimer Disease; DLB: Dementia with Lewy bodies; FTD: Frontotemporal Dementia; MCI: Mild Cognitive Impairment; NPI: Neuropsychiatric Inventory NPS: Neuropsychiatric Symptoms; NA: Not applicable; PD: Parkinson's disease dementia; RoB: Risk of Bias; VAD: Vascular Dementia.

*New onset neuropsychiatric symptoms