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The medium and long-term effect of the COVID-19 pandemic and public health measures on modifiable risk factors for dementia and cognitive decline: A global perspective

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The medium and long-term effect of the COVID-19 pandemic and public health measures on modifiable risk factors for dementia and cognitive decline: A global perspective

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Prevalence of Behavioral and Psychological Symptoms in Patients With Cognitive Decline Before and During the COVID-19 Pandemic

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Objective: Preventive measures to limit the spread of COVID-19 are essential, but often cause social isolation, affecting the physical and mental health of older adults. Patients with dementia are likely to have worsening behavioral and psychological symptoms of dementia (BPSD) owing to pandemic restrictions. To examine this, we described BPSD before and during the COVID-19 pandemic.

Methods: We identified patients at a memory clinic in Japan between October 2018 and December 2019 (15 months before the pandemic began, $n = 1{,}384$) and between April 2020 and June 2021 (15 months after the State of Emergency was declared; $n = 675$ patients). A propensity score was used to match 576 patients from each group. The Mini-Mental State Exam was used to classify cognitive function into mild and moderate/severe. Dementia Behavioral Disturbance Scale was used to evaluate BPSD. The association between BPSD before and during the pandemic was evaluated using binomial logistic regression models.

Results: The levels of frequent night waking were higher in individuals before the pandemic than in those evaluated during the pandemic in both the mild group [adjusted odds ratio (AOR) = 1.82, 95% CI 1.02–3.23] and the moderate/severe group (AOR = 1.96, 95% CI 1.19–3.23). During the pandemic, physical attacks were higher in the mild group (AOR = 4.25, 95% CI 1.12–16.07), while night wandering was higher in the moderate/severe group (AOR = 2.22, 95% CI 1.03–4.81).

Conclusion: In patients with cognitive impairment, some BPSD were more prevalent during the pandemic, depending on dementia severity. The findings pertaining to the higher frequency of sleep disturbance and aggressiveness during COVID-19 should be used to guide BPSD screening in patients with dementia and to provide evidence-based interventions.

Keywords: behavioral and psychological symptoms (BPSD), social distancing (vaccine), dementia–Alzheimer's disease, coronavirus disease (COVID-19), mild cognitive impairment (MCI)

INTRODUCTION

Outbreaks of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue to be the most important issue in health risk management in Japan since the first case was found there in January 2020. The International Epidemiology Association's Dictionary of Epidemiology defines a pandemic as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people" (1). The complexity of this pandemic is that while minimizing the infection risk is extremely important, the most vulnerable members of society, such as patients with dementia and those requiring long-term care, are likely to be affected by long-term measures, such as social distancing.

Systematic reviews have shown that confinement and isolation are effective for infection control, including in the COVID-19 pandemic (2). However, in past outbreaks such as SARS and MERS, a public health challenge also emerged in that the countermeasure—long-term "quarantine"—compromised mental health and increased psychological symptoms, especially those related to stress responses such as anxiety, depression, and distress (3). In addition, increased vigilance due to fear of contagion and grief over the loss of family and friends due to the disaster can undermine mental health and wellbeing (4). These findings are based on the general population, but there are very few findings on the socially vulnerable elderly and people with dementia (5, 6). People with dementia are frail, often dependent on caregivers for activities of daily living (7), and they are frequently in need of nursing care and social services (e.g., dementia café, daycare, and residential care) (8, 9). Prolonged isolation keeps them away from these protective factors and negatively affects their behavior and psychology (i.e., behavioral and psychological symptoms of dementia, BPSD), thus amplifying the burden on caregivers (10). In a telephone survey of patients with dementia and mild cognitive impairment in Italy, 32% showed deterioration in memory and orientation, and 8% showed a functional decline in daily life, described mainly in terms of reduced levels of independence in personal care and housekeeping (11). BPSD, mainly agitation/aggression, apathy, and depression, worsened or developed in more than 50% of patients, mainly in dementia patients (11). In a survey of dementia patients and their families after COVID-19 in Japan, 39% of medical and nursing facilities and 38% of care support specialists reported that their dementia patients were affected in some way, such as the appearance or worsening of BPSD, decline in cognitive function, and decline in physical activity (12). In a survey of care support specialists and physicians certified in dementia care by academic societies in Japan, 40% of dementia patients experienced a worsening of their condition, most frequently a worsening of cognitive function (47%) and an increase or worsening of BPSD (46%).

Previous studies have suggested that BPSD could worsen or develop in patients with dementia after the COVID-19 pandemic (11–13), but their designs did not include the normal condition (i.e., before COVID-19). In addition, the severity of dementia is closely related to the development of BPSD (14, 15). Therefore, describing BPSD before and after the COVID-19 pandemic as well as considering dementia severity could provide a more detailed context and clinical insights. The purposes of this study were to describe the prevalence of behavioral and psychological symptoms, mainly BPSD, before and during the COVID-19 pandemic in patients with cognitive decline and to obtain knowledge to improve the quality of medical care for patients with dementia during and after COVID-19.

METHODS

Study Cohort

Participants were patients of the memory clinic of the National Center for Geriatrics and Gerontology (NCGG) in Aichi, Japan, from October 2018 to December 2019 (15 months before the onset of the COVID-19 pandemic; "before COVID-19", $n = 1{,}382$) or from April 2020 to June 2021 (15 months after the declaration of the COVID-19 emergency; "during COVID-19", $n = 675$ patients), and had a dementia-related diagnosis according to the criteria of the National Institute on Aging-Alzheimer's Association workgroups (16, 17). Specifically, mild cognitive impairment (MCI) due to Alzheimer's disease (AD) (16) and dementia were classified as either probable or possible AD (17), probable or possible dementia with Lewy bodies and Parkinson's disease (DLB/PD) (18, 19), and vascular dementia (VaD) (20).

The period from the beginning of January 2020 to the end of March 2020 was excluded because it was the early stage of the pandemic, and the relationship between the disease and people's behavior was unclear. Only the first assessment of those with multiple assessments was included (before COVID-19 = 982, during COVID-19 = 615, with no overlap between the groups). We selected 883 before-COVID-19 and 576 during-COVID-19 participants who had also completed the Dementia Behavioral Disturbance Scale (DBD) (21), the primary outcome of this study. To ensure that the analysis took into account the characteristics of the participants before and during COVID-19, the 2 groups were matched using propensity scores. To calculate the propensity score, age, gender, and type of dementia (13) were used as the predictor variables to estimate the probability of belonging to the before- and during-COVID-19 groups. We matched participants with similar propensity scores at 1:1 to create a dataset of 576 individuals in each group (**Supplementary Figure**). The study was conducted after the participants approved that their data would be included in the study and the Ethics Committee of the NCGG approved the study protocol.

Variables

Behavioral and Psychological Symptoms of Dementia

BPSD was assessed with the DBD developed by Baumgarten et al. (21). The DBD consists of 28 observable behaviors related to dementia, and the frequency of each item is rated by a primary caregiver on a scale of 0 to 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = always), with higher scores indicating greater severity of BPSD. DBD includes various domains of observable behavioral disorders such as passivity, agitation, eating disturbances, aggressiveness, diurnal rhythm disturbances, and sexual disinhibition. The reliability and validity of the Japanese version of the DBD have been established (22), and the scale is widely used internationally in the field of dementia. The DBD was completed by the primary caregiver (patient's spouse or child, 90.5%) independent of the patient and collected by an outpatient health care provider. Several measures have been developed to assess BPSD [e.g., Neuropsychiatric Inventory (NPI) (23) and DBD], and there are differences in the way BPSD is assessed by medical professionals and caregivers. These measures have been widely used mainly for dementia patients, but research that assesses behavioral and psychological symptoms in people with MCI has also been published (24, 25).

Sociodemographic and Clinical Variables

Cognitive function in the elderly was assessed by use of the Mini-Mental State Exam (MMSE) (26). Scores range from 0 to 30, with higher scores reflecting a higher level of global cognitive performance. In this study, total MMSE scores were classified into three groups: mild (MMSE 21–30 points, equivalent to Clinical Dementia Raring; CDR 0–1), moderate (11–20 points, equivalent to CDR 2), and severe (0–10, equivalent to CDR 3), according to studies that examined the relationship between CDR and MMSE (27). The results showed unbalanced groups, with 55.6% placed in the mild, 46.2% in the moderate, and only 4.1% in the severe categories. To make the groups more balanced, the moderate and severe groups were combined into one category.

Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS), with higher scores indicating greater depressive symptoms (28). In addition, the ability to walk and balance was assessed with the Timed Up and Go Test (TUG) (29). Other information such as gender, age, education, marital status, living environment, comorbidity (diabetes mellitus, hypertension, dyslipidemia, cardiac disease, and stroke), polypharmacy (5 or more prescribed medications) (30), and body mass index were obtained from medical records.

Informant-Based Variables

Using a questionnaire, the primary caregiver reported the following about the patient: (a) Basic activities of daily living (ADL), assessed by the Barthel Index (31), and Instrumental ADL (IADL), assessed by the Lawton Index (32), with higher scores indicating better status; (b) Financial status was determined by the need for assistance on a 4-point scale (25); (c) Use of care services: home care service, daycare, or residential care; (d) Status of care needs: 7 levels of Long-term Care Insurance System (LTCI) certification, "requiring support" levels 1 and 2, and "requiring long-term care" levels 1 to 5 (33); (e) Patient lifestyle: light exercise/physical training, regular exercise/sport, regular drinking, regular smoking, quality of sleep, napping, weight loss, and fatigue. The LTCI certification was classified into "mild" ("requiring support" levels 1 and 2 and "requiring long-term care" level 1) or "severe" ("requiring long-term care" levels 2 to 5) based on studies by Saito et al. (33) and Fujiwara et al. (34).

Statistical Analysis

To analyze socioeconomic status and lifestyle-related variables, physical functioning, and psychological functioning between the

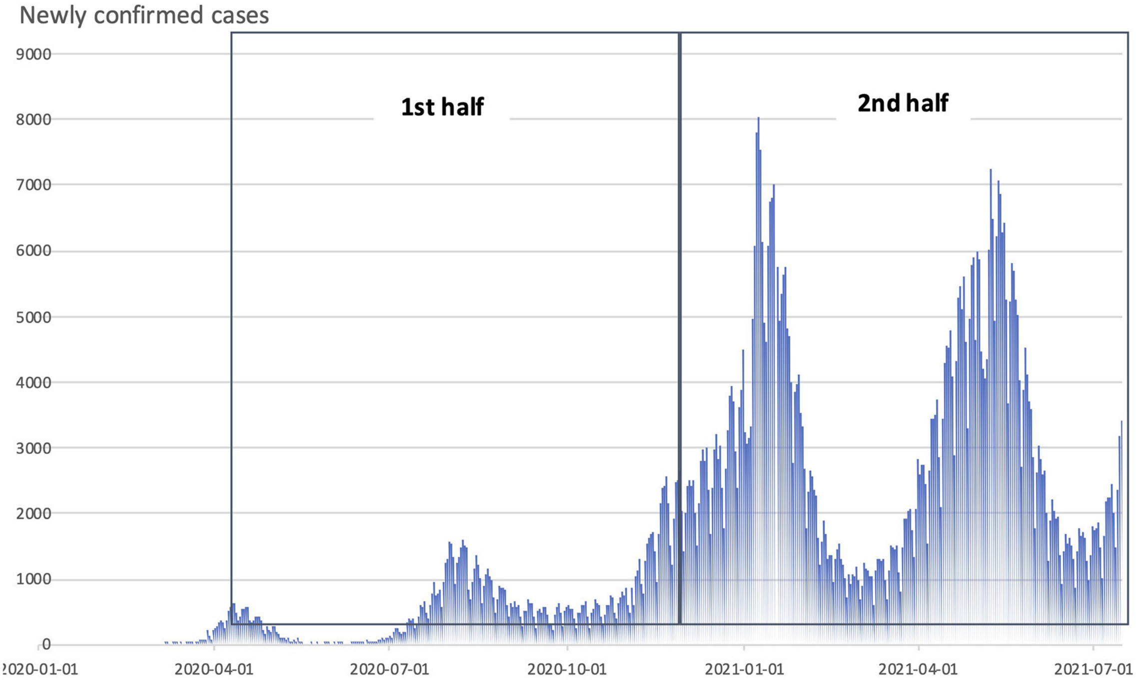

FIGURE 1 | Monthly trends in the number of new COVID-19 infections in Japan and the period of the pandemic covered by this study (divided into first half and second halves: the first half was set at 7½ months, from April 2020 to mid-October 2020,and the second from then until the end of June 2021).

mild and moderate/severe groups before and during the COVID-19 pandemic, we used independent-sample *t*-tests for continuous variables and chi-squared tests for categorical variables. Next, we analyzed the prevalence of each DBD item in the 2 groups before and during COVID-19. The presence of BPSD was defined by responses of "sometimes," "often," or "always," (21) and the prevalence before and during the pandemic were analyzed using the chi-squared test stratified by dementia severity. Items that were significant in the univariate analysis were selected for further multivariate analysis to explore the association between DBD and the period related to the COVID-19 pandemic. Binomial logistic regression analysis was performed with each item of the DBD as an outcome and before and during COVID-19 as the explanatory variable. Odds ratios (ORs) and confidence intervals (Cis) were estimated. The models were adjusted for three sets of variables: (a) socioeconomic status (financial burden, living alone, and educational history); (b) physical functioning and use of medical and nursing care services (IADL, polypharmacy, and LTCI certification); and (c) cognitive and psychological functioning (MMSE and GDS).

Because the during-COVID-19 observation period was 15 months, during which time the state of emergency was declared and various infection prevention measures were taken, we conducted a subanalysis of BPSD items in the early (first half) and late (second half) of the pandemic period (**Figure 1**). All analyses were carried out in SPSS v. 27.0 (IBM Corporation, Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

RESULTS

The analysis of MMSE scores before and during the pandemic showed no difference between the two groups (20.96 ± 5.15 and 20.27 ± 5.20, respectively; $p = 0.912$). The Mild group included 327 before-COVID-19 patients and 313 during-COVID-19 patients. The moderate/severe group included 249 and 261, respectively. Age group, gender, clinical diagnosis, and comorbidities did not differ between the "before" and "during" groups (**Table 1**). But the following variables did differ between them: In the mild group, significantly more people were married ($P = 0.003$), had more than 12 years of education ($P = 0.047$), and were less likely to live alone ($P = 0.032$) during COVID-19 than before. In the moderate/severe group, more people had worse sleep ($P = 0.040$), with higher scores in the GDS ($P < 0.001$). Further, we observed a trend of less residential care use during the COVID-19 pandemic ($P = 0.050$).

The five most prevalent BPSD items were as follows: "Asks the same question over and over again," "Loses, misplaces, or hides things," "Shows lack of interest in daily activities," "Sleeps excessively during the day," and "Hoards things for no obvious reason," which were frequent in all the groups (**Table 2**). However, these items were more frequent in the moderate/severe group than in the mild group (specifically, for the question "Asks the same question over and over again," 78.3% of the mild group vs. 94.0% of the moderate/severe group showed higher prevalence before COVID-19, and 78.3% of the mild group vs. 91.2% of the moderate/severe group showed higher prevalence during COVID-19). Whereas, items related to sexual disinhibition, specifically the items of "Makes inappropriate sexual advances" and "Exposes himself/herself indecently," were not frequent, ranging from 0 to 1.6%. Urinary and fecal incontinence was also not frequent, ranging from 6.4 to 21.0% for urinary incontinence, and from 0 to 0.9% for fecal incontinence. Comparing prevalence before and during COVID-19 by severity, we found "before" and "after" differences in several items in patients with mild and moderate/severe dementia (**Table 2**), such as "Wakes up at night for no obvious reason" (6.9 vs. 12.2%) and "Physical attacks" (0.9 vs. 3.5%) in the mild group, and "Wakes up at night for no obvious reason" (15.9 vs. 28.9%), "Sleeps excessively during the day" (41.9 vs. 51.3%), "Paces up and down" (12.9 vs. 20.4%), "Wanders in the house at night" (5.7 vs. 11.2%), and "Gets lost outside" (6.5 vs. 11.9%) in the moderate/severe group (**Table 2**). Those items were further analyzed by multivariate analysis. In the unadjusted model, all of the items remained significant (**Table 3**); however, in the adjusted models, only "Wakes up at night for no obvious reason" (AOR = 1.82, 95% CI 1.02–3.23 in the mild group; AOR = 1.96, 95% CI 1.19–3.23 in the moderate/severe group), "Physical attacks" (AOR = 4.25, 95% CI 1.12–16.07 in the mild group), and "Wanders in the house at night" (AOR = 2.22, 95% CI 1.03–4.81 in the moderate/severe group) remained significant.

In the subanalysis of the prevalence of BPSD in the first and second halves of the COVID-19 period, four items were significantly less prevalent in the mild group, specifically "Asks the same question over and over again," "Loses, misplaces, or hides things," "Sleeps excessively during the day," and "Hoards things for no obvious reason" and two in the moderate/severe group, specifically "Paces up and down" and "Repeats the same action over and over again" (**Supplementary Table**). However, there was no difference in the items that were significant in the analysis of "before" and "during" using the chi-squared test.

DISCUSSION

The prevalence of behavioral and psychological symptoms showed a different trend after the onset of the COVID-19 pandemic in patients with cognitive decline. Differences in behaviors related to the severity of dementia were also observed. Prevalent BPSD, such as memory impairment and apathy, showed a similar proportion before and during the pandemic, whereas sleep disturbance and aggressiveness were observed to be more prevalent during COVID-19.

Among the BPSD, the prevalence of "Waking up at night for no obvious reason" was higher during the pandemic, regardless of the degree of dementia. Prior research suggests that with increasing restrictions on behavior, such as the declaration of a state of emergency, it is possible that the frequency of going out decreases (35), social interaction is reduced (11), necessary care services are not available (6), daytime napping increases and the amount of physical activity decreases, resulting in the disturbance of circadian rhythm (36). An analysis of this study's sample characteristics shows that the percentage of individuals who were physically active tended to be lower

TABLE 1 | Relationship between basic characteristics and lifestyle before and during COVID-19 according to the severity of cognitive impairment.

	Total group		***P*-value**	**Mild group (MMSE 21–30)**		***P*-value**	**Moderate/severe group (MMSE 11–20)**		***P*-value**
	Before (*n* = 576) *n* (%)	**During (*n* = 576) *n* (%)**		**Before (*n* = 327) *n* (%)**	**During (*n* = 313) *n* (%)**		**Before (*n* = 249) *n* (%)**	**During (*n* = 261) *n* (%)**	
Socioeconomic status									
Age group									
Under 64	28 (4.9)	30 (5.2)	0.884	21 (6.4)	17 (5.4)	0.865	7 (2.8)	13 (5.0)	0.321
65–74	99 (17.2)	104 (18.1)		63 (19.3)	60 (19.2)		36 (14.5)	44 (16.8)	
75 and over	449 (78.0)	442 (76.7)		243 (74.3)	236 (75.4)		206 (82.7)	205 (78.2)	
Gender (female)	359 (62.3)	338 (58.5)	0.206	188 (57.5)	174 (55.6)	0.633	171 (68.7)	162 (61.8)	0.115
Marital status (married)	557 (96.7)	563 (98.1)	0.195	315 (96.3)	310 (99.7)	**0.003**	242 (97.2)	252 (96.2)	0.625
Education (12 y or above)	258 (44.9)	302 (52.5)	**0.011**	168 (51.4)	186 (59.4)	**0.047**	90 (36.4)	116 (44.4)	0.071
Living alone	97 (16.9)	75 (13.1)	0.082	56 (17.2)	35 (11.3)	**0.032**	41 (16.5)	40 (15.3)	0.718
Need for financial support	38 (6.6)	42 (7.4)	0.644	15 (4.6)	16 (5.2)	0.854	23 (9.3)	26 (10.1)	0.881
Use of care services									
Visiting home	19 (3.3)	10 (1.7)	0.131	9 (2.8)	5 (1.6)	0.420	10 (4.0)	5 (1.9)	0.194
Day care	119 (20.7)	106 (18.4)	0.373	48 (14.7)	41 (13.1)	0.570	71 (28.5)	64 (24.4)	0.316
Residential care	17 (3.0)	5 (0.9)	**0.016**	4 (1.2)	0 (0.0)	0.124	13 (5.2)	5 (1.9)	0.050
Needed support/Long-term care									
Certification (mild)	128 (22.3)	100 (17.6)	0.106	53 (16.4)	36 (11.6)	0.214	75 (30.1)	64 (25.0)	0.404
Certification (severe)	42 (7.3)	51 (9.0)		13 (4.0)	15 (4.8)	0.214	29 (11.6)	35 (13.7)	
Medical condition									
Clinical diagnosis									
MCI	232 (40.3)	237 (41.1)	0.771	204 (62.4)	206 (65.8)	0.335	28 (11.2)	31 (11.8)	0.443
AD	293 (50.9)	279 (48.4)		99 (30.3)	83 (26.5)		194 (77.9)	194 (74.0)	
DLB/PD	35 (6.1)	41 (7.1)		18 (5.5)	13 (4.2)		17 (6.8)	28 (10.7)	
VaD	16 (2.8)	19 (3.3)		6 (1.8)	11 (3.5)		10 (4.0)	8 (3.1)	
Polypharmacy (5 or above)	209 (36.3)	207 (35.9)	0.951	119 (36.4)	103 (32.9)	0.362	90 (36.1)	104 (39.7)	0.414
Comorbidity									
Diabetes mellitus	97 (53.0)	86 (47.0)	0.606	56 (17.7)	42 (13.4)	0.154	41 (17.1)	44 (16.9)	1.000
Hypertension	265 (49.7)	268 (50.3)	0.486	148 (46.7)	138 (44.1)	0.523	117 (48.8)	130 (49.8)	0.858
Dyslipidemia	120 (52.4)	109 (47.6)	0.209	75 (23.7)	62 (19.8)	0.248	45 (18.8)	47 (18.0)	0.908
Cardiac disease	93 (55.0)	76 (45.0)	0.134	60 (18.9)	42 (13.4)	0.066	33 (13.8)	34 (13.0)	0.896
Stroke	31 (43.7)	40 (56.3)	0.441	22 (6.9)	26 (8.3)	0.551	9 (3.8)	14 (5.4)	0.404
Lifestyle-related variables									
Light exercise/physical training	277 (48.6)	258 (45.0)	0.236	166 (51.2)	152 (48.7)	0.579	111 (45.1)	105 (40.4)	0.323
Regular exercise/sport	140 (24.5)	126 (22.0)	0.327	97 (29.8)	73 (23.4)	0.074	43 (17.6)	53 (20.3)	0.496
Regular drinking	92 (16.1)	98 (17.1)	0.692	57 (17.6)	59 (18.9)	0.682	35 (14.2)	38 (14.6)	1.000
Regular smoking	40 (7.0)	32 (5.6)	0.332	22 (6.8)	17 (5.4)	0.512	18 (7.3)	15 (5.7)	0.590
Quality of sleep (worse)	52 (9.2)	60 (10.5)	0.487	34 (10.6)	26 (8.4)	0.416	18 (7.4)	34 (13.1)	**0.040**
Napping (often)	57 (10.1)	80 (14.0)	**0.045**	29 (9.1)	34 (10.9)	0.507	28 (11.4)	45 (17.4)	0.058
Weight loss	88 (15.4)	99 (17.3)	0.380	51 (15.7)	53 (17.0)	0.669	37 (15.0)	46 (17.8)	0.404
Fatigue	94 (16.5)	90 (15.8)	0.748	58 (18.0)	40 (13.0)	0.099	36 (14.7)	50 (19.2)	0.194
				Mean ± SD	**Mean ± SD**		**Mean ± SD**	**Mean ± SD**	
Physical functioning									
IADL (Lawton Index Score)									
Male	3.6 ± 1.4	3.5 ± 1.4	0.587	4.0 ± 1.2	4.1 ± 1.1	0.595	2.8 ± 1.4	2.8 ± 2.5	0.698
Female	5.9 ± 2.1	5.9 ± 2.2	0.854	6.7 ± 1.6	6.8 ± 1.5	0.409	5.0 ± 2.3	5.0 ± 2.3	0.895
Barthel Index score	95.3 ± 10.8	94.0 ± 12.4	0.061	97.7 ± 5.9	97.0 ± 7.9	0.204	92.0 ± 14.4	90.5 ± 15.5	0.247
BMI	22.2 ± 3.5	22.1 ± 3.3	0.706	22.5 ± 3.5	22.4 ± 3.3	0.348	21.8 ± 3.6	21.8 ± 3.2	0.998
TUG	12.4 ± 4.6	12.2 ± 3.7	0.509	11.5 ± 3.6	11.4 ± 2.9	0.815	13.7 ± 5.5	13.4 ± 4.4	0.612

(Continued)

TABLE 1 | Continued

	Total group		P-value	Mild group (MMSE 21–30)		P-value	Moderate/severe group (MMSE 11–20)		P-value
	Before (n = 576) n (%)	During (n = 576) n (%)		Before (n = 327) n (%)	During (n = 313) n (%)		Before (n = 249) n (%)	During (n = 261) n (%)	
Psychological functioning									
GDS	3.1 ± 2.9	3.6 ± 3.1	**0.015**	3.1 ± 3.0	3.3 ± 2.9	0.251	3.0 ± 2.7	4.1 ± 3.1	**<0.001**

P-values in bold indicate statistical significance.
AD, Alzheimer's disease; BMI, body mass index; DLB/PD, Lewy body disease/Parkinson's disease dementia; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; TUG, Timed Up and Go; VaD, vascular dementia.

in the mild group, while the percentage of individuals who reported worsening sleep quality and increased napping was higher in the moderate/severe group. In terms of long-term care services, the proportion of individuals using day care tended to be lower during COVID-19, and the proportion of individuals using alternative care services (day care and home visits) was not relatively higher. Based on the results of previous studies (13, 37), we believe that these factors are involved in the occurrence or worsening of BPSD; however, an analysis based on social factors is desirable.

Cagnin et al. reported that sleep disorders were the most frequent new-onset BPSD during COVID-19, at 21.3%, and the frequency of sleep disorders increased as the dementia severity increased (13). Our results show a similar trend, with 12.2% in the Mild group vs. 28.9% in the moderate/severe group. They also indicate that the frequency is higher in emergencies than in normal times. Furthermore, a subanalysis of early and late periods during the pandemic showed that the prevalence of sleep disorders was 13.0% in the early period and 11.0% in the late period in the mild group, and 31.7 and 24.5% in the moderate/severe group, with neither differences being significant. Thus, the increased prevalence of sleep disorders reported after COVID-19 persists for a long time. Sleep disturbance is an important early sign of mental health problems in the elderly who have experienced major changes in their living environment or psychological trauma due to disasters (38–41). Sleep disturbances not only have a negative impact on patients with AD but also contribute to the physical and mental burden of the primary caregiver (42). Therefore, there is a need for a system to monitor sleep status at an early stage and link it to evidence-based programs to improve sleep, such as pharmacotherapy and cognitive behavioral therapy (43).

Other than sleep symptoms, only the symptom of "Physical attacks" appeared more prevalent after COVID-19 after adjusting for related factors. In the subanalysis of the Mild group, no difference was observed, suggesting that the symptoms persisted overtime during the pandemic. Relatedly, and interestingly, symptoms attributed to the relationship between caregivers and dementia patients, such as "Makes unwarranted accusation" and "Is verbally abusive, curses," showed higher prevalence later in the subanalysis, suggesting the need to pay attention to these symptoms when emergencies are prolonged. For people with dementia, the impact of changes in their living environment is highly stressful, and verbal abuse and violence can occur in the early stages of cognitive decline, leading to a significant increase in caregiver burden (44, 45). Previous studies have reported that aggression associated with dementia often arises from rejection of care, when the person does not understand the need for care, or misinterprets the caregiver's intention (46). If the caregiver insists on providing care, the person with dementia defends himself or herself from this unwanted attention and may become combative. In the context of behavioral restrictions associated with COVID-19, it is possible that aggression increases as those with dementia and family caregivers spend more time at home and are less likely to receive care services, such as in day cares. Deterioration in the psychological state of both patients and caregivers may lead to a vicious cycle, with deterioration in the health and quality of life of both. To overcome this issue, online programs for social participation and psychological support have been developed, and online video platforms for non-pharmacological therapies (e.g., life review program), which are considered effective for patients with BPSD, are being used (47), possibly reducing patient distress. Dementia patients had difficulty receiving necessary care services (especially residential services) after COVID-19 emerged, and the use of other services (such as day-care services) as alternatives had not increased, suggesting that BPSD and care burden are currently increasing.

To date, only a few studies have been conducted on people with special needs, especially dementia (48). A study of 40 cognitively impaired patients assessed BPSD in the early stages of the COVID-19 pandemic using the NPI questionnaire: ∼30% of the patients reported the worsening of BPSD, and apathy was prominent (37). Using a cross-sectional design after COVID-19, an 87 multicenter Italian study of family caregivers of dementia patients reported worsening apathy in 34.5% and new-onset apathy in 17.1% (13). Apathy is one of the most frequent BPSD symptoms from the early to late stages of AD (49), and apathy during MCI is considered a predictor of the transition to dementia (50). In the present study, there was no difference in the prevalence of apathy before and after COVID-19 in both the mild and moderate/severe groups. Although these results are seemingly contradictory, the study design differs in that the

TABLE 2 | Proportion of patients with behavioral disorders in each item of DBD: before and during COVID-19 pandemic, by severity of cognitive impairment.

	Total group			**Mild group (MMSE 21–30)**			**Moderate/severe group (MMSE 11–20)**		
	Before	**During**	***P*-value**	**Before**	**During**	***P*-value**	**Before**	**During**	***P*-value**
01. Asks the same question over and over again	490 (85.1)	484 (84.0)	0.684	256 (78.3)	245 (78.3)	1.000	234 (94.0)	239 (91.2)	0.244
02. Loses, misplaces, or hides things	433 (75.3)	416 (72.3)	0.283	221 (67.6)	199 (63.6)	0.318	212 (85.5)	216 (82.8)	0.467
03. Shows lack of interest in daily activities	285 (49.7)	288 (50.4)	0.813	136 (41.7)	125 (40.2)	0.747	149 (60.3)	161 (62.2)	0.715
04. Wakes up at night for no obvious reason	61 (10.8)	113 (19.9)	**<0.001**	22 (6.9)	38 (12.2)	**0.029**	39 (15.9)	74 (28.9)	**<0.001**
05. Makes unwarranted accusations	104 (18.1)	118 (20.5)	0.331	48 (14.7)	50 (16.0)	0.662	56 (22.6)	67 (25.7)	0.469
06. Sleeps excessively during the day	219 (38.2)	245 (42.6)	0.133	115 (35.3)	110 (35.1)	1.000	104 (41.9)	134 (51.3)	**0.041**
07. Paces up and down	44 (7.7)	70 (12.2)	**0.010**	12 (3.7)	17 (5.4)	0.343	32 (12.9)	53 (20.4)	**0.024**
08. Repeats the same action over and over again	68 (11.8)	81 (14.1)	0.255	23 (7.0)	26 (8.3)	0.556	45 (18.1)	54 (20.8)	0.502
09. Is verbally abusive, curses	91 (15.8)	104 (18.1)	0.346	43 (13.2)	49 (15.7)	0.430	48 (19.3)	54 (20.7)	0.740
10. Dresses inappropriately	101 (17.6)	102 (17.8)	0.938	40 (12.3)	29 (9.3)	0.252	61 (24.6)	72 (27.8)	0.421
11. Cries or laughs inappropriately	34 (5.9)	46 (8.0)	0.166	9 (2.8)	17 (5.4)	0.109	25 (10.0)	29 (11.2)	0.774
12. Refuses to be helped with personal care	110 (19.2)	124 (21.6)	0.341	55 (16.9)	51 (16.3)	0.915	55 (22.3)	73 (28.0)	0.153
13. Hoards things for no obvious reason	134 (23.3)	151 (26.4)	0.246	64 (19.6)	65 (20.9)	0.694	70 (28.3)	85 (32.6)	0.335
14. Moves arms or legs in a restless or agitated way	33 (5.7)	35 (6.1)	0.804	16 (4.9)	10 (3.2)	0.320	17 (6.9)	25 (9.6)	0.334
15. Empties drawers or closets	35 (6.1)	48 (8.4)	0.139	10 (3.1)	12 (3.9)	0.287	25 (10.0)	36 (13.8)	0.219
16. Wanders in the house at night	19 (3.3)	38 (6.7)	**0.014**	5 (1.5)	9 (2.3)	0.591	14 (5.7)	29 (11.2)	**0.037**
17. Gets lost outside	21 (3.7)	43 (7.5)	**0.005**	5 (1.5)	12 (3.9)	0.085	16 (6.5)	31 (11.9)	**0.046**
18. Refuses to eat	16 (2.8)	23 (4.0)	0.328	5 (1.5)	9 (3.1)	0.288	11 (4.4)	14 (5.4)	0.685
19. Overeats	92 (16.0)	82 (14.3)	0.459	46 (14.1)	34 (10.9)	0.234	46 (18.5)	48 (18.5)	1.000
20. Is incontinent of urine	73 (12.7)	77 (13.4)	0.793	21 (6.4)	26 (8.3)	0.368	52 (21.0)	50 (19.2)	0.658
21. Wanders aimlessly outside or in the house during the day	24 (4.2)	39 (6.8)	0.053	6 (1.8)	7 (2.2)	0.784	18 (7.2)	32 (12.3)	0.073
22. Physical attacks	10 (1.7)	22 (3.8)	**0.032**	3 (0.9)	11 (3.5)	**0.030**	7 (2.8)	11 (4.2)	0.475
23. Screams for no reason	11 (1.9)	17 (3.0)	0.258	4 (1.2)	9 (2.9)	0.167	7 (2.8)	8 (3.1)	1.000
24. Makes inappropriate sexual advances	6 (1.0)	2 (0.3)	0.287	3 (0.9)	0 (0.0)	0.249	3 (1.2)	2 (0.8)	0.679
25. Exposes himself/herself indecently	2 (0.3)	1 (0.2)	1.000	0 (0.0)	0 (0.0)	1.000	2 (0.8)	1 (0.4)	0.615
26. Destroys property or clothing	7 (1.2)	5 (0.9)	0.773	3 (0.9)	3 (1.0)	1.000	4 (1.6)	2 (0.8)	0.440
27. Is incontinent of feces	24 (4.2)	32 (5.6)	0.277	5 (1.5)	10 (2.2)	0.570	19 (7.6)	24 (9.2)	0.633
28. Throws food	3 (0.5)	2 (0.3)	1.000	3 (0.9)	0 (0.0)	0.249	0 (0.0)	2 (0.8)	0.499

DBD, Dementia Behavioral Disturbance Scale; MMSE, Mini-Mental State Examination.

Italian study focused on changes at a single point after COVID-19, while this study focused on prevalence before and after the pandemic. Moreover, in the Italian study, caregivers were only asked about the presence or absence of each symptom of BPSD, and no quantitative assessment using a standardized scale was conducted. In addition, although the subjects of each study were patients of the memory clinic, the Italian study included caregivers of all patients who visited the clinic, whereas the present study included patients and their families who had made their first visit to the outpatient memory clinic, which may better reflect the current problems of the patients and their families. Although we cannot directly compare these studies on apathy in patients with dementia after COVID-19, the fact that this study reported a prevalence of ∼40% in the mild group and 60% in the moderate/severe group suggests that patient condition is deteriorating and that apathy should be carefully considered in patients with dementia.

Another important BPSD is depressive symptoms. Tsugawa et al. evaluated 126 AD patients during the pandemic using the same GDS scale as in this study, and found that patients with severe AD were less aware of the spread of infection than patients with mild AD, and therefore also had lower depressive symptoms than patients with mild AD (12). However, we evaluated a larger number of patients over a longer period of time and found higher GDS scores in patients with moderate to severe AD, different from Tsugawa et al. Previous studies among the elderly

TABLE 3 | BPSD before and during COVID-19: results of multivariate analysis.

Group/BPSD related symptoms	Unadjusted		Adjusted model	
	OR	95% CI	AOR	95% CI
Mild group (MMSE 21–30)				
Wakes up at night for no obvious reason	1.89	1.09–3.28	1.82	1.02–3.23
Physical attacks	3.95	1.09–14.28	4.25	1.12–16.07
Moderate/severe group (MMSE 11–20)				
Wakes up at night for no obvious reason	2.16	1.39–3.34	1.96	1.19–3.23
Sleeps excessively during the day	1.47	1.04–2.09	1.45	0.93–1.05
Paces up and down	1.74	1.08–2.80	1.49	0.86–2.58
Wanders in the house at night	2.09	1.08–4.06	2.22	1.03–4.81
Gets lost outside	1.96	1.05–3.69	1.80	0.88–3.66

In Adjusted model, the outcome was a BPSD-related variable; MMSE, long-term care, GDS, Need for financial support, polypharmacy, living status, IADL, and Education were included as covariates in a binomial logistic regression analysis.

AOR, adjusted odds ratio; BPSD, behavioral and psychological symptoms of dementia; CI, confidence interval; FRI, Fall Risk Index; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

in Japan have shown a negative association between MMSE and GDS scores, with a tendency toward depression as cognitive function declined (51), which is consistent with the results of this study. Although the previous study by Tsugawa et al. provides an important dataset from the early stages of COVID-19 (May–June 2020), we believe that the small sample size, differences based on dementia subtype, and gender distribution could explain the different findings compared to our study. Our data indicates that depressive symptoms and other psychological stresses should be addressed even in patients with moderate to severe AD.

STRENGTHS AND LIMITATIONS

We examined the behavioral and psychological symptoms of patients with cognitive decline before and during the COVID-19 pandemic, using propensity score matching and adjusted models for possible confounders. As the results did not support cognitive decline similar to that reported in a previous study (11), and since we were unable to analyze the same subjects before and after the pandemic, we cannot refer to clear changes between the study periods; however, the results showed different BPSD symptoms expressed in the target group with the same degree of cognitive function. There are some limitations to this study. One is that the design of the study is not longitudinal, since we did not follow the same subjects from before COVID-19, it is not possible to track individual changes. In addition, because the study was conducted at a single institution and most of the subjects were accompanied by their family members, we cannot completely exclude information bias. Third, although a previous study pointed out that BPSD varied depending on the type of dementia (13), the present study has the limitation of including all dementia types within one single dementia group. In the future, it will be necessary to analyze each type of dementia with a larger number of cases, conduct follow-up longitudinal studies, as well as comparative studies in multiple facilities with different environments, such as urban and rural areas.

This study showed that the profile of behavioral and psychological symptoms in patients with cognitive decline differed in the individuals that were evaluated during the pandemic than in those evaluated before the pandemic, and some symptoms were associated with the severity of dementia. BPSD prevalence, such as memory impairment and apathy, showed similar profiles before and during the pandemic, whereas sleep disturbance and aggressiveness were more prevalent during the pandemic. The latter symptoms should be screened for during periods of disturbance and require evidence-based interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the NCGG. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YKu and TSa designed the study and planned recruitment. YKu performed statistical analyses and wrote first draft. TSu, NM, KU, YKi, CS, and TSa contributed to the interpretation and discussion of results and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.839683/full#supplementary-material

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Minimal Impact of COVID-19 Pandemic on the Mental Health and Wellbeing of People Living With Dementia: Analysis of Matched Longitudinal Data From the IDEAL Study

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Objective: Research suggests a decline in the mental health and wellbeing of people with dementia (PwD) during the COVID-19 pandemic; however few studies have compared data collected pre-pandemic and during the pandemic. Moreover, none have compared this change with what would be expected due to dementia progression. We explored whether PwD experienced changes in mental health and wellbeing by comparing pre-pandemic and pandemic data, and drew comparisons with another group of PwD questioned on two occasions prior to the pandemic.

Methods: Community-dwelling PwD enrolled in the IDEAL programme were split into two groups matched for age group, sex, dementia diagnosis, and time since diagnosis. Although each group was assessed twice, one was assessed prior to and during the pandemic (pandemic group; $n = 115$) whereas the other was assessed prior to the pandemic (pre-pandemic group; $n = 230$). PwD completed measures of mood, sense of self, wellbeing, optimism, quality of life, and life satisfaction.

Results: Compared to the pre-pandemic group, the pandemic group were less likely to report mood problems, or be pessimistic, but more likely to become dissatisfied with their lives. There were no changes in continuity in sense of self, wellbeing, and quality of life.

Discussion: Results suggest the pandemic had little effect on the mental health and wellbeing of PwD, with any changes observed likely to be consistent with expected rates of decline due to dementia. Although personal accounts attest to the challenges experienced, PwD appear to have been resilient to the impact of lockdown and social restrictions during the pandemic.

Keywords: quality of life, wellbeing, sense of self, optimism, life orientation

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INTRODUCTION

The COVID-19 pandemic (hereafter referred to as "the pandemic") and consequent periods of lockdown and social restrictions forced individuals to change their routines, social interactions, and usual ways of accessing health and social care services (1–3). For instance, non-urgent clinical activities were postponed, conducted via phone, or interrupted. People considered clinically vulnerable were strongly advised to stay at home even in those periods when social restrictions were less severe. Clinically vulnerable people included some people with dementia (PwD) who also had other health conditions. Social support services for community dwelling PwD and their carers were also interrupted. PwD living in the community may have been particularly affected by these changes related to the pandemic.

However, existing evidence based on carer reports and self-reports from PwD provided mixed results (4, 5). On one hand some studies (6–10) found that the pandemic accelerated decline in the cognitive, physical, functional, and mental health of PwD, as well as increased neuropsychiatric symptoms, behavioral problems, and loneliness among PwD (3, 5–17). On the other hand, some studies found that the pandemic had minimal negative impact or no impact on these outcomes (7, 8, 12, 18). These inconsistent findings may be due to the methodological limitations of cross-sectional analyses based on self- and informant reports (6).

Although some studies examined changes in the mental health and wellbeing of PwD by using data collected both prior to and during the pandemic (3, 7, 11, 18, 19), they lacked a matched comparison group providing data on changes in mental health and wellbeing over time prior to the pandemic. Because of this they could not determine whether a decline in the mental health and wellbeing of PwD was due to the pandemic or to the normal progression of dementia. Studies such as that conducted by Tondo et al. (20) found that during the pandemic PwD experienced a greater cognitive decline compared to what was expected for people in their same stage of the illness. However, to the best of our knowledge, no study has undertaken a similar approach to that of Tondo et al. (20) to explore the effects of the pandemic on the mental health and wellbeing of PwD.

Using longitudinal data from the IDEAL (Improving the experience of Dementia and Enhancing Active Life) cohort, we found that during the pandemic PwD were more likely to report discontinuity in sense of self, poorer quality of life, and lower life satisfaction, but also better mood, greater optimism, and similar levels of physical health, when compared to mean scores for the cohort prior to the pandemic, but we could not establish whether the observed changes were attributable to conditions during the pandemic (19).

Building on our earlier findings and on longitudinal data from the IDEAL programme, the current study investigated the mental health and wellbeing of PwD by comparing longitudinal change seen in a group of participants assessed both prior to and during the pandemic with that seen in a matched comparison group of PwD assessed on two occasions prior to the pandemic. To capture mental health and wellbeing, measures assessing mood, continuity/discontinuity in sense of self, wellbeing, optimism, quality of life, and life satisfaction were employed. We hypothesized that, compared to the experience of their matched counterparts prior to the pandemic, PwD during the pandemic were more likely to be anxious or depressed, perceive discontinuity in sense of self, report lower psychological wellbeing, be less optimistic, have poorer quality of life, and be dissatisfied with their life. We also expected that the changes in mental health and wellbeing experienced by PwD during the pandemic would be greater than the changes over time experienced by a matched group of PwD whose data were collected during two assessment waves prior to the pandemic.

MATERIALS AND METHODS

Design

We report a comparison of data from two matched groups of PwD, each assessed on two occasions. One group was assessed prior to and during the pandemic, and the other group was assessed on two occasions prior to the pandemic.

This study is embedded in the ongoing IDEAL programme. The IDEAL programme centers on a longitudinal cohort study following a large group of PwD and their carers for up to 6 years (21, 22). PwD were recruited for baseline interviews (T1) through 29 National Health Service (NHS) sites in England, Scotland, and Wales between 2014 and 2016. Participants lived in the community, and had a clinical diagnosis of dementia and a Mini-Mental State Examination (MMSE) (23) score ≥15 at baseline. For those who agreed to participate, trained researchers conducted structured interviews during home visits. Follow-up interviews occurred 12 (T2) and 24 (T3) months later. A follow-up study (IDEAL-2) began in 2018 and aimed to comprise three further waves of data collection (T4–T6); the T4 interviews were scheduled 2 years after T3. T4 was due to end in July 2020 and T5 was due to end 12 months later but data collection for both waves was interrupted by the COVID-19 pandemic. The INCLUDE (Identifying and mitigating the individual and dyadic impact of COVID-19 and life under physical distancing on people with dementia and carers) study was introduced at this point to understand the impact of COVID-19 on the IDEAL cohort. Those who had participated in IDEAL and IDEAL-2 were invited to take part in INCLUDE. Interviews for INCLUDE were conducted remotely by trained researchers between September 2020 and April 2021, see (24) for details.

Participants

Two matched groups of participants were identified from the INCLUDE and IDEAL datasets:

- The "pandemic group" ($n = 115$) comprised PwD who were assessed for both IDEAL T3 and INCLUDE.
- The "pre-pandemic group" ($n = 230$) comprised PwD who were assessed for IDEAL T1 and T3 but did not take part in INCLUDE.

Participants in the pre-pandemic group were matched 2:1 to participants in the pandemic group. Matching was based on age group, sex, dementia diagnosis, and time since dementia diagnosis. The pool of participants from which the matched pre-pandemic group was chosen consisted of those who took part in IDEAL T1 and T3 but not INCLUDE (as described above, $n = 736$). Two participants from this pool were matched to each participant from the pandemic group. However, using these criteria it was not possible to identify two exact matches for every participant in the pandemic group. Therefore, for the first match, 70 out of 115 of the pandemic group were matched exactly on age group (<65, 65–69, 70–74, 75–79, 80+ years), sex, dementia subtype (Alzheimer's disease, vascular dementia, mixed Alzheimer's and vascular dementia, frontotemporal dementia, Parkinson's disease dementia, dementia with Lewy bodies, unspecified/other) and time since diagnosis (<1, 1–2, 3–5 6+ years). Another 14 out of 115 of the pandemic group were matched exactly on age group, sex, binary dementia subtype (Alzheimer's disease, vascular dementia, mixed, vs. other), and time since diagnosis. Seven out of 115 had exact first matches on age group, sex, binary dementia subtype, and binary time since diagnosis (≤2, ≥3 years). The remaining 24 from the pandemic group had exact first matches on age group, sex, and binary dementia diagnosis. For second matches 113 out of 115 matched on age group, sex, and binary dementia diagnosis, and two out of 115 matched only on age group, and sex.

There were two "waves" of data available for each group:

- Wave 1 (W1) refers to IDEAL T1 for the pre-pandemic group and IDEAL T3 for the pandemic group.
- Wave 2 (W2) refers to IDEAL T3 for the pre-pandemic group and INCLUDE data collection for the pandemic group.

These time-points were selected as the time between assessments was the nearest match we could achieve for the two groups.

Measures

Single items from standardized measures were used to assess self-reported mood (depressed or anxious; not depressed or anxious) (25), continuity in sense of self (discontinuity; continuity) (24), wellbeing (high; moderate; low) (26), optimism (optimistic; pessimistic or neutral) (27), quality of life (poor or fair; good; excellent) (28), and life satisfaction (satisfied; dissatisfied) (29); see **Supplementary Table 1**.

Covariates included marital status (spouse/partner; single; widowed), education (no qualifications; school leaving certificate at age 16; school leaving certificate at age 18; university), social class (high; intermediate; low), living alone (yes; no), cognition [MMSE score (23) 0–21, 22–25, 26–30], diagnosed depression (depressed; not depressed) and months between waves. Number of health conditions other than dementia was a count of heart problems (heart attack or congestive heart failure), hypertension, peripheral vascular disease, stroke or hemiplegia, transient ischaemic attack, chronic bad chest, inflammation of the joints, peptic/stomach ulcer disease, skin ulcer, diabetes, moderate or severe kidney disease, cancer, and liver disease. The count was categorized into either 0–1 or 2+ co-morbidities.

Statistical Methods

Binary outcomes (anxiety or depression, continuity in sense of self, optimism, life satisfaction) were analyzed using mixed effect logistic regression models with waves grouped within participant as a random intercept to account for correlation over waves within a participant. For outcomes with more than two categories (wellbeing, quality of life) mixed effect multinomial logistic regression models were used, again with the random intercept grouping waves within participants. Due to low participant numbers the random intercept was constrained to be equal for all outcome categories instead of having separate random intercepts for each category of the outcome. To understand the difference in trends over time (waves) in the outcome between the pre-pandemic group and the pandemic group, an interaction between the pandemic group indicator variable and wave variable was included in the model. All models were adjusted for the matching variables (age group, sex, dementia subtype, time since dementia diagnosis) and for other covariates that were important to the model. A sensitivity analysis was conducted for the mood model where diagnosed depression was included as a covariate to control for long-term depression.

RESULTS

In the whole sample ($n = 345$) the average age was 72.6 years and 48.7% were women. As participants were matched for age group rather than age, mean age was 72.7 years in the pre-pandemic group and 72.4 years in the pandemic group. In the whole sample the majority of participants had a partner, had education to age 18 or university level, were in the higher social class group, and had Alzheimer's disease (**Table 1**). Average time between waves was 24.9 months for the pre-pandemic group and 39.1 months for the pandemic group. Including time between waves as a covariate or interaction with pandemic group in the model did not lead to significantly different results, so this was excluded.

Number and proportions of participants in each category of mental health and wellbeing indicators are reported in **Table 2**. Results from the mixed effect models are shown in **Table 3**.

In the pre-pandemic group 34.5% at W1 and 32.6% at W2 were depressed or anxious. At W1 38.3% of the pandemic group were depressed or anxious, decreasing to 25.4% at W2; the trend for this decrease in feeling depressed or anxious in the pandemic group differed to the trend between W1 and W2 in the pre-pandemic group; interaction odds ratio (OR): 0.4, 95% confidence interval (CI): 0.1–1.0 (**Table 3**; **Supplementary Figure 1**). The results were robust when adjusted for diagnosed depression in the sensitivity analysis (**Supplementary Table 2**).

In the pre-pandemic group (W1: 30.5%, W2: 32.3%) and pandemic group (W1: 33.0%, W2: 34.5%) there was no evidence of change in the proportion of participants reporting discontinuity in sense of self and no evidence of any difference in trends between groups (interaction OR: 1.1, 95% CI: 0.4–2.6) (**Table 3**; **Supplementary Figure 2**).

At W1 67.3% of the pre-pandemic group had a high level of wellbeing; by W2 this had dropped to 61.7%. In the pandemic group the proportion of participants reporting high levels of wellbeing was similar at W1 (63.2%) and W2 (61.1%). There was some evidence to suggest an increase in the proportion reporting

TABLE 1 | Demographic profiles of the pre-pandemic and pandemic groups.

		Pre-pandemic		Pandemic	
		N	**%**	***N***	**%**
Age group	<65	38	16.5	19	16.5
	65–69	44	19.1	22	19.1
	70–74	56	24.4	28	24.4
	75–79	40	17.4	20	17.4
	≥80	52	22.6	26	22.6
		Mean:	72.7	Mean:	72.4
Sex	Men	118	51.3	59	51.3
	Women	112	48.7	56	48.7
Marital status	Spouse/partner	184	80.0	84	73.0
	Single	17	7.4	22	19.1
	Widowed	29	12.6	9	7.8
Education	No qualifications	64	27.8	23	20.4
	Qualification at 16	39	17.0	17	15.0
	Qualification at 18	78	33.9	49	43.4
	University	49	21.3	24	21.2
Social class	High	90	41.7	52	47.7
	Intermediate	96	44.4	36	33.0
	Low	30	13.9	21	19.3
Living situation	Living with others	191	83.4	91	79.1
	Living alone	38	16.6	24	20.9
Health condition count in addition to dementia	0–1	144	63.7	64	56.6
	2+	82	36.3	49	43.4
Diagnosed depression	Not depressed	189	83.6	93	82.3
	Depressed	37	16.4	20	17.7
Dementia subtype	Alzheimer's disease	142	61.7	61	53.0
	Vascular dementia	16	7.0	15	13.0
	Mixed (Alzheimer's and vascular)	38	16.5	21	18.3
	Frontotemporal dementia	13	5.7	8	7.0
	Parkinson's disease dementia	6	2.6	4	3.5
	Lewy body dementia	7	3.0	0	0.0
	Unspecified/Other	8	3.5	6	5.2
Length of time since Diagnosis	<1 year	93	42.5	0	0.0
	1–2 years	83	37.9	51	47.2
	3–5 years	37	16.9	43	39.8
	≥6 years	6	2.7	14	13.0
Average time (months) between W1 and W2		Mean	Range	Mean	Range
		24.9	18–38	39.1	27–51

moderate wellbeing by W2 in the pre-pandemic group (OR: 1.5, 95% CI: 0.8–2.6) with no difference in trend for the pandemic group (interaction OR: 0.8, 95% CI: 0.3–2.1, **Table 3**).

Most (73.9%) of the pre-pandemic group were optimistic at W1, reducing to 68.0% at W2. At W1 67.8% of the pandemic group were optimistic, increasing to 74.3% at W2 (**Supplementary Figure 3**). The models provided some evidence to suggest a difference in trends between the two groups (interaction OR: 0.5, 95% CI: 0.2–1.2) (**Table 3**; **Supplementary Figure 3**).

The proportion of those reporting good quality of life decreased for the pre-pandemic group (W1: 56.1%, W2: 52.9%) and pandemic group (W1: 60.0%, W2: 47.8%). Whereas, in the pre-pandemic group there was some evidence to suggest an increase in the proportion feeling their quality of life was poor or fair (OR: 1.6, 95% CI: 0.9–2.9), in the pandemic group there was some evidence to suggest an increase in the proportion feeling quality of life was excellent (interaction OR: 1.8, 95% CI: 0.7–4.6), as well as in the proportion feeling quality of life was poor or fair (**Table 3**).

The proportion reporting they were satisfied with life in the pre-pandemic group was similar at W1 (83.9%) and W2 (85.0%). At W1, 91.3% of the pandemic group were satisfied with life, decreasing to 85.8% at W2. There was

TABLE 2 | Outcomes at wave 1 and wave 2 in the pre-pandemic and pandemic groups.

		Pre-pandemic				Pandemic			
		Wave 1		Wave 2		Wave 1		Wave 2	
		N	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Mood	Depressed or anxious	79	34.5	73	32.6	44	38.3	29	25.4
	Not depressed or anxious	150	65.5	151	67.4	71	61.7	85	74.6
Sense of self	Discontinuity	69	30.5	71	32.3	38	33.0	39	34.5
	Continuity	157	69.5	149	67.7	77	67.0	74	65.5
Wellbeing	Low	25	10.9	26	12.2	13	11.4	13	12.0
	Moderate	50	21.8	56	26.2	29	25.4	29	26.9
	High	154	67.3	132	61.7	72	63.2	66	61.1
Optimism	Pessimistic or neutral	59	26.1	70	32.0	37	32.2	29	25.7
	Optimistic	167	73.9	149	68.0	78	67.8	84	74.3
Quality of life	Poor or fair	37	16.2	51	23.1	25	21.7	31	27.4
	Good	128	56.1	117	52.9	69	60.0	54	47.8
	Excellent	63	27.6	53	24.0	21	18.3	28	24.8
Life satisfaction	Dissatisfied with life	36	16.1	33	15.0	10	8.7	16	14.2
	Satisfied with life	188	83.9	187	85.0	105	91.3	97	85.8

TABLE 3 | Odds ratios from mixed effect logistic regression models and multinomial logistic regression models with 95% confidence intervals.

		Pandemic vs. pre-pandemic at wave 1		Wave 2 vs. wave 1 for pre-pandemic group		Interaction between pandemic group and wave	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Mood[a]	Depressed or anxious	Ref.		Ref.		Ref.	
	Not depressed or anxious	1.1	0.5–2.8	0.8	0.5–1.4	0.4	0.1–1.0
Sense of self[b]	Discontinuity	1.1	0.5–2.4	1.1	0.7–1.9	1.1	0.4–2.6
	Continuity	Ref.		Ref.		Ref.	
Wellbeing[c]	Low	1.1	0.4–3.1	1.2	0.6–2.4	1.0	0.3–3.4
	Moderate	1.0	0.4–2.4	1.5	0.8–2.6	0.8	0.3–2.1
	High	Ref.		Ref.		Ref.	
Optimism[d]	Pessimistic or neutral	1.4	0.7–2.8	1.5	0.9–2.4	0.5	0.2–1.2
	Optimistic	Ref.		Ref.		Ref.	
Quality of life[e]	Poor or fair	1.4	0.7–3.1	1.6	0.9–2.9	0.9	0.3–2.3
	Good	Ref.		Ref.		Ref.	
	Excellent	0.7	0.3–1.4	0.9	0.6–1.6	1.8	0.7–4.6

Results for main effects and interaction between pandemic group indicator variable and wave variable. Main effect of wave gives the odds ratio (OR) comparing the pandemic groups to the pre-pandemic group at wave 1. Main effect for Wave compares wave 2 to wave 1 for the pre-pandemic group. The interaction compares the trend over waves in the pandemic group to the trend over waves in the pre-pandemic group. 95% confidence interval (95% CI); Ref. indicates reference category for the outcome. All models adjusted for age group, sex, binary time since diagnosis, and binary dementia diagnosis.

[a] *Additionally adjusted for education, health condition count, and MMSE group.*

[b] *Additionally adjusted for education, marital status, health condition count, depression diagnosis, and MMSE group.*

[c] *Additionally adjusted for social class, and marital status.*

[d] *Additionally adjusted for education, marital status, health condition count, and depression diagnosis.*

[e] *Additionally adjusted for education, social class, marital status, health condition count, depression diagnosis, and MMSE group.*

some evidence to show the trend over waves differed between the pre-pandemic and pandemic group (interaction OR: 3.3, 95% CI: 0.9–13.0, **Supplementary Table 3**). However, these results should be interpreted with caution as, due to low numbers of those dissatisfied with life, the estimate for the interaction was inflated when adjusting for matching variables. Adjustment for further covariates did not improve the estimates (**Supplementary Table 3**).

DISCUSSION

This study investigated whether the experience of living through the pandemic and associated social restrictions affected the mental health and wellbeing of PwD living in the community in Britain. Contrary to our hypotheses, COVID-19 restrictions appeared to have little negative impact on whether PwD experienced continuity in sense of self and on how PwD appraised their wellbeing and quality of life, and in the case of mood and optimism, COVID-19 restrictions appeared to have a positive impact. Although the hypothesis that, compared to pre-COVID-19, PwD during COVID-19 were more likely to be dissatisfied with their lives was partially supported, estimations were inflated. Overall, findings for six outcomes capturing different facets of mental health and wellbeing consistently suggest that, when considering PwD enrolled in the IDEAL cohort as a group, the pandemic was associated with minimal negative change in mental health and wellbeing and with an improvement in mood and optimism.

The small decline in the proportion of PwD who reported mood problems in both the pre-pandemic and pandemic groups is consistent with previous evidence (19, 30). This effect was larger in the pandemic group, suggesting that some circumstances related to COVID-19 led to a reduction in the proportion of PwD having mood problems. It may be that during lockdown carers provided greater social support to PwD, or, as qualitative studies have found, PwD perceived the home environment as a safe place where they could enjoy quiet time, learn new skills, or return to past hobbies without fearing failure or comparison with peers (31). The engagement of PwD in activities such as reading and playing computer games during the lockdown is documented in other studies (7, 19). Due to stigma, embarrassment or awareness of being less able to engage in activities in normal times PwD may experience social anxiety and, as a consequence, withdraw from social activities (32–36), so in this sense restrictions may have had positive aspects. Nonetheless, further understanding of the mechanisms through which pandemic experiences decreased the likelihood of mood problems in PwD could help to identify ways of promoting better mood in PwD post-pandemic.

This was the first study exploring whether the pandemic had an influence on continuity in sense of self in PwD. We found that COVID-19 restrictions had no impact on continuity in sense of self in PwD. Again, it may be that during the lockdown PwD engaged in a range of activities and hobbies that contributed to the experience of continuity in sense of self.

Between September 2020 and April 2021, the pandemic did not influence the wellbeing and quality of life of PwD and only marginally influenced their optimism. Indeed, although PwD in the pandemic group were more likely to be optimistic about the future compared to those in the pre-pandemic group, differences between groups were minimal. Moreover, PwD who were more optimistic about the future prior to the pandemic maintained this optimistic outlook during the pandemic. This pattern of results suggests that the pandemic may not have influenced pre-existing levels of optimism (O'Rourke, 2015). This may be due to optimism being a relatively stable trait among older people (37).

There was some evidence to support the hypothesis in relation to life satisfaction, as during the pandemic PwD were more likely to feel dissatisfied with their lives. However, the number of PwD expressing dissatisfaction with their lives was low both before and during the pandemic, and this significant effect is due to only six people becoming dissatisfied with their lives during COVID-19. Comparison of baseline levels of life satisfaction between the pandemic group and the pre-pandemic group also shows that the proportion of PwD feeling dissatisfied with their lives was lower in the pandemic group and, despite a significant increase in the number of PwD becoming dissatisfied with their life during COVID-19, this number remained lower than the pre-pandemic group.

Compared to previous evidence (5) this study provides a more positive picture of the mental health and wellbeing of PwD during COVID-19. The disparity with previous studies on this topic may be due to several major methodological differences. First, although previous longitudinal studies identified a decline in the mental health and wellbeing of PwD during the pandemic compared with pre-pandemic information (11, 38–42), they could not discern whether the observed change was due to the typical course of dementia or to the impact of pandemic-related social restrictions. In contrast, by using longitudinal data to compare the change experienced by PwD during the pandemic with that experienced by a matched sample of PwD whose data were collected prior to COVID-19, our results suggest that most of the negative changes experienced by PwD during the pandemic are parallel to those that would be expected in a group of PwD with similar demographic characteristics under normal conditions. For instance, although the current analyses confirmed some of the previous results from the IDEAL cohort (e.g., a decrease in mood problems) that were based on comparison of pre-pandemic and pandemic data without a matched comparison group (19) it did not confirm others (e.g., poorer quality of life). The methodological advancements of this study suggest that the previously-described increase in the proportion of PwD reporting discontinuity in sense of self, poorer quality of life, and dissatisfaction with their life may have been due to the progress of dementia rather than to the pandemic.

Second, another possible reason for the disparity between our findings and those of previous studies is that previous studies relied on informant ratings provided by carers (7, 10, 12, 17, 43–45) whereas this study considered the self-ratings of PwD. As carer ratings differ from self-ratings (46) and the subjective perceptions of people with mild-to-moderate dementia are widely accepted as valid (47), our study may have produced more reliable results than existing research. Third, whereas many previous studies collected data at the beginning of the pandemic and therefore during the period of strict lockdown (5), data collection for this study started in September 2020 and therefore encompassed both periods of lockdown and periods of significant easing of restrictions. The more positive results found in this study may be due to participants having had the time to overcome the initial shock caused by the pandemic, adapt to a new lifestyle, and cope with changes related to the pandemic and/or to people looking forward to enjoy reduced restrictions (48).

Fourth, as those IDEAL participants who could not use telephones and/or had deteriorated markedly since their previous assessment were underrepresented in INCLUDE, study analyses are based on a self-selected group of PwD who may have been well-positioned to adapt to the lockdown and social restrictions. Hence, our positive results may not generalize to all PwD. Fifth, many individual effects of the pandemic on the mental health and wellbeing of PwD may have remained hidden in our analyses that considered PwD as a group. Indeed, qualitative studies suggest a heterogenous picture in relation to the mental health and wellbeing of PwD during the pandemic (48). For instance, the majority of our sample lived with someone else. However, those PwD who live alone found it harder to cope with some of the changes related to the pandemic, such as increased loneliness, and were therefore more likely to experience poorer mental health and wellbeing (48).

Overall, study results suggest that COVID-19 did not have a negative impact on the mental health and wellbeing of our sample of PwD. Instead, it may have had a small beneficial effect particularly in relation to mood. Qualitative interviews conducted during the pandemic with 11 PwD participating in the IDEAL study and their carers suggest that in some cases the resilience shown by PwD may reflect positive social circumstances and use of previously-learned coping strategies (48). Despite our positive pattern of results, we should be mindful that some negative feelings and experiences, such as the perception of being abandoned by services, have been reported by PwD (19, 48). These should be addressed as they may lead to poorer mental health and wellbeing in the long term.

This study has some limitations. Exact matches on all variables could not be found for everyone in the pandemic group. However, all matching variables were included as covariates in the models, and in an effort to mitigate this limitation, the pre-pandemic group included two matches for each PwD in the pandemic group. Mental health and wellbeing were assessed with single-item measures that, although reducing the burden for participants (19), may not have adequately captured the constructs. There was also a longer timeframe between assessments for the pandemic group. However, the models controlling for the difference between timepoints led to the same results as those models not controlling for this difference between timepoints, suggesting that the difference between timepoints did not influence study findings. Moreover, there was generally little effect from COVID-19 on the mental health and wellbeing of PwD so it was unlikely that the longer gap between assessments for the pandemic group affected the results, especially as the expectation was for a greater effect from COVID-19 on this group.

Despite these limitations, our unique study design made it possible to investigate whether observed changes in mental health and wellbeing were due to the pandemic and concomitant social restrictions rather than reflecting the typical course for PwD. In this sample of PwD the COVID-19 pandemic appears to have had little to no negative effect on mental health and wellbeing, and little impact on continuity and discontinuity in sense of self, wellbeing, quality of life, and life satisfaction. If anything, there was a small positive impact on mood and optimism. Future research is needed to understand the mechanisms behind this unexpected positive effect as it may help to identify ways to address mood disturbance in PwD. The remarkable resilience shown by PwD in this study adds to current understanding of what is possible in adjusting to the diagnosis and living with the condition and offers hope that it is possible to "live well" with dementia. Although this study found that the radical changes imposed by the pandemic did not have a negative effect on the mental health and wellbeing of PwD as a group, some PwD may have been less resilient than others. Indeed, previous studies documented how some PwD had negative experiences of the pandemic (19, 48). Future research could therefore focus on identifying the characteristics of those PwD who found it harder to adapt to the pandemic and would therefore benefit the most from post-pandemic support. Finally, as the social support provided by carers may be one of the reasons why PwD showed resilience in being able to maintain their mental health and wellbeing against the radical changes imposed by the pandemic, future work with the IDEAL dataset will explore whether carers' mental health and wellbeing have instead been affected during the pandemic.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because IDEAL data were deposited with the UK data archive in April 2020 and will be available to access from April 2023. Details of how the data can be accessed after that date can be found at: http://reshare.ukdataservice.ac.uk/854293/. INCLUDE data will be archived in connection with the IDEAL dataset in March 2022. Requests to access the datasets should be directed to http://reshare.ukdataservice.ac.uk/854293/ or Linda Clare L.Clare@exeter.ac.uk.

ETHICS STATEMENT

INCLUDE was approved by Wales Research Ethics Committee 5 as an amendment to IDEAL-2 for England and Wales (18/WS/0111 AM12). IDEAL was approved by Wales Research Ethics Committee 5 (reference 13/WA/0405) and IDEAL-2 by Wales Research Ethics Committee 5 (reference 18/WS/0111) and Scotland A Research Ethics Committee (reference 18/SS/0037). IDEAL and IDEAL-2 are registered with the UK Clinical Research Network (UKCRN), numbers 16593 and 37955, respectively. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC, AM, CP, RC, LA, AB, RL, CQ, FM, SS, and HB conception and design. HB conducted study analysis and drafted the methods and results sections. SS interpreted the data and drafted the introduction and discussion sections. All authors critical appraisal and review of the manuscript and final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.849808/full#supplementary-material

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The Impact of Social Isolation Due to COVID-19 on Symptom Progression in People With Dementia: Findings of the SOLITUDE Study

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Background: People with dementia (PWD) are vulnerable to abrupt changes to daily routines. The lockdown enforced on the 23rd of March 2020 in the UK to contain the expansion of the COVID-19 pandemic limited opportunities for PWD to access healthcare services and socialise. The SOLITUDE study explored the potential long-term effects of lockdown on PWD's symptoms and carers' burden.

Methods: Forty-five carers and 36 PWD completed a telephone-based assessment at recruitment (T0) and after 3 (T1) and 6 months (T2). PWD completed measures validated for telephonic evaluations of cognition and depression. Carers completed questionnaires on their burden and on PWD's health and answered a customised interview on symptom changes observed in the initial months of lockdown. Longitudinal changes were investigated for all outcome variables with repeated-measures models. Additional *post hoc* multiple regression analyses were carried out to investigate whether several objective factors (i.e., demographics and time under social restrictions) and carer-reported symptom changes observed following lockdown before T0 were associated with all outcomes at T0.

Results: No significant changes were observed in any outcomes over the 6 months of observations. However, *post hoc* analyses showed that the length of social isolation before T0 was negatively correlated with episodic and semantic memory performance at T0. Carers reporting worsening of neuropsychiatric symptoms and faster disease progression in PWD also reported higher burden. Moreover, carer-reported worsening of cognitive symptoms was associated with poorer semantic memory at T0.

Conclusion: PWD's symptoms and carers' burden remained stable over 6 months of observation. However, the amount of time spent under social restrictions before

T0 appears to have had a significant detrimental impact on cognitive performance of patients. In fact, carer-reported cognitive decline during social isolation was consistent with the finding of poorer semantic memory, a domain sensitive to progression in Alzheimer's disease. Therefore, the initial stricter period of social isolation had greater detrimental impact on patients and their carers, followed then by a plateau. Future interventions may be designed to maintain an optimal level of social and cognitive engagement for PWD in challenging times, to prevent abrupt worsening of symptoms and associated detrimental consequences on patients' carers.

Keywords: dementia, COVID-19, social isolation, neuropsychiatric symptoms, cognitive decline

INTRODUCTION

Quality of health and life expectancy are deeply influenced by the characteristics of our social environment. It has long been established that a series of quantitative and qualitative features of one's social connections, and the social support that may derive from these, can variably but significantly affect several health domains, including cognitive health (1). Such detrimental effects appear to be particularly evident in the ageing population. Evans et al. (2) found that socially isolated older people with depression and/or anxiety show worse cognitive performance than those who are more socially connected. Both loneliness and social isolation have also been found to be associated with greater cognitive decline in older adults above 50 years of age, independently of depressive symptoms (3). Along these lines, several epidemiological studies and meta-analyses have consistently observed that smaller social networks (4), lack of close relationships (5), poor social engagement (6), loneliness and social isolation (7–9) are all associated with a higher risk of dementia. These findings suggest that an impoverished social environment can either foster or worsen cognitive decline in older adults both via a direct, e.g., lack of mental stimulation, and an indirect pathway, e.g., as a consequence of the impact on mental health.

In early 2020, strict limitations to social contacts were imposed in the United Kingdom to contain the Coronavirus Disease 2019 (COVID-19) pandemic. Although these campaigns have seen periods of strict restrictions (including lockdowns) alternating to phases of more relaxed regulations, people have been unable to carry out a normal and light-hearted social life for a prolonged period of time. This has brought unprecedented changes to daily-life conditions of people less accustomed to communication technology (e.g., older adults), and has resulted in a severe long-term reduction of light-hearted social life. Leaving aside all criticisms that have been raised by stakeholders on the adoption of social isolation measures (the discussion of which is not relevant to the aim of this paper), repeated and prolonged periods of lockdown have offered a unique opportunity for "natural experiments" that have enabled researchers to investigate, in an ecological setting, the impact of abruptly imposed social isolation on older people's health. As expected, the detrimental effects of social restrictions on mental health and cognitive decline in older adults with or without cognitive impairments were observed early on during the COVID-19 pandemic (10). This impact may have been particularly severe in older people with selective risk factors, e.g., hearing loss (11), that may exacerbate isolation and, in turn, increase subjective perceptions of loneliness, and of decline in cognitive and mental health. Indeed, several observational studies carried out across the world have consistently detected worsening of existing and emergence of new neuropsychiatric symptoms in patients with dementia, after the introduction of a range of diverse measures of social isolation (12–16). As a possible consequence of the behavioural alterations experienced by people with dementia (PWD), negative effects were also reported on the burden and mental health of their carers (13, 17, 18).

In a similar fashion, the sudden and unforeseeable adoption of significant forms of restriction to social contacts may have fostered a worrying acceleration in the annual rates of cognitive decline in people with cognitive impairments compared with those observed in the years prior to the beginning of the COVID-19 pandemic (19, 20). Memory was found to be a particularly vulnerable cognitive domain (19). These results suggest that social restrictions may have created the ideal conditions for an acceleration of decline in PWD. This has been observed in a recent survey of 339 Greek carers of PWD: cognitive decline was reported in patients, especially in those with moderate-to-severe dementia, together with an increase in carers' burden (21). Gan et al. (22) found signs of significant objective decline in several screening measures of global cognitive status, behavioural symptoms and daily-living activities in a sample of 205 older people with and without cognitive impairment assessed before and after enforcement of lockdown in China. A study that investigated the pre- vs. post-lockdown cognitive changes in patients with mild cognitive impairment and dementia due to Alzheimer's disease found significant decline especially in verbal long-term memory and phonemic fluency (23).

These early findings support the claims that social isolation may be, indeed, detrimental to cognitive health in older adults, in general, and even more so in PWD. However, the impact that lockdown and quarantine measures may have had on specific cognitive domains and quality of life of patients with cognitive impairments and their potential long-lasting effects have not been clarified. Indeed, so far most investigations have only used screening measures for global cognitive decline (e.g., Mini Mental State Examination and Montreal Cognitive Assessment) and/or assessed patients' cognitive performance only once, a few weeks after the introduction of social isolation measures. The SOcial LImitations Turn Up DEmentia (SOLITUDE) (24, 25) study was set up as a multi-centre observational longitudinal study to investigate these issues in the longer term, to document changes in cognitive performance, mental health and quality of life of PWD and to assess burden of their carers over 6 months since the first lockdown was enforced in the UK [for details of the full protocol see (26)].

MATERIALS AND METHODS

Participants

Thirty-six PWD-carer dyads and 9 unaccompanied carers were recruited between September 2020 and March 2021 from 6 secondary-care neurology/old age psychiatry clinics in the UK. Inclusion criteria were: (1) a clinical diagnosis of dementia due to any neurodegenerative aetiology (mixed cases were included if the neurodegenerative condition was the main aetiology); (2) availability of a clinical assessment of global cognitive status with a score equivalent to a Mini Mental State Examination (MMSE) score $\geq$ 18 (for participants screened with a scale different from MMSE, the scores were converted to an equivalent MMSE score using available conversion tables).

PWD were excluded based on the following criteria: (1) major medical diagnoses other than dementia that could affect patient's and carer's physical and mental wellbeing; (2) non-neurodegenerative conditions as the primary cause of dementia; (3) history of long-term psychiatric conditions; (4) history of significant acute neurological events (e.g., stroke, traumatic brain injury); (4) absence of a reliable carer; (5) major sensory or speech impairments preventing telephone assessment; (6) no telephone service in place; (7) insufficient mastery of English. If an eligible PWD was not willing to participate, but his/her carer was, the sole carer was recruited. Exclusion criteria 5–7 were applied to the carer as well.

Protocol of Assessments

All procedures were carried out in compliance with the Declaration of Helsinki. Ethical approval was granted by the NHS Health Research Authority, North West—Preston Regional Ethics Committee, reference n. 20/NW/0305 (protocol version 1).

The recruitment process, as already reported in a previous study (26), involved an initial screening of eligible candidates who were first contacted by a clinician and provided with the study's information sheet. No longer than 1 week since receipt of the information material, all people (both PWD and carers) willing to take part in the study provided their audio-recorded informed consent over the telephone.

Participants underwent 3 telephone assessments: at recruitment (T0), at 3 months (T1) and at 6 months (T2) (see **Figure 1** for a full timeline). The outcome variables collected during each assessment included cognitive tests validated for telephone administration and a series of questionnaires designed to be used with PWD and carers. Patients' cognitive abilities were assessed using: the telephone Mini Mental State Examination (t-MMSE) (27) and the Telephone Assessment of Cognitive Function (28), i.e., a brief battery of tests comprising the Digit Span (forward and backward) and Digit Ordering tests, the Logical Memory test (immediate and delayed recall) and the Category Fluency test (animals and vegetables). Moreover, participants also completed the 9-item Patient Health Questionnaire validated for telephone assessment (29).

Outcome measures collected from carers were assessed by using 3 questionnaires validated for telephone assessments (30–32): the Neuropsychiatric Inventory Questionnaire (NPI-Q) (33) to evaluate PWD's behavioural symptoms; the Quality of Life in Alzheimer's Disease questionnaire (34) to provide information on several areas contributing to PWD's quality of life; and the 12-item Zarit Burden Interview (ZBI-12) (35) to assess carer's burden associated with caring for the PWD.

Moreover, only at T0, each carer completed a semi-structured interview adapted from one used in previous studies (15, 17). This interview included questions on patients, living conditions and socialisation before lockdown, carers' personal mental health problems experienced and help received during lockdown, as well as carer-reported changes in PWD's symptoms during lockdown (up to T0). Findings from the carer semi-structured interview have already been reported in Manca et al. (26). For the purpose of this study, only carer-reported changes in existing neuropsychiatric and cognitive symptoms, the emergence of new neuropsychiatric symptoms and carers' concerns about progression of dementia were considered, among the variables collected as part of this customised interview, as predictors of all of the outcome measures.

Statistical Analysis

First, all tests of the Telephone Assessment of Cognitive Function were z-transformed and used to calculate five composite indices at each time point: global cognition (average of all z-transformed tests), declarative memory (average of Logical Memory and Category Fluency z scores), episodic memory (average of Logical Memory z scores), semantic memory (average of Category Fluency z scores), and working memory (average of Digit Span and Digit Ordering z scores).

Longitudinal changes from T0 to T1, from T1 to T2 and from T0 to T2 were assessed for all outcome measures using repeated-measures ANCOVA models (the threshold of statistical significance was set to $p = 0.05$). The covariates included in the analyses were: patients' age in years at T0, years of education, sex, last clinical MMSE score available before lockdown (as described in the section on inclusion criteria), time elapsed between last pre-lockdown MMSE and T0 assessment (in days) and time elapsed between the official beginning of lockdown in the United Kingdom (23rd March 2020) and the T0 assessment (in days). For variables pertaining to carers' mental health, the carers' years of age at T0, years of education and sex were included in the models as covariates.

Since the procedures of recruitment for the SOLITUDE study began 24 weeks after lockdown had been announced (this was to comply with completion of administrative requirements by the organisation sponsoring the study and obtain ethical approval), we decided to investigate whether the time spent under social restrictions enforced in the United Kingdom was

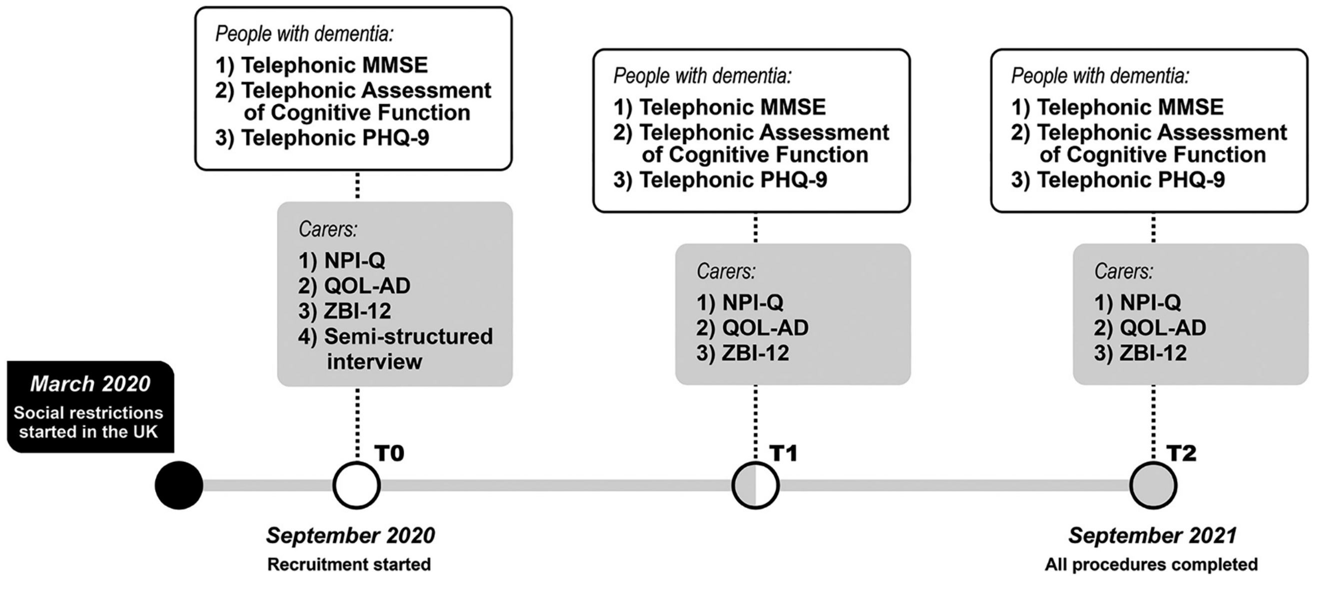

FIGURE 1 | Timeline of the SOLITUDE study.

associated with cognitive performance and wellbeing outcomes at T0. Therefore, several *post hoc* analyses were carried out additional to those planned *a priori* in the registered SOLITUDE study protocol: (1) a repeated-measures ANCOVA model to investigate changes in MMSE scores from pre-lockdown to T0, including the difference in time between the two assessments as a covariate; (2) multiple regression models to predict cognitive performance and wellbeing of both carers and PWD at T0 including the time elapsed between 23rd March 2020 and T0 assessment as predictor and the same covariates used in the repeated-measures models (i.e., age, education, pre-lockdown MMSE score, time elapsed between pre-lockdown MMSE and T0); (3) repetition of the same multiple regression models including also carer-reported changes in PWD's symptoms (i.e., existing behavioural, cognitive, and motor, as well as new behavioural symptoms observed in the T0 semi-structured interview reported in **Supplementary Table 1**) as binary predictors (changes reported vs. no changes) to investigate the association between carers' observation (covering the period of time between the enforcement of social isolation measures and T0) and objectively assessed outcome measures; (4) same regression models described in point (2) and point (3), but with the exclusion of pre-lockdown MMSE score from the covariate range, to predict changes in MMSE scores occurred before T0 captured by an MMSE difference score (pre-lockdown t-MMSE—T0 t-MMSE, calculated after converting the pre-lockdown MMSE to an equivalent t-MMSE score using conversion tables).

RESULTS

Demographic and clinical characteristics of all PWD and carers are reported in **Table 1**. The majority of patients received a clinical diagnosis of Alzheimer's disease and the carer was their spouse/partner in most cases [for more details on our sample see (26)].

Of the 36 PWD who agreed to take part and completed study procedures at T0, only 32 completed the full assessment at T1 (1 patient completed only the t-MMSE at this time point) and 29 (80.5%) completed the full study (**Table 2**). Forty-five carers were recruited and, of these, 36 (80%) completed all assessments.

TABLE 1 | Demographic characteristics of people with dementia and carers (mean ± *SD*).

Variable	All PWD (*n* = 45)	PWD directly assessed (*n* = 36)	Carers (*n* = 45)
Age (years)	74.04 ± 9.33	72.25 ± 8.55	69.24 ± 10.23
Education (years)	12.96 ± 3.01	13.25 ± 3.12	13.67 ± 2.99
Sex (M/F)	25/20	23/13	18/27
Pre-lockdown t-MMSE	20.93 ± 3.37	21.26 ± 3.37	–
Diagnosis[a]:			
AD	34 (75.6%)	28 (77.8%)	–
Mixed aetiology	5 (11.1%)	2 (5.6%)	–
DLB	3 (6.7%)	3 (8.3%)	–
PCA	2 (4.4%)	2 (5.6%)	–
CBD	1 (2.2%)	1 (2.7%)	–
Relation with PWD[a]			
Spouse/partner	–	–	38 (84.5%)
Child	–	–	6 (13.3%)
Friend/acquaintance	–	–	1 (2.2%)

[a] Frequencies (proportions).

AD, Alzheimer's disease; CBD, Corticobasal degeneration; DLB, Dementia with Lewy Bodies; PCA, Posterior cortical atrophy; PWD, People with dementia; t-MMSE, telephone Mini Mental State Examination.

Frequencies of carer-reported changes in patients' symptoms over the first months spent under social restrictions are summarised in **Supplementary Table 2**.

Repeated-measures ANCOVA models revealed no changes in any of the outcome measures between any time points, apart from a weak improvement on the semantic memory composite index between T1 and T2 ($F = 5.34$, $p = 0.03$) (**Table 2**; see **Supplementary Table 3** for full descriptive statistics).

Post hoc analyses showed no significant changes in t-MMSE scores from before lockdown ($F = 0.013$, $p = 0.91$). However, multiple regression analyses revealed that the time spent under social restrictions before T0 was negatively associated with cognitive performance of PWD on the Logical Memory test, both immediate ($\beta = -0.39$, $p = 0.03$, $r^2_{part} = 0.11$) and delayed recall ($\beta = -0.46$, $p < 0.01$, $r^2_{part} = 0.16$), and with scores on the Category Fluency test—animals ($\beta = -0.44$, $p < 0.01$, $r^2_{part} = 0.14$) (**Table 3**). Similarly, a negative association was also detected with all composite indices, apart from the working memory composite index, with small-to-medium effect size (36) (global cognition: $r^2_{part} = 0.14$, declarative memory: $r^2_{part} = 0.18$, episodic memory: $r^2_{part} = 0.15$, semantic memory: $r^2_{part} = 0.13$). Lower pre-lockdown MMSE score was significantly associated with worse global cognitive and episodic memory performance. Higher levels of education significantly predicted higher scores on most cognitive tests. Moreover, both higher education and younger age were associated with less severe neuropsychiatric symptomatology (i.e., lower NPI-Q scores).

Carer-reported cognitive decline was associated with worse performance on the Category Fluency test ("animals" category) and with lower semantic memory composite indices at T0 (**Figure 1**; see **Supplementary Table 4**). Carers' impression of faster disease progression was associated with higher NPI-Q scores and worse carers' distress and burden. Moreover, worsening of behavioural symptoms observed by carers was also significantly associated with higher carer-reported burden (i.e., higher ZBI-12 scores) (**Figure 2**).

Finally, no significant associations were detected between any of the objective and subjective (i.e., carer-reported) factors investigated and the MMSE difference score (**Supplementary Table 5**).

TABLE 2 | Changes in cognitive and clinical variables over the 6 months of observation.

Variable	T0-T1 change		T1-T2 change		T0-T2 change	
PWD—cognitive battery	***F*^{a}**	***p***	***F*^{a}**	***p***	***F*^{a}**	***p***
t-MMSE	0.12	0.73	2.70	0.11	3.11	0.09
DSF	0.13	0.72	0.86	0.36	1.90	0.18
DSB	0.19	0.77	0.86	0.36	0.15	0.70
DO	0.08	0.78	1.39	0.25	0.01	0.91
LM—IR	0.19	0.77	0.06	0.81	0.07	0.80
LM—DR	0.37	0.55	0.68	0.42	0.04	0.83
CFa—total	1.64	0.21	3.15	0.09	0.70	0.41
CFv—total	0.09	0.76	0.83	0.37	0.11	0.74
CFa—I	0.73	0.40	0.10	0.76	0.11	0.74
CFa—P	0.12	0.73	0.03	0.87	0.10	0.75
CFv—I	0.02	0.89	0.02	0.89	0.03	0.87
CFv—P	0.10	0.76	0.48	0.49	0.12	0.73
PWD—composite indices						
GC-CI	0.07	0.79	1.12	0.30	1.03	0.32
WM-CI	0.08	0.78	0.06	0.82	0.34	0.56
DM-CI	0.54	0.47	0.42	0.52	0.41	0.53
EM-CI	0.01	0.93	0.04	0.85	0.00	0.96
SM-CI	1.04	0.32	**5.34**	**0.03**	0.89	0.36
PWD—mental health						
PHQ-9	0.89	0.35	0.58	0.45	1.50	0.23
Carer-reported						
QoL-AD	0.47	0.50	0.03	0.85	0.04	0.83
NPI-Q—total	0.67	0.42	0.07	0.79	0.06	0.82
NPI-Q—distress	2.52	0.12	0.06	0.81	0.01	0.93
ZBI-12	0.38	0.54	0.12	0.73	2.86	0.10

[a] F-statistic associated with the variable "Time" in repeated-measures models.
CFa/CFv, Category Fluency test–animals/vegetables (I, Intrusions; P, Perseverations); DM-CI, Declarative Memory Composite Index; DO, Digit Ordering test; DSB, Digit Span test—backward; DSF, Digit Span test–forward; EM-CI, Episodic Memory Composite Index; GC-CI, Global Cognitive Composite Index; LM, Logical Memory test (DR: Delayed recall, IR: Immediate recall); NPI-Q, Neuropsychiatric Inventory Questionnaire; PHQ-9, 9-item Patient Health Questionnaire; PWD, People with dementia; QoL-AD, Alzheimer's Disease Quality of Life; SM-CI, Semantic Memory Composite Index; t-MMSE, telephone Mini Mental State Examination; WM-CI, Working Memory Composite Index; ZBI-12, 12-item Zarit Burden Interview. All significant results are reported in bold.

DISCUSSION

Our sample of PWD primarily due to neurodegenerative aetiologies had been cognitively and behaviourally stable over the 6-month timeframe of the SOLITUDE study, despite their adherence to the rules imposing restrictions to social contacts. Similarly, no significant changes were observed in the levels of carers' distress and burden. This period of observation, however, occurred at a time when people had already been experiencing restrictions to their social routines for several months. This might have given them the opportunity to develop a degree of adjustment and might have prompted them to make targeted adaptations to cope with the practical consequences of enforced social limitations. Investigations into the factors that might have been associated with the outcome measures assessed at T0 highlighted that the number of days spent under social restrictions was negatively associated with patients' performance. This was particularly detectable on tests of episodic and semantic memory. Moreover, scores on the Category fluency test at T0 were found to be significantly lower in PWD who were judged by their carers to have worsened cognitively over the first months of lockdown than in those who had been said to have remained stable. Carers who thought that the PWD experienced symptom worsening, both behaviourally and/or in association with their general clinical profile, also reported significantly higher burden and distress scores than carers who noticed no changes.

The findings of the SOLITUDE study are in line with those of similar recent studies and seem to suggest lockdown-related

TABLE 3 | Results of the multivariate multiple regression models (βs and standard errors) to predict cognitive and clinical characteristics of PWD and carers at T0.

T0 variables	Age (years)	Education (years)	Sex	Pre-lockdown MMSE	Time of social restrictions (days)
PWD—cognitive battery					
t-MMSE	0.03 (0.07), $p = 0.87$	**0.32 (0.17), $p = 0.03$**	0.09 (1.13), $p = 0.53$	**0.44 (0.17), $p < 0.01$**	−0.27 (0.01), $p = 0.11$
DSF	0.22 (0.03), $p = 0.25$	**0.51 (0.07), $p < 0.01$**	−0.11 (0.46), $p = 0.50$	−0.20 (0.07), $p = 0.26$	−0.04 (0.01), $p = 0.85$
DSB	0.24 (0.04), $p = 0.22$	−0.03 (0.08), $p = 0.87$	−0.21 (0.50), $p = 0.26$	0.36 (0.07), $p = 0.06$	−0.12 (0.01), $p = 0.54$
DO	0.09 (0.02), $p = 0.59$	**0.37 (0.07), $p = 0.02$**	0.26 (0.47), $p = 0.08$	0.29 (0.07), $p = 0.07$	−0.13 (0.01), $p = 0.41$
LM—IR	0.03 (0.01), $p = 0.87$	0.17 (0.23), $p = 0.29$	−0.02 (1.48), $p = 0.88$	**0.50 (0.22), $p < 0.01$**	**−0.39 (0.01), $p = 0.03$**
LM—DR	0.02 (0.01), $p = 0.91$	0.14 (0.31), $p = 0.35$	−0.14 (2.06), $p = 0.38$	**0.51 (0.31), $p < 0.01$**	**−0.46 (0.02), $p < 0.01$**
CFa—total	0.01 (0.01), $p = 0.97$	**0.41 (0.19), $p = 0.01$**	0.16 (1.22), $p = 0.30$	0.11 (0.18), $p = 0.47$	**−0.44 (0.01), $p = 0.01$**
CFv—total	−0.16 (0.08), $p = 0.39$	0.22 (0.20), $p = 0.20$	−0.03 (1.30), $p = 0.84$	0.27 (0.19), $p = 0.14$	−0.32 (0.01), $p = 0.09$
CFa—I	−0.04 (0.01), $p = 0.86$	0.13 (0.01), $p = 0.49$	−0.07 (0.09), $p = 0.71$	−0.09 (0.01), $p = 0.66$	−0.12 (0.01), $p = 0.59$
CFa—P	0.18 (0.03), $p = 0.35$	−0.09 (0.09), $p = 0.63$	−0.21 (0.57), $p = 0.25$	0.04 (0.08), $p = 0.82$	0.19 (0.01), $p = 0.34$
CFv—I	**0.36 (0.02), $p = 0.05$**	−0.05 (0.05), $p = 0.73$	0.27 (0.31), $p = 0.10$	−0.19 (0.05), $p = 0.28$	−0.31 (0.01), $p = 0.09$
CFv—P	−0.02 (0.03), $p = 0.93$	−0.06 (0.07), $p = 0.73$	−0.34 (0.42), $p = 0.07$	−0.01 (0.06), $p = 0.98$	0.05 (0.01), $p = 0.81$
PWD—composite indices					
GC-CI	0.10 (0.01), $p = 0.52$	**0.40 (0.03), $p < 0.01$**	−0.02 (0.19), $p = 0.88$	**0.42 (0.03), $p < 0.01$**	**−0.43 (0.01), $p = 0.01$**
WM-CI	0.28 (0.01), $p = 0.12$	**0.43 (0.03), $p = 0.01$**	−0.03 (0.21), $p = 0.87$	0.23 (0.03), $p = 0.19$	−0.15 (0.01), $p = 0.41$
DM-CI	−0.03 (0.02), $p = 0.87$	0.28 (0.04), $p = 0.05$	−0.01 (0.24), $p = 0.94$	**0.43 (0.04), $p < 0.01$**	**−0.49 (0.01), $p < 0.01$**
EM-CI	0.03 (0.02), $p = 0.87$	0.17 (0.04), $p = 0.26$	−0.09 (0.28), $p = 0.56$	**0.54 (0.04), $p < 0.01$**	**−0.46 (0.01), $p < 0.01$**
SM-CI	−0.85 (0.02), $p = 0.62$	**0.34 (0.04), $p = 0.03$**	0.07 (0.29), $p = 0.67$	0.21 (0.04), $p = 0.20$	**−0.42 (0.01), $p = 0.02$**
PWD—mental health					
PHQ-9	−0.34 (0.09), $p = 0.08$	−0.21 (0.22), $p = 0.23$	0.03 (1.47), $p = 0.88$	0.31 (0.22), $p = 0.10$	0.15 (0.01), $p = 0.44$
Carer-reported					
QOL-AD	−0.09 (0.15), $p = 0.64$	0.26 (0.36), $p = 0.13$	−0.19 (2.39), $p = 0.27$	−0.06 (0.36), $p = 0.73$	−0.12 (0.02), $p = 0.52$
NPI-Q—total	**−0.41 (0.11), $p = 0.03$**	**−0.39 (0.27), $p = 0.02$**	0.13 (1.79), $p = 0.43$	0.27 (0.27), $p = 0.14$	0.26 (0.02), $p = 0.17$
NPI-Q—distress	−0.30 (0.13), $p = 0.09$	−0.09 (0.43), $p = 0.59$	−0.08 (2.46), $p = 0.62$	−0.02 (0.37), $p = 0.89$	0.32 (0.02), $p = 0.05$
ZBI-12	−0.07 (0.16), $p = 0.71$	−0.08 (0.55), $p = 0.65$	0.15 (3.15), $p = 0.38$	−0.08 (0.48), $p = 0.63$	0.06 (0.02), $p = 0.37$

CFa/CFv, Category Fluency test—animals/vegetables (I, Intrusions; P, Perseverations); DM-CI, Declarative Memory Composite Index; DO, Digit Ordering test; DSB, Digit Span test—backward; DSF, Digit Span test—forward; EM-CI, Episodic Memory Composite Index; GC-CI, Global Cognitive Composite Index; LM, Logical Memory test (DR, Delayed recall; IR, Immediate recall); NPI-Q, Neuropsychiatric Inventory Questionnaire; PHQ-9, 9-item Patient Health Questionnaire; PWD, People with dementia; QoL-AD, Alzheimer's Disease Quality of Life; SM-CI, Semantic Memory Composite Index; t-MMSE, telephone Mini Mental State Examination; WM-CI, Working Memory Composite Index; ZBI-12, 12-item Zarit Burden Interview. All significant results are reported in bold.

decline in some cognitive domains, i.e., semantic fluency and long-term memory, in patients with cognitive impairment due to AD (23) and even other types of neurodegenerative conditions (19). In fact, the duration of the period of forced social isolation was negatively associated with patients' memory performance at T0. On the contrary, no significant general decline was detected by means of the t-MMSE in the same timeframe, and changes on this scale were associated neither with the time spent under social restrictions nor with the carer-reported changes in patients' symptoms. This suggests that a sudden reduction in social stimulation that is protracted over a long period of time may exert detrimental effects on specific cognitive abilities in PWD, as also found by a longitudinal study that followed up patients with AD and Lewy Body dementia over 1 year (37). These specific declines are not captured if simple screening instruments like the MMSE are used and may go undetected if assessment of cognitive status of PWD is limited to global staging measures, especially in patients with a mild level of severity. A mildly significant improvement of the semantic memory composite index was, however, noted from T1 to T2. This finding could be due either to practice effect, since the same two semantic categories were used for all assessments, or to random variation in performance, since a non-significant trend toward a decline in this composite index was noted from T0 to T1. It must be noted that some degree of practice effect may possibly explain also the lack of decline over the 6-month time frame of this study in all cognitive domains assessed.

It is possible that protracted social isolation may have had a direct impact on cognitive health of PWD by limiting the opportunities either to practice their cognitive skills and strategies that were still preserved before the enforcement of lockdown or to acquire new strategies to cope with cognitive decline, i.e., cognitive reserve of patients may have been depleted by lack of social stimulation (38). The importance of cognitive reserve is suggested by the significant associations found between education and clinical profiles at T0, i.e., better performance on most cognitive tests and lower NPI-Q scores. Although we found no significant changes in PWD's neuropsychiatric symptoms, either patient- or carer-reported, it is also likely that socially isolated patients may experience more severe behavioural and psychological symptoms (12–16) that may precipitate cognitive decline (39, 40). Indeed, social networks can provide support for patients resulting in better physical and mental health (41).

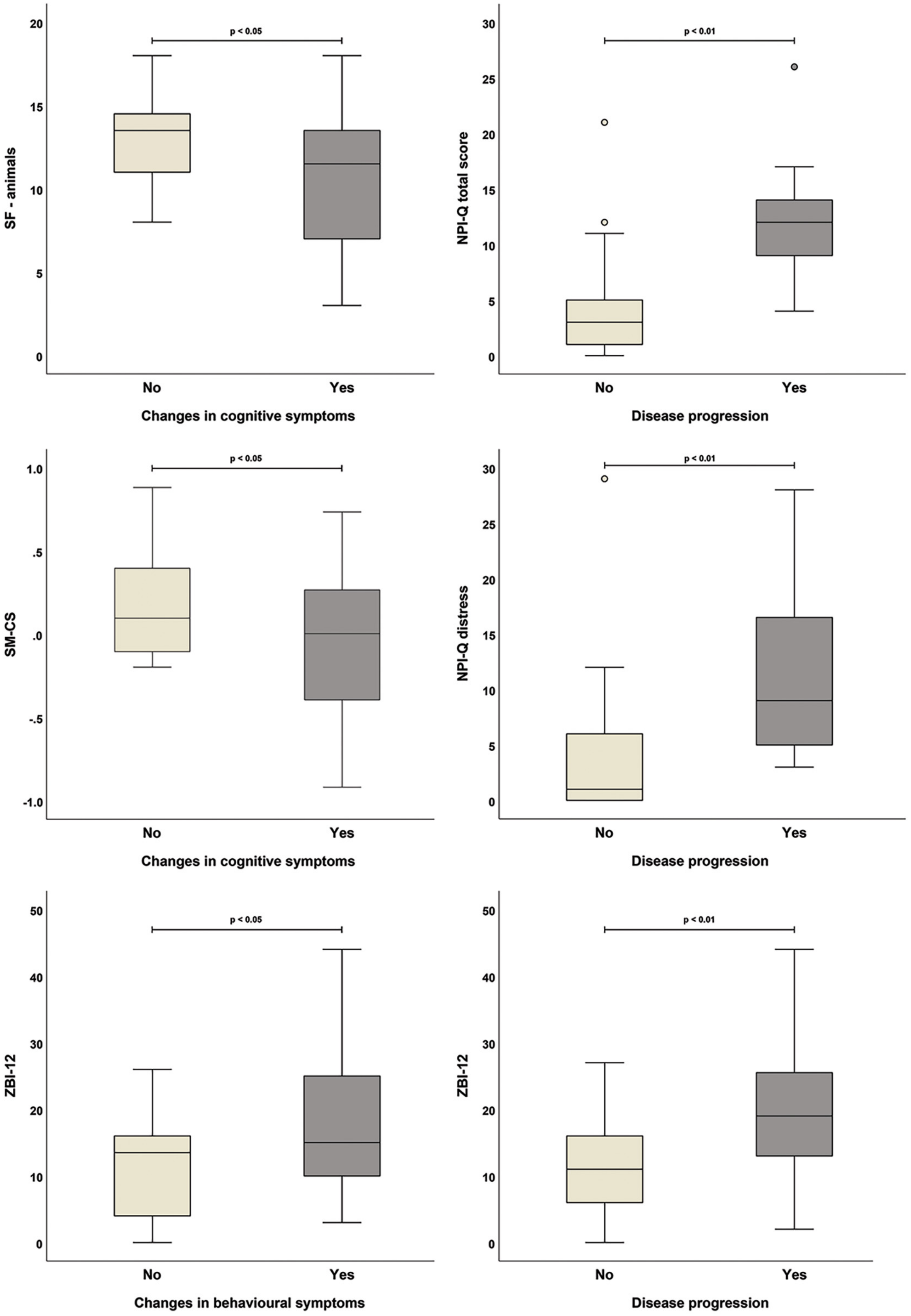

FIGURE 2 | Significant associations between carer-reported changes in patients' symptoms and outcome measures collected at T0 (all variables were treated as binary: yes, symptom changes/faster progression reported by carer; no, carer reported no symptom changes/faster progression).

These detrimental effects could explain the epidemiological link between social isolation and increased risk of dementia (42), and greater levels of AD-related neural damage, as highlighted by human neuropathological studies (43). Moreover, a few recent studies investigated experimentally the neural mechanisms that could underpin this association and found that social isolation seems to foster AD pathology accumulation in an animal model of this disease (43).

To the best of our knowledge, no PWD and carers were infected by SARS-CoV-2 either prior to or during participation in the SOLITUDE study, although we cannot fully rule out possible cognitive and/or behavioural disturbances that might have been caused by asymptomatic SARS-CoV-2 infections. Indeed, COVID-19 has been shown to cause neural damage and lead to cognitive decline (44), but this seems to be the case particularly in older people severely affected by the infection (45).

Levels of carers' burden and distress caused by neuropsychiatric symptoms of PWD were also found to be stable over the observation period and no association was detected between these carer-related outcomes and any of the objective factors investigated. However, carer-reported worsening in the neuropsychiatric symptoms of PWD and faster disease progression over the first months of lockdown were significantly associated with higher burden and distress scores. Although we cannot exclude that carers' mental health status might have influenced subjective perception of burden and distress (46), it must be noted that very similar findings emerged from other investigations into the consequences of measures of social restrictions enforcement due to the COVID-19 pandemic (13, 17, 18).

Interesting results emerged from the association between carer-reported cognitive decline and objectively assessed patients' neuropsychological performance at T0. In fact, carer-reported worsening of cognitive symptoms just after lockdown (until recruitment) was negatively associated with the Category Fluency score (number of animals) and the semantic memory composite index. Therefore, carers' judgments of cognitive health of PWD appeared to be in agreement with the objective observation of lower performance in semantic memory, a domain negatively affected by the amount of time spent in social isolation and that is sensitive to disease progression in AD (47). A recent cross-sectional study has also found greater cognitive and behavioural decline in PWD who were reported by their carers as more cognitively impaired since enforcement of social isolation regulations (48). This means that carers of PWD can provide clinically meaningful information on patients and this may be particularly helpful to clinicians when a direct assessment of the patient is not possible. Indeed, previous research has highlighted that carers can detect cognitive impairment accurately, although their assessment may not help differentiate different cognitive profiles (49, 50).

A first limitation of this study is the small sample size that, combined with a small number of drop-outs, might have prevented the detection of subgroups characterised by distinct patterns of longitudinal changes. However, despite the limited number of patients recruited, the association between the time spent under social restrictions and cognitive performance at T0 emerged as a significant finding [although with small and medium effect sizes, conventionally defined for multiple regression as effects in the range of 0.05–0.15 and of 0.15–0.35, respectively (36)]. As a consequence of the unforeseen circumstances that affected the great majority of the population, a control group of PWD who were not socially isolated could not be included. This prevents definite conclusions on the extent to which social isolation may have affected cognition in PWD. Second, our sample lacked patients from ethnic minorities, possibly due to a range of cultural (e.g., use of health services, interpretation of cognitive symptoms) and biological factors [e.g., higher rates of vascular cognitive impairment among certain ethnic minority groups, such as South Asians (51)]. Lack of evidence from ethnic minority groups, therefore, limits the generalisation of our conclusions to the whole clinical population of PWD due to neurodegenerative conditions, although it is highly likely that similar detrimental effects would be seen across populations of any ethno-racial background. Future studies are needed to clarify this pressing issue, considering that in the United Kingdom and other western countries, ethnic minorities have been affected by the COVID-19 pandemic more than White people (52). Third, the very small number of patients with non-AD dementias recruited for this study hindered any possibility of stratifying our sample by aetiology to gather insights into the differential impact of social isolation on people affected by different types of neurodegenerative diseases. Fourth, most carers were spouses/partners of PWD and this limited any possibility to analyse differences in outcome measures of burden between groups of carers differentially related to the PWD. Finally, it must be noted that the SOLITUDE protocol included no visuo-spatial, executive and social cognitive tests, primarily because of two reasons: (1) the nature of the assessment, i.e., telephone-based, that prevents the administration of visual stimuli, and (2) the lack of measures validated for remote research settings. Future efforts to develop tasks that could be delivered either via telephone or video-conference to assess a broader range of cognitive abilities in PWD will be beneficial to move the field of tele-neuropsychology forward.

Lockdown enforced to limit the current COVID-19 pandemic has extensively impacted everybody's life, but also offered the conditions to study the impact of social isolation on cognitive health. The SOLITUDE study, consistently with other thematically aligned investigations world-wide, provides some insights indicating that a long-lasting reduction in social connectedness has an impact on objectively assessed cognitive performance of PWD, especially on semantic abilities. This finding was also supported by the consistent information provided by carers about changes in cognitive symptoms. Further studies in larger cohorts should ascertain what factors may either worsen or protect against the negative influence of social isolation on cognitive health of PWD. Moreover, investigations of interventions with the potential to limit cognitive decline resulting from either a reduction or lack in social connections for PWD are needed to devise and provide evidence-based support during challenging times like those caused by the COVID-19 pandemic (53).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by NHS Health Research Authority, North West—Preston Regional Ethics Committee, reference n. 20/NW/0305 (protocol version 1). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RM contributed to the study inception and participant recruitment, collected (part of), analysed and interpreted the data, drafted, revised, and approved the final version of the manuscript for submission. MDM conceived the study design, contributed to data interpretation, revised, and approved the manuscript for submission. AC, VR, JA, RD, PK, GR, and DJB led site-specific recruitment and data collection, revised, and approved the manuscript for submission. AV conceived the study, contributed to recruitment and data interpretation, revised, and finalised the manuscript for submission. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Changes in Brain-Health Related Modifiable Risk Factors in Older Adults After One Year of COVID-19-Restrictions

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Background: The COVID-19 pandemic has major influence on lifestyle and mental health, which might affect brain-health and increase the risk of cognitive decline, particularly in older adults. We aimed to describe changes in modifiable risk factors related to brain-health in older adults after one year of COVID-19 restrictions.

Methods: An online survey was disseminated between February and March 2021 to 17,773 registrants of the Dutch Brain Research Registry, aged $\geq$50, without a self-reported diagnosis of mild cognitive impairment or dementia. Participants were asked to report potential changes in behaviors during the COVID-19 pandemic, compared to pre-pandemic, in eight domains related to brain health: physical activity, sleep, feeling of memory decline, perceived stress, feeling of loneliness, diet, alcohol consumption, and smoking. We used negative binomial regression analyses to relate (socio)demographics, subjective memory complaints and COVID-19 related aspects (fear of, or current/past COVID-19 infection) to the number of reported detrimental and beneficial changes as dependent variable.

Results: 3,943 participants (66 ± 8 years old; 76% female; 71% highly educated) completed the survey. After one year of COVID-19-restrictions, 74% reported at least one detrimental lifestyle change unfavorable for their brain health, most frequently reported were feelings of loneliness, sleep problems, and less physical activity. 60% of participants reported at least one beneficial change, which were most often more physical activity, healthier dietary habits, and less alcohol consumption. Individuals who are younger [incidence rate ratio (IRR) = 0.99, 95% CI = 0.98–0.99], female (1.20, 1.11–1.30), living alone (1.20, 1.11–1.28) and in urban environments (1.18, 1.08–1.29), who are less satisfied with their income (1.38, 1.17–1.62), experiencing subjective memory complaints (1.40, 1.28–1.52) and those with a past or current (1.19, 1.06–1.34) or fear of a COVID-19 infection (1.33, 1.25–1.42) reported higher numbers of detrimental changes.

Discussion: The COVID-19 pandemic has influenced lifestyle in both positive and negative ways. We identified (socio)demographic factors associated with more detrimental changes in modifiable risk factors related to brain health, suggesting that some individuals are more vulnerable for the impact of the COVID-19 pandemic. These findings provide an opportunity for targeted prevention and education to promote a healthy lifestyle during and after the pandemic.

Keywords: COVID-19, lifestyle, mental health, aging, risk factors, cognitive decline, prevention, lockdown

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has, due to public health recommendations and governmental measures, resulted in the closing of social, cultural and sports facilities and many restrictions on daily living, including isolation, social distancing, and home confinement. The pandemic and related restrictions have been reported to impact lifestyle and mental health in the general population (1, 2). In older individuals particularly, enduring unhealthy changes in lifestyle and mental health may affect brain-health, potentially altering the risk for accelerated cognitive decline. As such, serious concerns exist about the impact of the COVID-19 pandemic and related restrictions on brain-health (3). Since 40% of dementia cases are potentially attributable to modifiable factors (e.g., physical inactivity, depression, social isolation and smoking) (4), and evidence about effective prevention of cognitive decline with multi-domain lifestyle interventions is emerging (5–7), knowledge about the impact of the COVID-19 pandemic on brain-health related risk factors is important for the prevention of accelerated cognitive decline (8).

Throughout the pandemic, many countries experienced multiple "waves" in which infections and hospitalizations due to COVID-19 increased, resulting in constant adjustment of recommendations and governmental measures. In the Netherlands, the first wave was from March 2020 till mid May 2020, and the second wave was from October 2020 till February 2021 when additional to other restrictions a curfew was imposed. In March 2021 the number of infections rose again and a third wave made its entry which lasted until the end of April 2021. Surveys conducted during the first waves across multiple countries showed that the COVID-19 restrictions affected lifestyle behaviors, for example, decreases in physical activity (2, 9–12), more sleep problems (2, 9, 13), and increase in stress-related feelings (14) were repeatedly reported. Some studies showed that alcohol binge drinking and smoking decreased (15, 16) or remained unchanged (9) during the lockdowns while others reported an increase in alcohol consumption and smoking (2, 12), and several studies also reported changes in dietary habits (the type of food, snacks between meals, and number of main meals) (12, 17). Furthermore, during the first wave, an increase in subjective memory complaints was observed (14–37%) (13, 14, 18), which may be first signs of cognitive decline (19, 20). This emphasizes the importance of knowledge about lifestyle changes during the COVID-19 pandemic in the context of cognitive decline and brain health. In addition to detrimental lifestyle changes, favorable lifestyle changes have also been reported, although by a smaller proportion of participants (9, 12, 17), and in a large Dutch and Finnish sample, the majority of respondents reported no change in various lifestyle behaviors as a reaction to COVID-19 restrictions (9, 21). Conflicting findings may be due to differences in governmental measures, and for example if these measures were forced by law or appealed to the responsibility of the citizens. Also, social and cultural differences across countries may influence behavioral reactions to the COVID-19 restrictions. Given this mixture of findings and ongoing COVID-19 pandemic with related restrictions, insight in the long-term effects on lifestyle changes in different countries is needed.

Therefore, the World-Wide-FINGERS-SARS-CoV-2 survey was developed to assess changes in lifestyle and psychosocial factors as a result of the COVID-19 restrictions (9) within the context of the World-Wide FINGERS (WW-FINGERS) network of multi-domain prevention trials[1] (22, 23). We used this survey to explore which changes in modifiable risk factors related to brain-health occurred among older adults in the Netherlands during the first year of the COVID-19 pandemic which included the first and second wave (March 2020–2021). Our primary goal was to improve the knowledge of lifestyle changes due to COVID-19 restrictions. Campaigns throughout the pandemic primarily focused on recommendations to fight the spread of infections, with limited focus on healthy lifestyle. Our results may contribute to designing health education campaigns to promote a healthy lifestyle during and after pandemics. Secondly, we aimed to identify which participants' (socio)demographics and COVID-19-related factors were associated with detrimental or beneficial changes in lifestyle. Identification of individuals with

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[1] https://wwfingers.com

increased risk of future cognitive decline is important for targeted dissemination of health education and selection of potential candidates for multi-domain lifestyle interventions.

MATERIALS AND METHODS

Participants and Procedures

For this population-based cross-sectional study we recruited participants via the Dutch Brain Research Registry, a nationwide online platform for people interested in participating in brain-related research (24). From the Dutch Brain Research Registry, 17,773 registrants received a study invitation per email, of which 3,943 completed the online survey and were included in the study. Registrants aged 50 years and older and without a self-reported diagnosis of mild cognitive impairment or dementia were included. The online survey was offered from February 2021 till March 2021 and consisted of questions about lifestyle and mental health (9) and questions about psychosocial factors (25) (**Supplementary Table 1**). Information on (socio)demographics, subjective memory complaints including worries prior the COVID-19 pandemic and "LIfestyle for BRAin health" (LIBRA) score were collected from the Dutch Brain Research Registry.

Measures

(Socio)demographics and Subjective Memory Complaints

As (socio)demographic factors we included age, sex, education, professional status (unemployed, employed, or retired), subjective measure of financial situation (unsatisfactory, satisfactory or more than satisfactory), living alone (yes/no), population density (rural, urban <40.000 inhabitants, urban: >40.000 inhabitants). We dichotomized education level into low–medium (up to the equivalent of high school education) and high education (the equivalent of college education or higher). Presence of subjective memory complaints was defined as presence of complaints (yes/no) and worries about this (yes/no).

Individual's Health and Lifestyle Risk for Cognitive Decline

Information about modifiable health and lifestyle risk factors for cognitive decline and dementia was included, to provide an indication of an individual's potential for dementia risk reduction. For this we calculated the LIBRA, which is a validated risk score developed after triangulation of results from a systematic literature review and an expert consensus study (26, 27). Risk factors are coronary heart disease, diabetes, hypercholesterolemia, hypertension, depression, obesity, smoking, physical inactivity, and renal disease. Protective factors are a healthy diet (Mediterranean), cognitively active and low-to-moderate alcohol intake. The cut-off for low-to-moderate alcohol consumption is based on the Dutch Dietary Guidelines, which states that alcohol consumption should be avoided (no drinks) or not more than one drink per day (28). Based on a weighted sum score of nine risk factors and three protective factors (theoretical range from −5.9 to +12.7; with higher scores indicating greater risk of cognitive decline or dementia; see **Supplementary Table 2**), which were available for half of our participants (1,984/3,943, 50%).

Changes in Modifiable Factors Related to Brain Health During the COVID-19 Pandemic

We described changes based on eight modifiable factors related to brain health: physical activity, diet, alcohol consumption, smoking, feeling of memory decline, sleep, perceived stress, and loneliness (**Supplementary Table 1**). Participants were asked to indicate an increase or decrease on each of these domains, compared to before the COVID-19-outbreak, either on a three- or five-point scale. Questions formulated as a five-point scale were merged into a three-point scale ("decreased/increased a little" merged with "decreased/increased a lot," "clearly worse/better" merged with "slightly worse/better"), and coded as a minus one "detrimental change," plus one "beneficial change" and zero "no change" (**Supplementary Table 1**). For all questions, "does not concern me" was categorized as "no change." Questions for which a decrease was considered as beneficial (i.e., loneliness, sleep problems, unhealthy snacks, alcohol consumption and smoking) were reversely scored for ease of interpretation. If multiple items in the survey covered the same factor, these were averaged. For physical activity, the change in amount of leisure sport activities during COVID-19 pandemic and before was calculated from two separate questions (**Supplementary Table 1**). If participants reported to have a (sport) injury before (n = 97, 2.5%) or during (n = 121, 3.1%) the COVID-19 pandemic this was considered as "no change" since change was clearly not due to the COVID-19 restrictions. For each participant, we counted the number of detrimental and the number of beneficial factors (both; range 0–8).

COVID Related Factors

As COVID-19-related factors we included two questions, if the participant experienced current or past COVID-19 infection (yes/no) or had fear of getting infected with COVID-19 (yes/no).

Statistical Analyses

Descriptive statistics include absolute frequencies and percentages for categorical variables, and mean ± standard deviation for continuous variables. Since our outcomes were count variables, we used multiple negative binomial regression analyses to explore associations between participant characteristics and the number of detrimental and beneficial changes (separate models) on modifiable factors related to brain-health during the COVID-19 outbreak. Participant characteristics included (socio)demographics, presence of subjective memory complaints and worries, the individual's LIBRA score, current/previous COVID-19-related infection, and fear of COVID-19 infection.

First, we performed univariate analyses for each predictor separately, adjusted for age and sex (Model 1). Secondly, all predictors were evaluated simultaneously in a multivariable model to estimate independent statistical associations (Model 2). Out of the total sample (n = 3943), 3274 participants (83.0%) provided response for all variables of interest and were included in the final model. We repeated the analysis in the subsample with available LIBRA score, where LIBRA score was evaluated as additional determinant set of analyses (n = 1984, 50.3%). In order to correct for the effect on lifestyle potentially caused by the illness due to a COVID-19 infection, we performed a sensitivity analysis in which we excluded participants who reported to have a past/current COVID-19-infection (n = 252, 6.4%). Estimates are presented as incidence rate ratio's (IRR) and their 95% confidence intervals (CI). The level of statistical significance was $p < 0.05$ in two-sided tests, due to the exploratory approach we did not correct for multiple testing. All analyses were performed in SPSS Statistics version 26.

RESULTS

Participant Characteristics

Participants were aged between 50 and 99 years (mean ± SD = 66 ± 8), the majority was female (n = 2988, 75.8%) and highly educated (n = 2799, 71.0%). **Table 1** shows participants' (socio)demographics including frequencies of self-reported risk and protective factors as measured by the LIBRA. The LIBRA score ranged from −5.9 to 7.8, with an average of −0.32 (±2.2) indicating a relatively healthy sample with generally more protective factors for cognitive decline (29). For the COVID-19 related aspects, 252 participants (6.4%) reported a current or past COVID-19 infection, and 1248 (31.7%) expressed fear of getting infected with COVID-19.

Description of Changes in Modifiable Lifestyle Factors Related to Brain Health

Figure 1 illustrates the percentages of self-reported change on the eight modifiable factors related to cognitive decline. Most often reported detrimental changes were more feelings of loneliness (38.6%), an increase of sleep problems and feelings of tiredness (33.5%) and a decrease in the amount of physical activities (31.5%). As beneficial changes, participants most often reported an increase in physical activities (34.1%), healthy changes in diet (25.8%), and a decrease in alcohol consumption (14.2%). Substantial proportions of participants also reported no change with regards to each individual factor (34.4–95.2%).

More than 7 in 10 respondents (n = 2852, 72.3%) reported at least one detrimental change (**Figure 2**), and 6 in 10 reported at least one healthy change (n = 2387, 60.5%); illustrating that many people showed both detrimental and beneficial lifestyle changes. When counting the number of reported factors that changed, 15.8% of participants (n = 622) reported detrimental changes on four or more factors compared to only 2.8% who reported (n = 111) four or more beneficial changes (**Figure 2**).

Associations Between (Socio)demographics, LIBRA-Score and COVID-Characteristics, and Detrimental and Beneficial Changes

We identified associations of detrimental changes and beneficial lifestyle change related to brain health (**Tables 2**, **3**). Similar relationships were found in Model 2 compared to Model 1 but slightly attenuated, only professional status was no longer statistically significant in Model 2. Participants with lower age (IRR = 0.99 [95% CI: 0.98–0.99]), female sex (IRR = 1.20 [1.11–1.30]), living alone (IRR = 1.20 [1.11–0.46]), presence of subjective memory complaints (IRR = 1.40 [1.28–1.51]), a current or past COVID-19 infection (IRR = 1.19 [1.06–1.34]) and a fear of a COVID-infection (IRR = 1.33 [1.25–1.42]) were more likely to report more detrimental changes compared to their reference groups. Those who were less satisfied with their income (compared to participants that were more than

TABLE 1 | Participant characteristics.

	Total (*n* = 3943)
Female	2,988 (75.8%)
Age in years	66 ± 8
Education[a]	
Low-medium education	1,144 (29.0%)
Higher education	2,799 (71.0%)
Professional status	
Unemployed	317 (8.0%)
Employed	1,607 (40.8%)
Retired	1,871 (47.5%)
Financial situation	
Unsatisfactory	129 (3.3%)
Satisfactory	808 (20.5%)
More than satisfactory	2,968 (75.3%)
Living alone	1,011 (25.6%)
Living area, population density	
Rural	701 (17.8%)
Urban <40.000	1,525 (38.7%)
Urban >40.000	1,714 (43.5%)
Subjective memory complaints and worries	572 (14.5%)
LIBRA-score[b]	−0.32 ± 2.2
LIBRA Risk factors	
Coronary heart disease	277/1,984 (14.0%)
Chronic renal disease	14/1,984 (0.7%)
Diabetes	133/1,984 (6.7%)
Obesity	325/1,984 (16.1%)
High cholesterol	461/1,984 (23.2%)
Hypertension	605/1,984 (30.5%)
Depressive feelings	193/1,984 (9.7%)
Physical inactivity	487/1,984 (24.5%)
Current smoking	90/1,984 (4.5%)
LIBRA Protective factors	
Alcohol (no or low/moderate)	1,159/1,984 (58.4%)
Healthy diet (Mediterranean)	1,365/1,984 (68.8%)
High cognitively active	1,728/1,984 (87.1%)
Past COVID-19-infection (yes)	252 (6.4%)
Fear of COVID-19-infection (yes)	1,248 (31.7%)

Data are presented as n/N (%) were N is the total number of participants with available data or mean ± SD.

[a] *Higher education represents higher professional education and university degrees and low-medium education completed primary school and/or lower/middle vocational education.*

[b] *LIBRA score was available for n = 1984, negative score represents more protective factors, and positive score more modifiable risk factors for cognitive decline.*

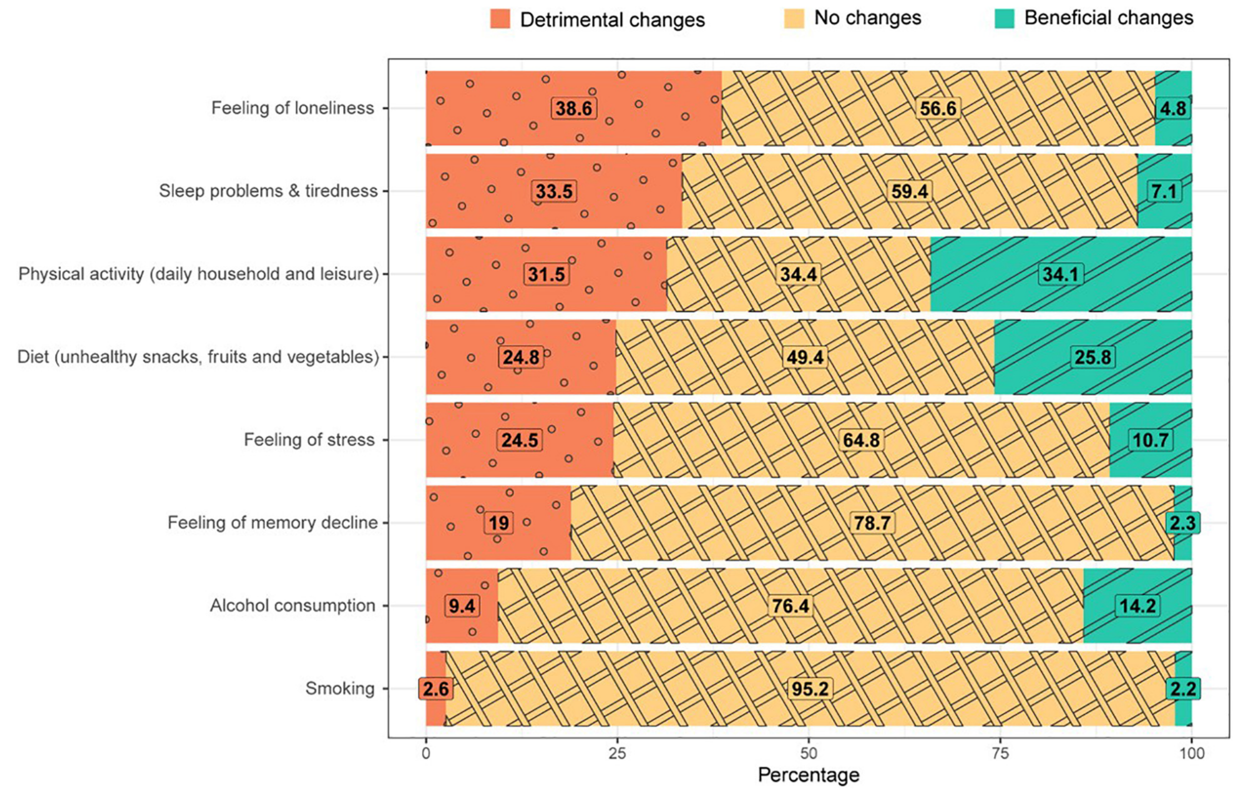

FIGURE 1 | Self-reported changes in percentages across eight modifiable factors related to brain health after one year of COVID-19 restrictions (n = 3943).

satisfied with their income; IRR = 1.38 [1.17–1.62]) and those living in an urban environment (compared to living in rural environment; IRR = 1.18 [1.08–1.29]) were also more likely to report more detrimental changes. When we evaluated the factors associated with beneficial changes (**Table 3**), we found that women (IRR = 1.16 [1.06–1.27]) and participants that reported fear of COVID-19 infection (IRR = 1.14 [1.06–1.24] were more likely to report beneficial changes. We found no other factors associated with beneficial changes (**Table 3**). As a *post hoc* analysis we conducted the multivariable analyses stratified by sex (see **Supplementary Tables 3, 4**), where living area, satisfactory financial situation (compared to a more than satisfactory financial situation), a current or past COVID-19 infection and high-risk for cognitive decline (measured by LIBRA) were associated with higher likelihood for reporting more detrimental lifestyle changes in women, but not in men.

Participants with high-risk for cognitive decline (in the upper tertile of LIBRA scores) were more likely to report a higher number of detrimental changes (IRR = 1.15 [1.03–1.28]) compared to participants with low-risk for cognitive decline (in the lowest tertile of LIBRA scores). For beneficial changes, participants with intermediate-risk on the LIBRA score reported less beneficial changes (IRR = 0.85 [0.75–0.96]). For participants with high-risk, we identified similar effect on trend level (IRR = 0.89 [0.78–1.00], p = 0.056).

Finally, when we conducted a sensitivity analysis, excluding participants with a current or past COVID-19 infection (n = 252) results remained essentially unchanged for detrimental changes (**Supplementary Tables 5, 6**). For beneficial changes, we additionally found that the likelihood for reporting more beneficial changes decreased (IRR = 0.89 [0.81–0.98]) for participants living alone.

DISCUSSION

After one year of COVID-19 pandemic and related restrictions in Netherlands, 72.3% respondents aged ≥50 reported at least one detrimental lifestyle change unfavorable for their brain health, while 60.5% reported at least one beneficial change. The most often reported detrimental changes were more feelings of loneliness (38.6%), more sleep problems (33.5%), and less physical activity (31.5%). Most frequently reported beneficial changes were more physical activity (34.1%), healthier dietary habits (25.8%), and less alcohol consumption (14.2%). Lower age, female sex, living alone and in urban environments, presence of subjective memory complaints, a current or past COVID-19 infection and fear of getting infected was associated with experiencing more detrimental changes in lifestyle. In contrast to our expectations, we found only few associations of social determinants with beneficial changes including female sex and fear of COVID-19 infection.

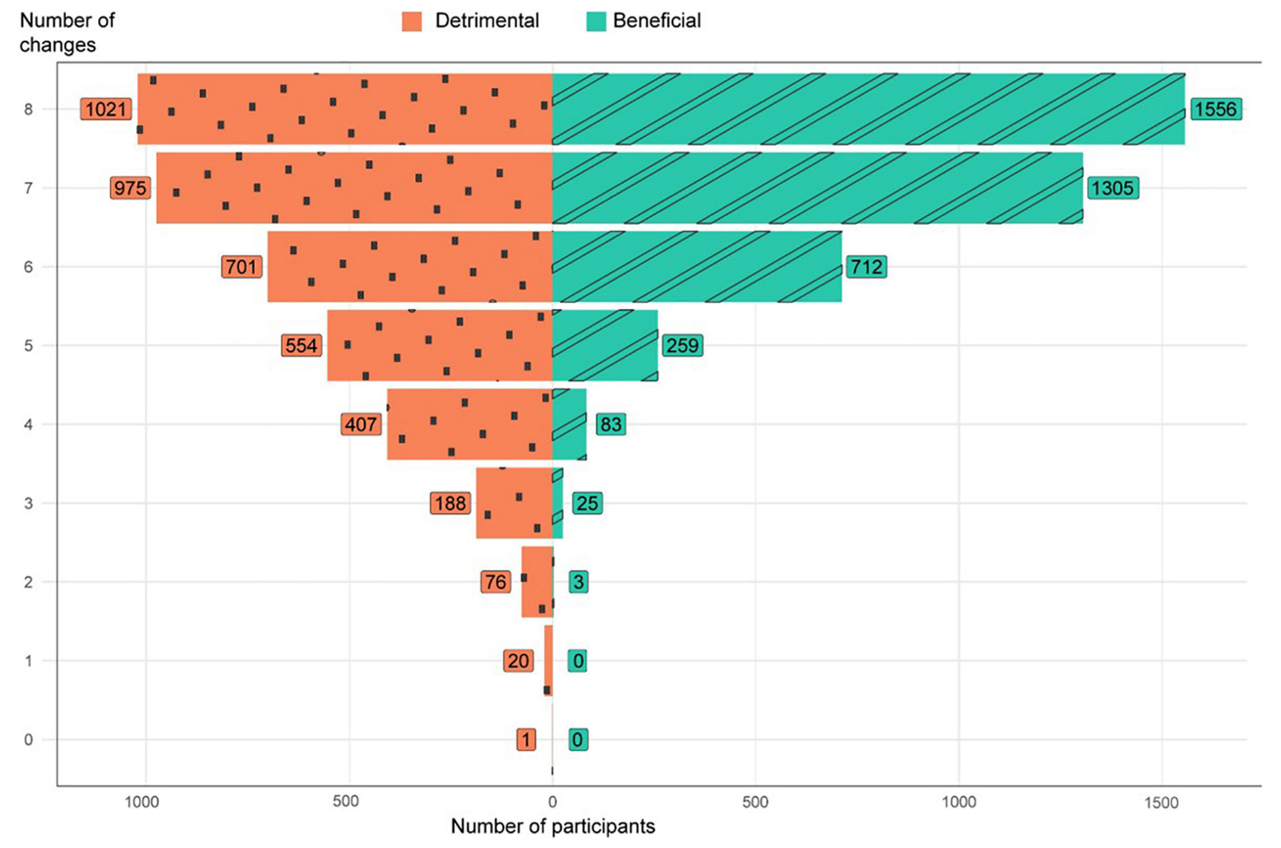

FIGURE 2 | Frequencies of participants reporting number of detrimental or beneficial changes on modifiable factors related to brain health after one year of COVID-19 restrictions (*n* = 3943).

Interestingly, women report both more detrimental and more beneficial lifestyle changes compared to men. In addition, women in our sample were more often employed compared to men (45% compared to 32%). Possible reasons why COVID-19 pandemic creates greater challenges especially for women may be that on average, women earn less money (30), and are more likely to work in healthcare (31), all of which could be expected to impose a greater burden during a pandemic and thereby influencing their ability to maintain a healthy lifestyle (32). On the other hand, our results also suggest that women seemingly do have the ability to improve their lifestyle during the pandemic. Alternatively, women might be likely to observe and report change. In order to draw conclusion about the motives of women changing their lifestyles, more research and qualitative studies are needed.

Fear of getting a COVID-19 infection was associated with increased likelihood of reporting more detrimental lifestyle and more beneficial lifestyle changes. Campaigns during COVID-19 pandemic primarily focus on fear appeal and solidarity with more vulnerable citizens. Previous research has reported that campaigns using fear appeal (33) and stressful life events with subsequent effects (34) can positively influence attitude, intentions, and behaviors. On the other hand, effects of prolonged fear may differ, and in a context of public health and economic uncertainty such the COVID-19 pandemic, fear appeal may also induce negative side effects among vulnerable individuals (21). Additionally, a cross-national survey conducted suggested that controlling fear response would help to improve health outcomes, however, they observed differences across countries emphasizing possible social, cultural and economic influences on fear response and health outcomes (16).

In line with other studies (12, 21), younger elderly are more prone to report higher number of detrimental lifestyle changes during the pandemic, which might be due to persistent difficulty of balancing work (21) and less work-related commute and social interactions, possibly causing stress and social isolation. Unhealthy lifestyle has been related to social determinants like education, income and physical environment (9, 12, 35, 36). More specifically, a previous study showed that those with lower social economic status had higher risk for dementia due to accumulation of modifiable health and lifestyle risk factors (measured by LIBRA) (37). This is in line with our findings, as we found that participants with lower income were more likely to report multiple detrimental changes. Participants with more modifiable health and lifestyle risk factors (measured by LIBRA) report a higher number of detrimental lifestyle changes during the COVID-19 pandemic, pointing at a potential further risk of cognitive decline and dementia. These results contribute to the

TABLE 2 | Univariable and multivariable analyses of the association of participant characteristics with multiple detrimental lifestyle changes.

	Model 1		Model 2	
	IRR [95% CI]	***p*-value**	**IRR [95% CI]**	***p*-value**
Age (years)[a]	**0.99 [0.98–0.99]**	**<0.0001**	**0.99 [0.98–0.99]**	**<0.0001**
Female[a]	**1.39 [1.29–1.49]**	**<0.0001**	**1.20 [1.11–1.30]**	**<0.0001**
Low-medium education	1.02 [0.96–1.09]	0.473	1.00 [0.93–1.07]	0.893
Professional status				
Unemployed	**1.19 [1.06–1.35]**	**0.004**	1.07 [0.94–1.22]	0.286
Employed	1.03 [0.94–1.13]	0.054	1.05 [0.96–1.16]	0.293
Retired	Ref		Ref	
Financial situation				
Unsatisfactory	**1.55 [1.35–1.79]**	**<0.0001**	**1.38 [1.17–1.62]**	**<0.0001**
Satisfactory	**1.26 [1.18–1.35]**	**<0.0001**	**1.21 [1.12–1.30]**	**<0.0001**
More than satisfactory	Ref		Ref	
Living alone (yes)	**1.24 [1.16–1.32]**	**<0.0001**	**1.20 [1.11–1.28]**	**<0.0001**
Living area, population density				
Rural	Ref		Ref	
Urban: small city <40.000	**1.17 [1.08–1.28]**	**<0.0001**	**1.13 [1.03–1.23]**	**0.011**
Urban: big city >40.000	**1.24 [1.14–1.34]**	**<0.0001**	**1.18 [1.08–1.29]**	**<0.0001**
Subjective memory complaints and worries	**1.49 [1.38–1.60]**	**<0.0001**	**1.40 [1.28–1.51]**	**<0.0001**
Current or past COVID-19 infection	**1.18 [1.05–1.32]**	**0.004**	**1.19 [1.06–1.34]**	**0.002**
Fear of COVID-19 infection	**1.36 [1.28–1.45]**	**<0.0001**	**1.33 [1.25–1.42]**	**<0.0001**
Health and lifestyle risk for cognitive decline (LIBRA score)[b]	**1.05 [1.03–1.07]**	**<0.0001**		**0.004**
Low-risk [<−1.6]	Ref		Ref	
Intermediate-risk [1.6 to 0.4]	1.08 [0.97–1.19]	0.166	1.07 [0.96–1.19]	0.250
High-risk [>0.4]	**1.24 [1.12–1.37]**	**<0.0001**	**1.15 [1.03–1.28]**	**0.011**

CI, confidence interval; IRR, incidence rate ratio; ref, reference category. In bold are statistically significant. Model 1, univariable models corrected for sex and age; Model 2, multivariable analysis (n = 3274) where all predictors were entered simultaneously.

[a] Variables are not corrected. [b] LIBRA score was analyzed as additional determinant in a subsample, Model 1 (n = 1981), univariable models corrected for sex and age; Model 2, multivariable analysis (n = 1697) where all predictors from model 1 were entered simultaneously.

notion the COVID-19 pandemic may amplify health inequalities in brain health and dementia risk (38, 39).

In a relatively young elderly sample (mean age 66 ± 8 years), we found that roughly a quarter reported more feelings of loneliness. Additional *post hoc* analysis showed that living alone was associated with reporting more often feelings of loneliness (data not shown). Also, those living in urban environments (compared to living in rural environment) reported more detrimental lifestyle changes. Therefore living conditions seem to be risk factors for more detrimental lifestyle changes, as in line with previous studies (9).

Moreover, pre-existent subjective cognitive complaints were associated with more detrimental changes in modifiable factors related to cognitive decline, suggesting that those at risk of dementia may further increase their dementia risk during the pandemic (40). In line with this observation, a previous Italian study of older adults with pre-existing cognitive problems (subjective cognitive decline or mild cognitive impairment) reported more lifestyle behaviors that are potentially harmful for future cognitive decline (41). These results emphasize the potential of lifestyle interventions, especially in those who are at-risk for cognitive decline and dementia.

In general, comparing impact of the COVID-19 pandemic on lifestyle across countries imposes challenges, since COVID-19 restrictions may differ over time, and different social and cultural aspects apply. Comparing our results to those of a study within Dutch individuals during the first wave (21), unhealthy changes were slightly more often reported by our study participants after one year of COVID-19-restrictions. Since restrictions were more severe during the second wave in October 2020 and February 2021 (closing of schools, non-essential shops and cultural- and sport facilities, and a curfew) compared to the first wave from March 2020 to July 2020, together with a prolonged exposure to the pandemic and related restrictions in our study, this may have influenced moral and motivation to improve or maintain a healthy lifestyle. When comparing results with findings of the World-Wide-FINGERS-SARS-CoV-2 survey carried out in a Finish population at risk for cognitive decline (FINGER participants) during the first wave, some proportions are similar for detrimental and beneficial changes (physical activity, dietary habits, memory complaints) while others seem to be higher in our study (feelings of loneliness, sleep problems, alcohol intake, and smoking) (9). This may imply that some factors deteriorate with longer duration of the pandemic, while others factors remain relatively stable or happened in a similar extent.

This study had several limitations; the assessment of lifestyle behavior was done online, relied on self-report surveys and retrospective assessment, and therefore not objective or validated.

TABLE 3 | Univariable and multivariable analyses of the association of participant characteristics with multiple beneficial lifestyle changes.

	Model 1		**Model 2**	
	IRR [95% CI]	***p*-value**	**IRR [95% CI]**	***p*-value**
Age (years)[a]	**1.38 [1.05–1.82]**	**0.026**	1.00 [1.00–1.00]	0.407
Female[a]	**1.14 [1.05–1.23]**	**0.002**	**1.16 [1.06–1.27]**	**0.001**
Low-medium education	0.96 [0.89–1.03]	0.245	0.98 [0.90–1.06]	0.571
Professional status				
Unemployed	0.94 [0.81–1.09]	0.430	0.91 [0.77–1.07]	0.244
Employed	1.06 [0.95–1.17]	0.308	1.06 [0.94–1.18]	0.344
Retired	Ref		Ref	
Financial situation				
Unsatisfactory	1.00 [0.83–1.20]	0.968	1.12 [0.91–1.37]	0.291
Satisfactory	0.95 [0.87–1.03]	0.192	0.93 [0.84–1.02]	0.119
More than satisfactory	Ref		Ref	
Living alone (yes)	0.93 [0.86–1.01]	0.086	0.93 [0.85–1.01]	0.088
Living area, population density				
Rural	Ref		Ref	
Urban: small city <40.000	1.00 [0.91–1.16]	0.944	1.01 [0.91–1.12]	0.891
Urban: big city >40.000	1.03 [0.97–1.16]	0.222	1.07 [0.96–1.19]	0.215
Subjective memory complaints and worries	0.98 [0.89–1.08]	0.698	1.00 [0.90–1.12]	0.938
Current or past COVID-19 infection	0.94 [0.82–1.08]	0.403	0.97 [0.84–1.12]	0.636
Fear of COVID-19 infection	**1.13 [1.05–1.22]**	**0.001**	**1.14 [1.06–1.24]**	**0.001**
Health and lifestyle risk for cognitive decline (LIBRA score)[b]	1.19 [1.07–1.33]	0.077	0.98 [0.96–1.01]	0.350
Low-risk [<−1.6]	Ref		Ref	
Intermediate-risk [−1.6 to 0.4]	**0.87 [0.77–0.97]**	**0.014**	**0.85 [0.75–0.96]**	**0.012**
High-risk [>0.4]	**0.89 [0.79–0.99]**	**0.039**	0.89 [0.78–1.00]	0.056

CI, confidence interval; IRR, incidence rate ratio; ref, reference category. In bold are statistically significant. Model 1, univariable models corrected for sex and age; Model 2, multivariable analysis (n = 3274) where all predictors were entered simultaneously.

[a]Variables are not corrected. [b]LIBRA score was analyzed as additional determinant in a subsample, Model 1 (n = 1981), univariable models corrected for sex and age; Model 2, multivariable analysis (n = 1697) where all predictors from model 1 were entered simultaneously.

Additionally, past or current COVID-19 infection was not validated with clinical records. The survey was widely distributed among a population sample, the voluntary approach may have led to a selection bias and consequently detrimental lifestyle changes may have been over reported. However, the online nature of the survey and the use of a nation-wide registry (24) allowed us to include a large sample of participants. Another limitation of this sample was that it was mainly female, highly educated and had a higher income compared to the general Dutch population, hence findings on average percentages reporting no, mainly beneficial or mainly detrimental change might not generalize. Due to our exploratory and cross-sectional approach, replication, follow-up and additional qualitative research is required to further explore the impact of COVID-19 pandemic and associations of social determinants with lifestyle changes. Lastly, The World-Wide-FINGERS-SARS-CoV-2 survey was not validated and a subset of questions was selected. Complete results of the survey will be combined with results of the same surveys conducted in other countries, and will be published elsewhere.

Among the strengths was that the study was conducted after a period of one year of COVID-19 restrictions in the Netherlands, thus capturing medium-long term health consequences rather than the initial response to the COVID-restrictions. Enduring unhealthy changes in lifestyle will be more detrimental, thus making our results more imperative. Furthermore, we focused on both detrimental and beneficial lifestyle changes. Additionally, to estimate the future risk of cognitive decline we used the LIBRA score, which is a well-validated measurement for predicting cognitive decline and higher dementia risk in various general population and patient-studies (42). Further, LIBRA focuses solely on modifiable risk factors, making participants with higher LIBRA scores especially susceptible for lifestyle changes and altering their future cognitive decline.

It has been suggested that the COVID-19 pandemic provides an opportunity for healthcare professionals to promote lifestyle change (43, 44). When regarding dementia risk, the general population is mostly unaware of its relation with lifestyle (45, 46). Our results show that the COVID-19 pandemic creates a window of opportunity for lifestyle intervention for the prevention of accelerated cognitive decline, especially for a specific population who seems to be more vulnerable for the detrimental changes in modifiable risk factors related to brain health during the COVID-19 pandemic. Therefore, providing evidence and motivation for health initiatives to (i) create awareness among health care professionals and the population about the relationship between lifestyle and dementia risk (e.g., by encouraging multi-domain lifestyle interventions to prevent cognitive decline), (ii) create (targeted) educational tools to promote/maintain a brain-healthy lifestyle, and (iii) implement health surveillance to monitor lifestyle changes during lockdowns, preferably using online technologies to fit to the current health care situation in the COVID-19 pandemic. As there has been little to no cost-benefit analysis prior to the introduction of governmental measures and restrictions during the COVID-19 pandemic, actual costs of health outcomes and lifestyle changes may become more apparent in the future. Additionally, for future lockdowns preventative strategies such as promoting a healthy lifestyle are important alternative options to fight the spread of disease or reduce the risk of severe complications or hospitalization due an infection, as it is a boost for one's individual natural resistance. Furthermore, from a broader public health perspective, preventive strategies are also very important to consider to reduce an individuals' risk of other non-communicable diseases for instance vascular and metabolic diseases.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical reasons. Data contains large amount of sensitive information and public data deposition may pose privacy concerns. Further, it is not possible as this dataset is part of an WW-FINGERS initiative. The study participants provided online informed consent for local analysis at Alzheimer Center Amsterdam and only to share pseudonymized data with WW-FINGERS partners. Requests to access the datasets should be directed to MZ, m.zwan@amsterdamumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medisch Ethische Toetsingscommissie VU Medisch Centrum. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements.

AUTHOR CONTRIBUTIONS

MZ and WF revised the study objectives. FM and MK provided the WW-FINGERS survey. LW and EB translated the survey and were responsible for data collection. MZ and LW interpreted the results. LW conducted the data analysis and wrote the manuscript. All authors critically revised the manuscript and contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.877460/full#supplementary-material

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ORIGINAL RESEARCH
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Psychological Resilience Among Older Japanese Adults With Mild Cognitive Impairment During the COVID-19 Pandemic

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Psychological resilience refers to the ability to cope with adversities, and deficits in resilience might lead to mental illness. The COVID-19 pandemic has had impact on psychological resilience for older adults, but there are as yet no data on its impacts on the mental health of older adults who were living with mild cognitive impairment (MCI). Therefore, the aim of this study was to investigate the impact of the COVID-19 pandemic on psychological resilience in older adults with MCI and to explore associated physical and psychosocial factors. In this cross-sectional study of 268 older adults aged 65–85, we defined MCI as age- and education-adjusted cognitive decline with a standard deviation of 1.0 or more from the reference threshold. During December 2020 to April 2021, we carried out to all participants the 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10) to measure psychological resilience. We also conducted a comprehensive geriatric assessment including sleep quality and depressive symptoms (Pittsburgh Sleep Quality Index and 15-item Geriatric Depression Scale, respectively). To identify factors associated with CD-RISC-10 scores (mean: 23.3 ± 0.4), multiple regression analysis revealed that older age [coefficient = 0.23, 95% confidence interval (CI) = 0.06–0.39] was significantly correlated with higher scores, whereas poor sleep quality (coefficient = −2.06, 95% *CI* = −3.93 to −0.19) and depressive symptoms (coefficient = −2.95, 95% *CI* = −5.70 to −0.21) were significantly correlated with lower scores. In this study, older adults with MCI showed low psychological resilience during the COVID-19 pandemic, and people with low psychological resilience indicated poor sleep quality and depressive symptoms. Our findings suggest directions for devising interventions to maintain mental health and psychological resilience among the vulnerable population of older adults with MCI living under the socially isolated conditions of COVID-19 pandemic restrictions. Our recommendation includes continuous assessment of this population and appropriate care for poor sleep quality and depressive symptoms.

Keywords: older adults, mild cognitive impairment, psychological resilience, CD-RISC-10, COVID-19, sleep quality, depressive symptoms

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began spreading in Japan in January 2020. Prevention measures such as social distancing effectively reduced new infections (1), but these measures severely restricted older adults' participation in physical, social, and community activities (2, 3). Although the number of participants was limited, the agitation, depression and anxiety of older adults with mild cognitive impairment (MCI) increased during lockdown (4). MCI or subjective cognitive decline showed decreased physical activity (43.4%) since the start of the lockdown, and there was an increase of 69.6% in the time spent sitting or lying down (5). These reports suggest that older adults with MCI have faced problems in mental health and physical activity during the COVID-19 pandemic.

Researchers found that isolation caused by infection prevention measures was linked to depression, anxiety, and cognitive decline as well as lower self-worth, which are factors involved in the concept of resilience (6).

Resilience is the ability to adapt positively in the face of adversity and maintain mental health (7), and it derives from a combination of genetic, biological, psychological, social, and cultural factors (8, 9). In one study before COVID-19, older adults showed higher psychological resilience than did young adults (10), although older adults with MCI showed lower resilience than did healthy older adults (11). High resilience is useful for recovering from stress (12), but some researchers found lower psychological resilience among adults during the pandemic compared with before (13–16). Given that older adults with MCI frequently showed mental health problems during the pandemic such as fear, anxiety, and frustration (17, 18), it is understandable that their psychological resilience would be affected as well. However, no researchers have yet investigated psychological resilience in older adults with MCI during the COVID-19 pandemic including factors related to their resilience. Therefore, we aimed with the present study to investigate these factors and the psychological resilience of older adults with MCI during the COVID-19 pandemic. Our identifying psychological resilience and these associated factors should help with developing effective mental health interventions for older adults with MCI.

METHODS

Study Design

We conducted this cross-sectional study as part of the World-Wide FINGERS SARS-CoV-2 survey (19) in World-Wide FINGERS (20), the global network of lifestyle intervention trials for dementia risk reduction and prevention. The 10-item version of the Connor-Davidson Resilience Scale (CD-RISC-10) (21) was used in the survey, which was conducted between December 2020 and April 2021, and a comprehensive geriatric assessment (CGA) in the present study was conducted between February 2020 and March 2021.

TABLE 1 | Demographic characteristics and comprehensive geriatric assessment results.

	All participants (*n* = 268)
Attribute information	
Age, mean ± SD	74.2 (5.0)
Female, *n* (%)	107 (39.9)
Marital status: married, *n* (%)	208 (77.6)
Living status: with someone, *n* (%)	242 (90.3)
Education, mean ± SD	12.5 (2.4)
Employment status: paid or self-employed, *n* (%)	59 (22.0)
Household income: *n* (%)	
< JPY 2,000,000	37 (13.8)
JPY 2,000,000–3,990,000	145 (54.1)
JPY 4,000,000–5,990,000	44 (16.4)
JPY 6,000,000–7,990,000	21 (7.8)
JPY 8,000,000–9,990,000	16 (6.0)
JPY 10,000,000–and above	5 (1.9)
Absolute alcohol, g/day, mean ± SD	8.6 (15.9)
Current smoker, *n* (%)	17 (6.3)
Polypharmacy, *n* (%)	80 (29.2)
One or more medical conditions, *n* (%)	211 (78.7)
Physical performance and lifestyle	
Physical frailty: *n* (%)	
Not frail	113 (50.9)
Prefrail	97 (43.7)
Frail	12 (5.4)
Barthel Index, median (IQR)	100 (100, 100)
Lawton Index	
Women, median (IQR)	8 (8, 8)
Men, median (IQR)	5 (5, 5)
EQ-5D, mean ± SD	0.9 (0.1)
MNA-SF, median (IQR)	13 (12, 14)
PSQI: poor sleep quality, *n* (%)	74 (27.6)
Social participation, cognitive function, and mental health	
LSNS-6: socially isolated, *n* (%)	74 (27.6)
Social participation, mean ± SD	1.4 (1.3)
MMSE, median (IQR)	28 (26, 29)
CD-RISC-10, mean ± SD	23.3 (0.4)
GDS: depressive symptoms, *n* (%)	29 (10.8)

CD-RISC-10, 10-item Connor-Davidson Resilience Scale; EQ-5D, EuroQol-5Dimensions; GDS-15, 15-item Geriatric Depression Scale; LSNS-6, Lubben Social Network Scale-6; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment Short-Form; PSQI, Pittsburgh Sleep Quality Index.

Participants

We recruited all participants from the Japan-multimodal intervention trial for prevention of dementia (J-MINT) conducted by the National Center for Geriatrics and Gerontology (NCGG) in Aichi Prefecture (22). The inclusion criterion of this study was older adults with MCI in the age group of 65–85 years. The diagnosis of MCI was made using the NCGG Functional Assessment Tool (FAT), which has been established as a screening tool for older adults at high risk of incident dementia (23, 24). All participants had age- and education-adjusted cognitive decline with a standard deviation (SD) of 1.0 or more from the reference threshold on at least one of the four cognitive domains of memory, attention, executive function, and processing speed as measured by the NCGG-FAT. The exclusion criteria were older adults diagnosed with dementia and having a Mini-Mental State Examination (MMSE) (25) score of < 24 points at baseline; respondents who self-reported a diagnosis of depression and those who had missing data on the CD-RISC-10 were excluded. Of 361 J-MINT participants at the NCGG, 298 took part in the present study. This study was approved by the NCGG Ethics Committee, and all participants underwent informed consent procedures prior to enrolling in the study, all participants gave their consent for participation in the study.

Measurements

Demographic Characteristics

We collected participants' demographic information (age, sex, marital status, living status, years of education, employment status, household income, absolute alcohol consumption per day, smoking status, polypharmacy, and self-reported medical history) by questionnaire. The response options for household income were in increments of JPY 2,000,000, and for self-reported medical history, we asked about the following diseases: diabetes, hypertension, dyslipidemia, atrial fibrillation, congestive heart failure, chronic kidney disease, liver disease, cerebrovascular disease, malignant tumor, thyroid disease, coronary artery disease, neurodegenerative disease, depression and insomnia. For our analyses, the self-reported medical history was divided no medical condition or one or more.

CD-RISC-10

We used the CD-RISC-10 score to evaluate respondents' psychological resilience. Respondents rate each item on a scale from 0 (not true at all) to 4 (true nearly all the time), so that the total score ranges from 0 to 40. Higher scores reflect greater psychological resilience.

Comprehensive Geriatric Assessment

To explore factors related to the older adults' psychological resilience in this study, we conducted a CGA, a inclusive method of assessing psychological and functional capability of older adults (26). For all participants, the CGA consisted of measuring physical performance, lifestyle, social participation, mental health, and cognitive function with the following full test battery: (1) We used the frailty phenotype proposed by Fried et al. (27), in the Cardiovascular Health Study to measure physical frailty (not frail, prefrail, or frail). (2) We used the Barthel Index (28) to assess basic activities of daily living (ADLs); this scale ranges from 0 to 100, with 100 points indicating complete independence. (3) We measured instrumental ADLs using the Lawton Index, for which perfect scores are 5 for men and 8 for women (29). (4) We used the EuroQol 5-Dimension (EQ−5D) to measure health-related quality of life. The scores for the five EQ-5D dimensions are combined to obtain up to 3,125 possible health states, from which a signal index (utility) score is computed; one score indicates better health status (30). (5) We measured the older adults' nutritional status with the Mini-Nutritional Assessment Short-Form (MNA-SF) (31), which consists of six items (score range: 0–14 points, normal ≥ 12). (6) Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI); the score ranges from 0 to 21, and a score of 6 or higher indicates poor sleep quality (32). (7) We used the Lubben Social Network Scale-6 (LSNS-6) to measure participants' social networks and connections (33); the LSNS-6 consists of six items, the score ranges from 0 to 30, and scores of 11 or lower indicate social isolation. (8) We measured social participation by asking participants if they belonged to any of eight types of organizations presented in a list (34). (9) We based global cognitive functioning on the MMSE scores, which ranged from 0 to 30. (10) We conducted the 15-item Geriatric Depression Scale (GDS) to measure depression; the score ranges from 0 to 15, and higher scores indicate depressive symptoms (35). For the Japanese version of the GDS, 7 or more points indicates depressive symptoms (36).

Statistical Analysis

All participants' demographic information is expressed as mean ± SD, median and interquartile range (IQR) or number of people and percentage. We used simple regression to analyze the associations between the CD-RISC-10 and each CGA variable, and we used multiple regression to analyze the CD-RISC-10-variable relationships that were statistically significant in the simple regressions, with the CD-RISC-10 score as the response variable and the statistically significant variables as explanatory variables. Moreover, we entered sex and education, which were related to psychological resilience in a previous study (16), as confounding variables. We conducted all analyses in Stata 16.1 (Stata Corp, College Station, TX, United States) and set $P < 0.05$ as statistically significant.

RESULTS

Of 298 original participants, 279 responded to the questionnaire of the CD-RISC-10 between December 2020 and April 2021 (response rate: 93.6%). From those 279, we excluded six respondents who self-reported depression and five whose CD-RISC-10 responses were incomplete, which left the data on 268 participants for the analysis. **Table 1** shows the demographic characteristics of the participants in this study. The mean CD-RISC-10 score was 23.3 points.

Simple regression analysis showed that higher CD-RISC-10 score was significantly associated with older age and higher household income and lower score was related to social isolation, depressive symptoms, and poor sleep quality (**Table 2**). The CD-RISC-10 score was not associated with sex, marital status, living status, years of education, employment status, absolute alcohol consumption per day, smoking status, polypharmacy, or one or more medical conditions. In the multiple regression analysis of all statistically significant variables from the simple regressions, older age (coefficient = 0.23, 95% *CI* = 0.06–0.39) was related to higher CD-RISC-10 score, and depressive symptoms (coefficient = −2.95, 95% *CI* = −5.70 to −0.21) and poor sleep quality

TABLE 2 | Simple and multiple regression analysis results for psychological resilience.

	Simple regression analysis		Multiple regression analysis	
	Coefficient	**95% CI**	**Coefficient**	**95% CI**
Age	0.22	0.05 to 0.39*	0.23	0.06 to 0.39**
Sex: female	−1.22	−2.95 to 0.52	−1.14	−2.91 to 0.62
Marital status: married	−0.01	−2.05 to 2.04	–	–
Living status: with someone	0.11	−2.77 to 2.99	–	–
Education	0.09	−0.27 to 0.45	0.02	−0.35 to 0.39
Employment status: paid or self-employed	1.58	−0.47 to 3.63		
Household income	0.12	−2.07 to 2.31*	0.53	−0.23 to 1.30
Absolute alcohol	0.04	−0.01 to 0.09	–	–
Smoking: current smoker	0.53	−2.97 to 4.02	–	–
Polypharmacy	1.03	−0.84 to 2.91	–	–
One or more medical condition	1.46	−0.61 to 3.54	–	–
Physical frailty				
Prefrail (vs. not frail)	0.27	−1.63 to 2.18	–	–
Frail (vs. not frail)	−0.12	−4.29 to 4.06	–	–
Barthel Index	−0.08	−0.36 to 0.20	–	–
Lawton Index	−0.39	−0.95 to 0.16	–	–
EQ−5D	4.81	−3.72 to 13.3	–	–
MNA-SF	−0.12	−0.64 to 0.40	–	–
PSQI: poor sleep quality	−2.84	−4.71 to −0.97**	−2.06	−3.93 to −0.19*
LSNS-6: social isolation	−2.12	−4.00 to −0.23*	−1.72	−3.67 to 0.22
Social participation	0.40	−0.24 to 1.05	–	–
MMSE	−0.43	−0.90 to 0.04	–	–
GDS: depressive symptoms	−4.04	−6.74 to −1.34**	−2.95	−5.70 to −0.21*

**$P < 0.05$. **$p < 0.01$.*

In multiple regression analysis, sex and education were entered as confounding variables. CD-RISC-10, 10-item Connor-Davidson Resilience Scale; EQ-5D, EuroQol-5Dimensions; GDS-15, 15-item Geriatric Depression Scale; LSNS-6, Lubben Social Network Scale-6; MMSE, Mini-Mental State Examination; MNA-SF, Mini-Nutritional Assessment Short-Form; PSQI, Pittsburgh Sleep Quality Index.

(coefficient = −2.06, 95% *CI* = −3.93 to −0.19) were associated with lower score (**Table 2**). The CD-RISC-10 score was not associated with sex, years of education, household income, or LSNS-6 scores.

DISCUSSION

Older adults with MCI had frequent mental health problems during the COVID-19 pandemic (17, 18), psychological resilience is also possibility to be affected, but no previous researchers have investigated the psychological resilience during COVID-19 of older adults who were living with MCI. With the present study, therefore, we clarified psychological resilience in this population, and we identified a number of relevant correlations as below.

The older adults in this study showed a mean CD-RISC-10 score of 23.3 points, which contrasted with scores of 31.7 and 31.1 points in, respectively, adults age 18 or older and older adults who had good cognitive function (16, 37). Researchers who measured resilience with a different test from the CD-RISC-10 found low resilience among older adults with cognitive impairment (11). Moreover, in a previous study during the COVID-19 pandemic, the mean CD-RISC-10 score for older adults was 28.4 points (14). Although we cannot directly compare the mean CD-RISC-10 score from the present study with the scores from previous studies, our findings do suggest lower psychological resilience among older adults with MCI during the pandemic; the mean score in the present study was similar to the mean of 23.6 points that other researchers found for veterans with post-traumatic stress disorder and depression (38). Owing to the nature of cross-sectional studies, we could not describe the pandemic's specific impacts on psychological resilience. However, given that resilience indicates stress coping ability (15, 16), our findings suggest that the major stress from the COVID-19 infection prevention and control measures in Japan put older adults with MCI at high risk for adverse health outcomes.

Many previous researchers reported that psychological resilience was related to age, sex, education level, financial situation, sleep quality, and depressive symptoms (10, 16, 37, 39–41), but we did not find associations with sex or education level. Researchers have reported conflicting results of higher resilience among men, higher resilience among women, and no gender differences (42–44), and other scholars found that higher levels of education were related to higher resilience (16). In our study, participants had a mean education level of 12.5 ± 2.4 years, and the group differences were small, which is likely why we did not find the association between education level and psychological resilience. We also found in the present study an association between high CD-RISC-10 score and older age, which supported earlier findings from reports on psychological resilience and age of higher psychological resilience among older adults than among adults who were middle-aged and younger (10, 39).

Some investigators found significant associations between good sleep quality and high resilience among adults aged 60 years or younger (40, 41), and we also found this significant association. Researchers identified poor sleep quality in respondents with a mean age of 35 during the COVID-19 pandemic (45), and there was another report of increased sleep latency, a component of sleep quality, during the pandemic compared with before (46). It was suggested that people with low psychological resilience are at risk of poor quality during the pandemic.

We also found in the present study a correlation between lower psychological resilience and depressive symptoms, which supported Gerino et al.'s (47), reporting that high resilience contributed to less anxiety and depression. Some people who experience prolonged stress develop psychiatric disorders such as depression, whereas many people can maintain normal psychological functioning through stress, and resilience might be a factor in this normal functioning (48). Researchers found higher prevalence of depressive symptoms among adults during COVID-19 than before (49), and in our study, older adults with depressive symptoms also had low psychological resilience, which would interfere with their coping capacities.

In simple regression analysis in this study, higher household income was related to higher psychological resilience, and social isolation was related to lower resilience. Higher incomes allow for more comfortable and secure lives (50), social ties play a beneficial role in maintaining psychological wellbeing (51), those could be related to higher resilience.

There were some limitations in the present study. First, we collected the data of the CD-RISC-10 for this study between December 2020 and April 2021, but Aichi Prefecture, where NCGG is located, was under a state of emergency from mid-January to February 2021; participants responded to our study questionnaire in different infection statuses, and our analyses did not reflect these differences. In addition, we did not include a control group in the present study, and sampling was not random; therefore, our results have limited generalizability to broader populations. To our advantage, however, we were able to collect data on many older adults with MCI in a short period of time because we recruited from individuals who were already participating in the ongoing J-MINT study. In an additional limitation, we conducted a cross-sectional study, and thus, we could not measure changes in psychological resilience over the course of the pandemic; future study needs to conduct longitudinal investigations of changes in psychological resilience over the course of and following the COVID-19 pandemic.

The World Health Organization declared COVID-19 a pandemic in March 2020, and it is ongoing as of this writing. Because it shows signs that its abatement will be slow, it is and will be necessary for involved stakeholders to attempt to minimize long-range impacts on populations affected. This study suggested particularly impact of psychological resilience on older adults with MCI. We found correlations in this study between sleep quality, depressive symptoms, older age, and psychological resilience, and we expect these findings to be useful in developing interventions to provide ongoing support to older adults with MCI who are at risk of poor mental health outcomes. We also recommend continuous assessment of these older adults to help them maintain optimal sleep quality and minimize their depressive symptoms during COVID-19 pandemic restrictions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the NCGG Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NM and TSu designed the study. NM performed statistical analyses and wrote first draft. NM, TSu, YKu, KU, YKi, HA, and TSa contributed to the interpretation and discussion of results and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Dementia and Mental Health During the COVID-19 Pandemic: A Systematic Review

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Objectives: The COVID-19 pandemic raised significant concerns related to the management of care for people with dementia, but few studies have examined the mental health of older adults with dementia and their caregivers during the pandemic, when compared to other populations. This systematic review thus aims to compare and discuss the impact of the COVID-19 pandemic on people with dementia and on their caregivers' mental health.

Methods: A search was performed in the PubMed/Medline and ISI databases according to the PRISMA methodology. We included studies published in 2020 and 2021 with the following combinations of keywords: "COVID-19 and mental health and elderly," "COVID-19 and mental health and dementia;" "COVID-19 and dementia and caregivers," "pandemic and mental health and elderly," and "pandemic and anxiety."

Results: Twenty-two studies were included. Technology has proven to be an essential ally during the pandemic, since all 22 studies performed remote data collection. Nearly all the studies emphasized that social isolation and withdrawal can lead to the emergence or increase of neuropsychiatric symptoms and motor difficulties. However, the findings were mixed concerning the pandemic's impact on the cognition of people with dementia. Caregivers also suffered from the pandemic's impact, experiencing an increase in the burden of care and symptoms of stress, depression, and anxiety. Few studies suggested measures to alleviate the difficulties of people with dementia and their caregivers. There are reports of the benefits of technology in communication and treatment through teleconsultations, however, not everyone has access to such technology, making it difficult to disseminate this tool to the target population.

Conclusions: The studies generally showed that social isolation can increase motor deficits and neuropsychiatric symptoms and caregivers' burden and anxiety. New avenues for care and intervention are thus needed for older adults with cognitive deficits and their caregivers to avoid the intensification of physical and psychological suffering. Technological initiatives and support should consider people with cognitive impairment and different levels of technology literacy.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/.

Keywords: COVID-19, dementia, anxiety, mental health, depression, caregiver

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INTRODUCTION

In late 2019, the novel coronavirus SARS-CoV-2 was identified as the cause of COVID-19, a respiratory disease with varying individual severity. In March 2020, as the disease was spreading worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic. Research and experience have shown that COVID-19 severity and case-fatality are associated with the individual's age and immune status (1). Older age is thus considered a risk factor. The mortality rate is higher in the elderly due to several characteristics such as comorbidities, lower antibody levels, and polypharmacy, among others (2). Various governmental guidelines on COVID-19 have thus focused on older adults (3).

Social isolation is a useful measure for controlling the spread of infectious diseases or protecting high-risk groups from negative health outcomes. However, social isolation can also result in sedentary behavior, which is detrimental to the prevention of physical, psychological, and social health problems (4). In older adults, social isolation can increase the risk of depression, anxiety, and suicide, with considerable impact on quality of life, burden of care, and use of resources. For example, Rana (5) described five reported cases of older adults who committed suicide due to recurrent depressive disorder. Older adults already suffering from mental disorders have been more vulnerable to COVID-19 and its social consequences (5).

Social isolation is difficult for people with dementia and their caregivers in this context. According to Dourado et al. (6), COVID-19 raised significant concerns in the management of care for people with dementia. This age group has experienced limited access to services and activities, resulting in aggravation of cognitive deficits, affecting such domains such as memory and orientation, besides behavioral impairments. Social isolation can also exacerbate preexisting stress, overburden, and depression in caregivers (6).

The pandemic has further aggravated the vulnerability of older adults, especially those with neurocognitive disorders such as Alzheimer's disease. For example, dementia can increase the risk of contracting COVID-19, due to difficulties in understanding or remembering the need for social isolation (6). The COVID-19 pandemic also involves caring for people with dementia and support from community centers for this patient population, when such centers are experiencing difficulties continuing their work (6). The main objective of this systematic review was thus to better understand the impacts of the COVID-19 pandemic on people with dementia and on their caregivers' mental health.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (7). The literature search was carried out from August 5 to 26, 2021, using the following electronic databases: Medline (PubMed) and Science Citation Index (Institute for Scientific Information – ISI). Based on Medical Subject Headings (Mesh), the search keywords included "COVID-19," "pandemic," "mental health," "dementia," "caregivers," and "elderly" in the following combinations: "COVID-19 and mental health and elderly," "COVID-19 and mental health and dementia," "COVID-19 and dementia and caregivers," "pandemic and mental health and elderly," and "pandemic and anxiety."

The search was performed according to the following PICOS:

Population: older adults
Intervention: COVID-19; social isolation
Control: older adults with dementia; caregivers of people with dementia
Outcome: mental health, stress, depression, anxiety, neuropsychiatric symptoms, cognition
Study design: a review of cross-sectional, longitudinal, randomized, nonrandomized, and case-control studies.

Inclusion criteria were: (1) publications from 2020 to 2021, (2) only studies with older adults with cognitive impairment and/or their caregivers, (3) research on people with dementia (cognition, neuropsychiatric symptoms, and functionality) and their caregivers' mental health (burden, anxiety, and depression) during the COVID-19 pandemic, and (4) publications in the English language. The exclusion criteria were: (1) studies published prior to 2020 and (2) mental health studies during the COVID-19 pandemic without people with dementia and/or their caregivers.

Study Selection

First Step

Two independent reviewers performed initial article screening by reading the titles and abstracts. Reviewers excluded articles that failed to meet the eligibility criteria and retained those that were possibly eligible. In cases where there was no clear consensus between the reviewers, the article remained among those potentially eligible and moved on to the next phase of eligibility assessment. A third independent reviewer (IL) resolved disagreements between reviewers.

Second Step

The full texts of articles selected in the first phase were read by two independent reviewers to verify eligibility. In this phase, the primary reasons for excluding articles were recorded in the PRISMA article selection flowchart.

Third Step

All selected articles were submitted to the Mixed Methods Appraisal Tool (MMAT), version 2018 (8), a critical quality appraisal tool for scientific studies. The MMAT establishes corresponding criteria for each research method, and scores are rated from one to five, considering the description of each stage of the method's implementation.

This systematic review was recorded in the International Prospective Register of Systematic Reviews (PROSPERO), CRD42021276339.

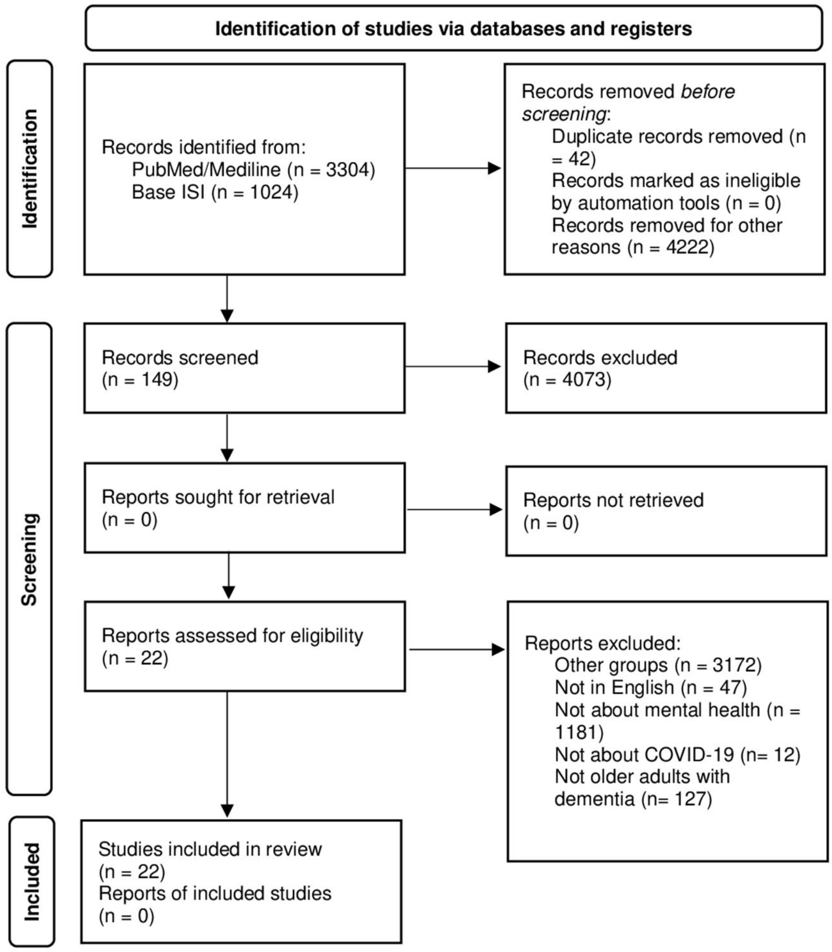

FIGURE 1 | Flow chart describing data extraction.

RESULTS

Initially, 4,328 records were identified through the database searches: 3,304 in PubMed/Medline and 1,024 in ISI. The 149 studies that remained after application of the exclusion criteria were retrieved for potential use, and the information of the full-text version of each study was evaluated. The reference lists of all selected articles were cross-referenced. After duplicates were removed, the total number of studies decreased to 22. **Figure 1** provides a flowchart of the different study selection phases. The included studies are shown in **Table 1**.

Participants

Some studies were only carried out in individuals with cognitive impairment (9–16). The types of dementia in the studies included Alzheimer's disease (9, 11, 14, 16–21), mixed dementia (20), vascular dementia (20), Lewy body dementia (20), Parkinson's disease (22–26), and frontotemporal dementia (20). Several studies focused only on caregivers' health and burden (12, 13, 16–18, 27–30).

Study Designs

Most of the studies used quantitative designs: one prospective study (22), one retrospective descriptive study (11), one longitudinal survey (12) and 16 cross-sectional studies (9, 10, 13–21, 23–30). There were also three qualitative studies (15, 28, 30). Based on the MMAT criteria, eight studies were classified as displaying high methodological quality (10, 12, 15, 18, 24, 28, 30).

Several cross-sectional studies (16, 17, 20, 21, 29) used caregivers' reports to evaluate changes before and during the pandemic. One study compared people with Parkinson's disease to controls (24). Some studies (18, 27) used online surveys targeted to groups dedicated to people with dementia and/or caregivers, online newspapers, and caregivers' associations. A single study (10) included community-dwelling seniors enrolled in a suspended randomized controlled trial. Some studies (14, 25, 26) included participants that had a previous evaluation as a normal procedure included in their unit. One study (23) consecutively enrolled participants who had a scheduled medical visit during COVID-19 lockdown. Another study (9) used data from databases and previous research from laboratories and clinics to assess measures before social isolation; during the

TABLE 1 | Selected studies.

Author/year	Country/ study design/ participants	Objective	Results	Quality assessment
El Otmani et al. (22)	Morocco/ prospective/50 people with PD	Determine the impacts of the pandemic on depression and anxiety in people with PD.	After 6 weeks of confinement, there was no statistically significant difference in either depression or anxiety compared to the first evaluation.	****
Gan et al. (11)	China/ retrospective descriptive/205 elderly people with cognitive impairment	Investigate cognitive and neuropsychological changes as well as proportions of rapid cognitive decline before and during the COVID-19 pandemic.	There was no significant difference in dementia severity scores or the proportions of neuropsychiatric symptoms between the initial and final evaluations. The scores on the C-MMSE, MoCA, ADLs, and global NPI differed significantly between baseline and follow-up evaluations after almost 14 months.	****
Giebel et al. (12)	United Kingdom/ Longitudinal/223 older adults, 285 caregivers and 61 PLWD	Explore how social support services and mental well-being for older adults, carers, and people with dementia changed over the first 3 months since the start of the pandemic.	Social support service usage dropped shortly after lockdown measures were imposed at T1, then increased again by T3. Access to paid care was least affected by COVID-19. Cases of anxiety dropped significantly across the study period, while cases of depression increased. Well-being increased significantly for older adults and PLWD from T1 to T3.	*****
Hanna et al. (28)	United Kingdom/ Qualitative/ 15 unpaid caregivers, 1 ex-caregiver, and 4 PLWD	Explore the change in impact of COVID-19 public health measures on the mental wellbeing of people with dementia and unpaid caregivers.	Loss of social support services was key in impacting this cohort mentally and emotionally, revealing the need for better psychological support for both caregivers and PLWD.	*****
Morii et al. (24)	Japan/ Cross-sectional/ 88 patients and their family members, 44 with Parkinson's disease, and 44 controls	Investigate the impact of social restrictions during the COVID-19 pandemic on neuropsychiatric symptoms in PD patients and identify risk factors associated with these symptoms.	PD patients may be more likely to develop clinical depression than those without PD in the presence of social stressors such as a pandemic, even in Japan where no legal penalties were imposed during the state of emergency.	*****
Manini et al. (20)	Italy/ cross-sectional/ 94 elderly people with dementia	Assess the impact of prolonged lockdown on behavioral and psychological symptoms of dementia.	Mean total NPI score before March 9 was 9.0 (SD 5.0), whereas the caregiver distress scale showed a mean score of 4.5 (SD 3.0). Scores increased respectively to 11.5 (9.0) and 5.5 (5.0) during nationwide lockdown.	****
Portacolone et al. (15)	USA/ Qualitative/ Adults aged 55 and older with cognitive impairment, living alone	Assess how older adults with cognitive impairment are coping with the pandemic.	The pandemic highlighted the precarity and unmet needs of older adults with cognitive impairment living alone. Findings underscore the need to expand access to home care and mental health services for this population.	*****

(Continued)

TABLE 1 | Continued

Author/year	Country/ study design/ participants	Objective	Results	Quality assessment
Tsapanou et al. (16)	Greece/ Cross-sectional/ 204 caregivers, 36 MCI, 58 all-stage dementia.	Analyze the impact of COVID-19 pandemic on older adults with MCI/dementia and their caregivers.	There was a significant overall decline for people with MCI/dementia in communication, mood, movement, and compliance with lockdown measures. Caregivers showed a major increase in their psychological and physical burden.	****
Altieri et al. (27)	Italy/ Cross-sectional/ 84 caregivers of people with dementia	Assess the psychological impact of the pandemic and COVID-19 social isolation on caregivers of people with dementia.	Multivariate analysis of variance revealed an effect of time (before and during lockdown) in the whole group on depression scores; a significant interaction between time and resilience was found on anxiety scores, where caregivers with high resilience showed a more significant increase in anxiety levels during lockdown than caregivers with low resilience. Caregiver burden was associated negatively with resilience scores and positively with higher functional dependence.	****
Barguilla et al. (9)	France/ Cross-sectional/ 60 people mild cognitive decline and dementia	Describe the influence of restrictive measures on patients with mild cognitive decline and dementia evaluating SARS-CoV-2 infection, changes in routines, cognitive decline, neuropsychiatric symptoms, delirium, falls, caregiver stress, and access to healthcare.	70% of patients abandoned previous daily activities, 60% had cognitive decline reported by relatives/caregivers, 15% presented delirium episodes, and 13% suffered increased incidence of falls. Caregivers reported increased burden in 41% of cases and burnout in 11% of cases. 16% reported difficulties accessing medical care, 33% received medical assistance via telephone, 20% needed emergency care, and 21% had changes in psychopharmacological therapies.	****
Boutoleau-Bretonnière et al. (17)	France/ Cross-sectional / 38 participants with clinical diagnosis of probable AD	Investigate the effects of confinement during COVID-19 on neuropsychiatric symptoms in patients with AD.	Only ten of 38 patients showed neuropsychiatric changes during confinement. Cognitive function of these ten patients, assessed with the Mini-Mental State Examination, was worse than that of patients who did not show neuropsychiatric changes. Duration of confinement correlated significantly with severity of symptoms as well as with their caregivers' distress.	****
Boutoleau-Bretonnière et al. (21)	France/ Cross-sectional/ 78 caregivers of people with bvFTD and AD	Investigate the impact of home confinement during COVID-19 on the burden of caregivers of bvFTD or AD patients.	22 bvFTD caregivers and 14 AD caregivers experienced an increase in burden. For bvFTD caregivers, this increased burden occurred regardless of behavioral changes, while AD caregivers experienced increased burden related to changes in patients' neuropsychiatric symptoms.	****
Cohen et al. (18)	Argentina/ Cross-sectional/ 119 individuals with AD and related dementia and their families	Study to what extent social isolation affected behavioral symptoms in persons with dementia after the first 8 weeks of quarantine.	Symptoms of anxiety, depression, and sleep disorders were reported in 33, 12.8, and 14.7% of the sample, respectively. New onset of behavioral symptoms or exacerbation of preexisting behavioral symptoms showed positive correlation with patient age and with presence of anxiety reported before	*****

(Continued)

TABLE 1 | Continued

Author/year	Country/ study design/ participants	Objective	Results	Quality assessment
			the epidemic and negative correlation with the global CDR score and the memory, community affairs, and home and hobby domains of CDR.	
Di Santo et al. (10)	Italy/ Cross-sectional/ 126 community-dwelling seniors with MCI or SCD	Explore the effects of COVID-19 and quarantine measures on the lifestyles and mental health of older adults at increased risk of dementia.	Over 1/3 of the sample reduced their physical activity and nearly 70% reported an increase in idle time. Adherence to the Mediterranean diet decreased in almost 1/3 of respondents, and over 35% reported weight gain. Social activities were abolished and 1/6 of participants also decreased productive and mentally stimulating activities. There was a significant association between depression and living alone or having poor relations with cohabitants and between anxiety and SCD, cold or flu symptoms, and reduction in productive and leisure-time activities.	*****
El Haj et al. (19)	France/ Cross-sectional/ 58 participants with clinical diagnosis of probable AD	Investigate the effects of measures against COVID-19 on the mental health of people with AD living in nursing homes.	Participants reported higher levels of depression and anxiety during the COVID-19 pandemic compared to data collected before the pandemic.	****
Goodman-Casanova et al. (13)	Spain/ Cross-sectional/ 93 people with MCI or mild dementia and their caregivers	Explore the impact of confinement on the health and well-being of community-dwelling older adults with MCI or mild dementia.	Health status was found to be optimal in 96% of respondents with no COVID-19 symptoms. Participants living alone reported greater negative feelings and more sleep problems. Concerning leisure-time activities, 57% respondents took walks, 35% played memory games, 60% watched TV, and 98% telephoned relatives.	****
Janiri et al. (23)	Rome/ Cross-sectional/ 134 individuals with Parkinson's disease	Identifying risk/protective factors associated with subjective worsening of psychiatric symptoms during COVID-19 in a sample of individuals with PD 65 years or older.	101 participants reported lifetime psychiatric symptoms. Among these, 23 displayed subjective worsening of psychiatric symptoms. In this group, the most frequent symptom was depression (82.6%), followed by insomnia (52.2%). Subjective worsening of neurological symptoms and lifetime irritability, together with younger age and female sex, were specific risk factors for worsening of psychiatric presentation. Lifetime preexisting delusions, having received antipsychotics, and not having received mood stabilizers were also associated with subjective worsening of psychiatric symptoms during the COVID-19 pandemic.	****

(Continued)

TABLE 1 | Continued

Author/year	Country/ study design/ participants	Objective	Results	Quality assessment
Lai et al. (29)	China/ Cross-sectional/ 60 caregivers of people with dementia	Evaluate whether supplementary telehealth via video-conferencing platforms could bring additional benefits for individuals with NCD and their spousal caregivers at home.	Supplementary telemedicine averted deterioration in the Montreal Cognitive Assessment, evident in the telephone-only group. It also reversed the downward trend in quality of life observed in the telephone-only group. Varying degrees of improvements in physical and mental health, perceived burden, and self-efficacy were observed among caregivers in the video-conferencing group, which were absent in the telephone-only group.	****
Lara et al. (14)	Spain/ Cross-sectional/ 40 people diagnosed with MCI or mild AD	Analyze the pandemic's impact on the neuropsychiatric symptoms of people with AD and MCI and their quality of life after a 5-week lockdown.	There was worsening in NPI scores after confinement ($P = 0.028$). The most frequently affected neuropsychiatric symptoms were apathy and anxiety in patients with MCI and apathy, agitation, and aberrant motor behavior in patients with AD. No differences were seen in quality-of-life scores during the re-evaluation. 30% of patients and 40% of caregivers reported worsening of patients' health status during confinement.	****
Prasad et al. (25)	India/ Cross-sectional/ 100 people with PD and their caregivers	Explore the effects of prolonged lockdown on people with PD.	There was a significant increase in inability to access health care and difficulty in obtaining medication. Patients also reported worsening of motor symptoms.	****
Vaitheswaran et al. (30)	India/ Qualitative/ 31 caregivers of people with dementia	Describe the experiences and needs of caregivers of persons with dementia during the COVID-19 pandemic and lockdown in a city in India.	Thematic data analysis showed two sets of issues that caregivers of persons with dementia experienced during the pandemic. The first was unique to caregivers directly related to their caregiving role, while the second was not related directly to their caregiving role. These two sets also appeared to display two-way interaction. These issues generated needs, some of which required immediate support while others required long-term support. Caregivers suggested several methods such as video-consultations, telephone-based support. and clinic-based in-person visits to meet their needs. They also wanted more post pandemic services.	*****
Xia et al. (26)	China/ Cross-sectional/ 119 Chinese with PD	Investigate the incidence of anxiety, depression, and sleep disorders in PD patients and compare to controls to determine the impact of PD on mental and sleep states.	Compared to healthy controls, sleep disorders were identified in 68.9% of PD patients. Sleep disorder was independently associated with exacerbation of PD symptoms and anxiety. Compared to male PD patients, female patients had higher PSQI scores as well as anxiety and depression prevalence.	****

*PD, Parkinson's disease; PLWD, people living with dementia; MCI, mild cognitive impairment; AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; SCD, subjective cognitive decline; NCD, neurocognitive disorder. Quality assessment: *lower quality to *****higher quality.*

pandemic, the same patients already belonging to the database were reassessed.

Assessments

All the selected studies followed recommendations from health authorities, so that the assessments were done remotely by phone calls or with an online form and video calls. Some studies used data stored in databases to compare characteristics before and during the pandemic (9, 11, 12). The scales used for the online assessment of depression and anxiety were the Hospital Anxiety and Depression Scale (HADS) (19, 22, 27), Personalized Health Questionnaire 9 (PHQ-9) (12, 24) and Generalized Anxiety Disorder 7 (GAD-7) (10, 12, 24). The Geriatric Depression Scale-5-item (GDS-5) was adapted (10, 13). The Adult Resilience Scale (RSA) (27), was used in the assessment of caregivers' resilience. Sleep quality was measured online with the Insomnia Severity Index (ISI) (24). Cognitive assessment was performed with the Mini-Mental State Examination (MMSE) (10, 11, 13, 19, 20). Montreal Cognitive Assessment – MoCA (11, 29), and Clinical Dementia Rating Scale (CDR) (9, 11, 18). Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI) (9, 11, 14, 17, 20). Functionality was assessed with the Functional Assessment Questionnaire (FAQ) (10) and Basic Activities of Daily Living (ABVD) (10, 11). Caregiver burden was assessed with the Caregiver Burden Inventory (CBI) (27) and Zarit Burden Interview Scale (ZBI) (29) Neurological characteristics were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) (23). Quality of life was measured with the Short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS) (12) and Quality of Life in Alzheimer's Disease Assessment (QoL-AD) (14).

Cognition

The review revealed mixed results concerning the pandemic's impact on the cognition of people with dementia. Gan et al. (11) found no significant differences in dementia severity but a significant difference in the MoCA and C-MMSE scores between baseline and follow-up of people with Alzheimer's disease. Conversely, Barguilla et al. (9) identified worsening of cognitive status in 60% of people with dementia as reported by caregivers. In addition, one study found worse cognition in Alzheimer's patients with increased levels of neuropsychiatric symptoms. Boutoleau et al. (17) also reported an association between neuropsychiatric changes and cognition during COVID-19 lockdown. The cognitive function of people with dementia with increased neuropsychiatric symptoms was worse than that of those who did not show neuropsychiatric changes (17).

Mood

Nine studies investigated changes in depression and anxiety in people with dementia (10, 12, 13, 16, 18, 19, 22–24). Most showed an increase in symptoms of anxiety and depression. In Di Santo et al. (10), the participants' scores indicated an increase in depressive symptoms during the pandemic associated with living alone or lack of good relations with others in stay-at-home isolation.

According to a longitudinal study by Giebel et al. (12), cases of anxiety decreased significantly during the study period, while cases of depression increased. Tsapanou et al. (16) reported a significant decline in communication, mood, movement, and compliance with new measures in individuals with mild cognitive impairment or dementia. Cohen et al. (18) found worsening of symptoms of depression, anxiety, and insomnia in individuals with milder stages of dementia than those in more severe stages, possibly because they were more aware of the pandemic's consequences. El Haj et al. (19) investigated the effects of COVID-19 containment measures on the mental health of people with Alzheimer's disease living in nursing homes and reported higher levels of depression and anxiety during the pandemic compared to before. Janiri et al. (23) found that subjective worsening of neurological symptoms and lifetime irritability, together with younger age and female sex, were specific risk factors for worsening of psychiatric status. Meanwhile, El Otmani et al. (22) and Kitani et al. (24) reported no significant changes in mood.

Neuropsychiatric Symptoms

The COVID-19 pandemic and social isolation have led to significant neuropsychiatric symptoms and cognitive changes in people with dementia. Agitation, delirium, irritability, apathy, aggression, anxiety, indifference, and mood were the most common symptoms found in the studies (9, 11, 14, 17, 18, 20). Barguilla et al. (9) reported the presence of delirium in individuals with more severe stages of dementia. According to Gan et al. (11), global NPI scores differed significantly between baseline and follow-up evaluations nearly 14 months later. Lara et al. (14) reported that apathy and anxiety were the most frequent in participants with mild cognitive impairment, compared to apathy, agitation, and aberrant motor behavior in participants with Alzheimer's disease. Additionally, 30% of patients and 40% of caregivers reported worse health status of people with dementia during confinement.

Bouteleau et al. (17) found a correlation between duration of confinement and severity of neuropsychiatric symptoms. One study (18) reported that neuropsychiatric symptoms were more frequent in individuals with mild dementia compared to advanced dementia. In addition, new onset of behavioral symptoms or exacerbation of preexisting behavioral symptoms were positively correlated with patient's age and presence of anxiety before the pandemic and negatively correlated with the global Clinical Dementia Rating scores and the domains of memory, community affairs, and home and hobbies (18).

Several studies specifically focused on persons with Parkinson's disease (22–26). Deterioration in motor performance was the most prominent deficit, with evident worsening of slowness, followed by depression. There was also a decrease in sleep quality, with a reduction in sleep time and the need for sleep medication. The results also suggested that poor sleep was significantly associated with postural instability and gait disturbance. Sleep disturbances in people with Parkinson's disease can exacerbate disease symptoms, anxiety, and depression (26).

El Otmani et al. (22) found no difference in anxiety and depression in people with Parkinson's disease. Conversely, Janiri et al. (23) reported depression in 26% of Parkinson's disease patients. Preexisting lifetime delusions, having received antipsychotics, and not having received mood stabilizers were also associated with subjective worsening of psychiatric symptoms during the COVID-19 pandemic (23). Morii et al. (24) found that Parkinson's disease patients were more likely to develop clinical depression than those without the presence of social stress, even in Japan where no legal penalties were imposed for failure to comply with social isolation. Prasad et al. (25) reported a significant increase in the inability to access healthcare and difficulty in obtaining medication.

Functionality

Barguilla et al. (9) evaluated changes in the routines of people with dementia and found that 70% of participants abandoned previous daily activities and 13% suffered increased incidence of falls. In Di Santo et al. (10), more than one-third of the sample reduced their physical activity and eliminated their social activities, one-sixth also decreased their productive and mentally stimulating activities, and nearly 70% reported an increase in idle time. Interestingly, according to Goodman-Casanova et al. (13), in Spain, health status was found to be optimal in 96% of respondents with no COVID-19 symptoms, 35% played memory games, 60% watched television, 98% telephoned relatives, and 57% of those with mild cognitive impairment or mild dementia took walks. (13) Lara et al. (14) reported that although there were no observed differences in quality of life scores during reevaluation, 30% of patients with mild cognitive impairment or mild Alzheimer's disease and 40% of caregivers reported worsening of patients' health status during confinement.

Caregivers

The pandemic and social isolation have also changed the lives of caregivers of older adults with dementia. Six studies assessed the pandemic's impact on caregivers (9, 16, 21, 27, 30). Only three of the six focused exclusively on caregivers (21, 27, 30). The others evaluated both caregivers and recipients of care. Two studies evaluated the caregivers qualitatively (28, 30), while the others used quantitative designs.

Increased burden of care, stress, and depressive symptoms had the most significant impact on caregivers. Altieri et al. (27) pointed to the association between resilience and symptoms of depression and anxiety. Caregivers with higher levels of resilience presented lower levels of depressive symptoms and high anxiety, and caregivers with low resilience showed an increase in anxiety symptoms alone. In addition, caregiver burden was associated with higher functional dependence. Vaitheswaran et al. (30) identified a two-way interaction between issues related to the caregiving role (protecting persons with dementia from infection or managing them when they were going to be hospitalized, isolated, or quarantined) and issues that were not related directly to their caregiving role (having to work from home due to lockdown). Additionally, caregivers suggested several methods such as video-consultations, telephone-based support, and in-person clinic-based visits to meet their needs (30). Boutoleau et al. (21) found that increased burden for caregivers of people with frontotemporal dementia (bvFTD) occurred regardless of behavioral changes, while caregivers of people with Alzheimer's disease experienced increased burden related to changes in the neuropsychiatric symptoms.

Use of Technology

Technology has been an essential ally during the pandemic. All the selected studies performed data collection remotely. One study (29) compared the impact of additional services delivered either to care recipients and caregivers via video conference or to caregivers by telephone alone. They found varying degrees of improvements in physical and mental health, perceived burden, and self-efficacy in caregivers in the video-conferencing group that were absent in the telephone-only group (29). Goodman-Casanova et al. (13) reported that phone calls and video calls can offer social support and that some interventions can serve as recreational activities during the pandemic. Additionally, there were no significant differences in health and well-being between the intervention and control groups (13). Respondents with TV-AssistDem performed more memory exercises than control respondents. TV-AssistDem is a technological tool to facilitate remote support to people with mild cognitive impairment. It uses TV-based data transmission and video-interactivity between health professionals, patients, caregivers, and family members and provides such services as reminders, health monitoring, and cognitive stimulation (13).

Giebel et al. (12), in a longitudinal online or telephone survey, found that many older adults and people with dementia (PLWD) were less likely to be digitally literate, making it difficult for them to access services equally. A qualitative study by Portacolone et al. (15) found that some participants were satisfied with their telephone interactions with their physicians, but that digital illiteracy was a barrier to use of teleconferencing for others.

DISCUSSION

This systematic review aimed to elucidate the impact of the COVID-19 pandemic on people with dementia and on their caregivers' mental health. The database search yielded several articles related to the COVID-19 pandemic and dementia, but most of these studies addressed the mental health of health professionals, who are active on the front lines of the fight against the novel coronavirus. We also found studies on the mental health of older adults without neurocognitive disorders. Interestingly, there were few studies of people with dementia, possibly due to current limitations on research in this group. For example, standard neuropsychological assessment methods rely on face-to-face interactions, which were not possible due to social isolation. Social isolation requires modifications to study protocols for remote data collection to continue participants' assessments (6). We thus observed that many rating scales for measuring cognitive, behavioral, or mood symptoms in people with dementia were applied through videoconferencing or phone calls.

In most of the selected studies, caregivers helped people with dementia respond to the scales, a critical aspect of the assessments' reliability. Considering this study bias, Crivelli et al. (31) developed recommendations to support standardized clinical procedures that recommend data generation through teleneuropsychological assessments. For example, people with visual or auditory deficits, acute confusional states, or severe communication difficulties should not be evaluated using teleassessments, nor should they provide recorded verbal consent or an electronic signature. If tests are interrupted, they should be readministered from the beginning when contact with the patient is resumed, or it should be clarified that some qualitative data usually collected from face-to-face consultations are no longer acquired, which may limit recommendations and conclusions (31).

Concerning the studies' designs, we found only one longitudinal study. The cross-sectional studies used different methods of evaluation to assess the pandemic's impact. For example, Tsapanou et al. (16) provided a self-report questionnaire to caregivers of people with mild cognitive impairment or dementia related to changes in physical, psychological, and routine activities during the pandemic. Bouteleau-Bretonnière et al. (17) contacted caregivers of people with AD who were confined to their homes for nearly 2 months and asked about the changes in neuropsychiatric symptoms during this period. Mori et al. (24) compared the presence of depression in persons with Parkinson's disease and controls. Manini et al. (20) contacted caregivers of 109 community-dwelling adults with dementia who had a telephone follow-up after their hospital visits were canceled.

Interestingly, we found few studies evaluating cognition and level of functional impairment in people with dementia (9–11, 13, 17). Considering the different cognitive functions such as memory, attention, or executive function and their impact on different types of activities of daily living (basic and instrumental), it was not possible for the selected studies to examine which functions were most affected by social isolation. Therefore, further longitudinal studies should help to better understand the lockdown's impact on specific cognitive functions and routine activities to help develop interventions to attenuate the impact of social isolation on this population.

Social isolation is a measure to prevent spread of the novel coronavirus, but people with dementia and their caregivers have experienced changes in routine life, health services, and support activities as a result. Neuropsychiatric symptoms are a common feature in dementia, affecting 80% of patients over the course of the disease (6). Thus, most of the selected studies focused on changes in neuropsychiatric symptoms during social isolation. Overall, social isolation exacerbated or led to the manifestation of various neuropsychiatric symptoms. Agitation, delirium, irritability, apathy, aggression, anxiety, indifference, and altered mood were the most common symptoms found (9, 11, 14, 16, 18, 20, 21). Cohen et al. (18) found that new onset of behavioral symptoms or exacerbation of preexisting behavioral symptoms was positively correlated with patient's age and presence of anxiety reported before the epidemic and negatively correlated with global CDR score and the domains of memory, community affairs, and home and hobbies. Importantly, meaningful recreational activity has been shown to increase positive emotions, improve activities of daily living, and attenuate challenging neuropsychiatric symptoms (32). These findings may help develop potential digital delivery of non-pharmacological intervention programs, but further studies should explore differences in neuropsychiatric symptoms according to the type of dementia or patient's age at onset.

The COVID-19 pandemic has worsened the situation of families caring for people with dementia by delaying diagnosis and increasing the burden on caregivers (33). Caregivers have faced many challenges in caring for their loved ones, such as fear and concern about protecting them from SARS-CoV-2 infection, since recipients of care may not know how to follow the protective measures. Caregivers have had to reconcile the new challenges of care for their elders that already led to the burden of care (30). Furthermore, it is important to consider regional and cultural differences in caregiver support. For example, in Greece, Tsapanou et al. (16) reported that most families have lacked significant support during this period. In India, caregivers suggested several methods such as use of video-consultations, telephone-based support, and clinic-based in-person visits to meet their needs. They also requested more post-pandemic services (30). In Italy, caregivers with high resilience showed a more significant increase in anxiety levels during lockdown than caregivers with low resilience (27). There is thus a need to consider the development of specific interventions tailored to different cultural backgrounds and different types of dementia, such as early-onset dementia and more complex syndromes such as frontotemporal dementia (33).

Telemedicine has been a widely used method in this period. Lai et al. (29) studied whether telehealth would benefit people with dementia and their caregivers. The complementary telehealth delivered through video-conferencing apps was associated with more positive effects for community-dwelling older adults with neurocognitive impairment and their caregivers compared to conventional telehealth conducted by phone conversation only (29). In addition, there was a positive impact of telehealth via videoconferencing on cognition and a notable improvement in quality of life (29). One study (30) has suggested that online psychoeducational support and specific guidelines for care can meet caregivers' needs and contribute to their well-being. The use of technology by people with dementia and their caregivers depends on expectations, perceived skills, and expertise in using the devices (34). Some studies (12, 15) reported that many people with dementia were less likely to be digitally literate, making equal access to the services difficult. Therefore, technological initiatives should consider both people with cognitive impairment as well as different technology literacy levels.

FUTURE DIRECTIONS

Another question is whether COVID-19 has a different clinical presentation in older people. Compared to younger people, the effect of COVID-19 on geriatric patients may be more serious because of higher rates of chronic illness, resulting in more severe cases of the disease. Unlike younger people, who present such symptoms as fever, cough, and chest discomfort, older adults may manifest COVID-19 through atypical symptoms such as mental confusion, falls, decreased mobility, tachycardia, blood pressure changes, decreased appetite, difficulty swallowing, and urinary incontinence (35). Therefore, caregivers of older adults may have difficulty recognizing the disease, especially in people with dementia, in whom these symptoms are already common. Older adults with dementia may also have other comorbidities that mask the infection. Prevention is still the safest measure against COVID-19, but screening services should consider that in older people, the infection can manifest itself through atypical symptoms. Thus, every geriatric patient should be tested and observed for all presenting symptoms (35). Medical teams and caregivers must be aware of any changes older adults may present, and hospitals must be prepared for the possible diagnosis. Misdiagnosis can lead to severe complications from the infection (36).

This systematic review has some limitations that should be considered. The first is the topic's broad scope, encompassing studies with multiple methods and outcomes. The second difficulty is transposing current evidence from one continent to another or from specific sociocultural and economic realities to others. The selected studies are also methodologically heterogeneous, thus limiting the comparison of their findings.

CONCLUSIONS

There are few publications on the mental health of older persons with dementia and their caregivers during the COVID-19 pandemic compared to studies in other population groups. The selected studies were nearly unanimous in emphasizing that social isolation and withdrawal can lead to (or exacerbate) neuropsychiatric symptoms, motor difficulties, and cognitive decline. Caregivers have also suffered from the pandemic's impact, with an increase in the burden of care and symptoms of stress, depression, and anxiety. Both patients and caregivers have experienced radical changes in their routines that have affected their health and quality of life.

Few studies suggested measures to alleviate the difficulties of people with dementia and their caregivers. There are reports of the benefits of technology for communication and treatment via teleconsultations, but such technologies are still not widely known and not everyone has access to them, thus limiting their use by the target population. New forms of care and intervention are needed for older adults with cognitive impairment and their caregivers to prevent the intensification of their physical and psychological suffering.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

JG performed the systematic search and wrote the first draft. IL assisted with articles inclusion and exclusion. MD designed the systematic review, assisted with articles inclusion and exclusion and approved the final version. All authors contributed to the article and approved the submitted version.

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E-mail-based health care in patients with dementia during the pandemic

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Introduction/aim: Frail and cognitively impaired older patients are particularly vulnerable groups during the pandemic. Lockdowns, social isolation, and physical inactivity considerably affect physical and mental wellbeing. During the pandemic process, routine medical checks and acute medical care services may be disrupted. The study aimed to demonstrate the feasibility and effectiveness of telemedicine in the delivery of healthcare services to elderly patients during the pandemic.

Materials and methods: E-mails sent to the e-mail address of the department of geriatrics, which has been actively used for 4 years, between April 2020 and June 2021, were retrospectively evaluated. The time and reason for each application, referral to the patients, demographic data of the patients, and chronic diseases were recorded. E-mail frequencies were considered monthly time series, and time series charts for e-mail frequencies from patients were produced.

Results: A total of 374 e-mails that 213 patients sent were assessed. A vast majority, 97.6% of the e-mails, were sent by proxies. The mean age of patients was 78.7 ± 8.1 years, and 59.2% were women. Hypertension and dementia were the most common comorbidities. The applications mostly occurred in April-May and October-November 2020. The most common complaint in dementia was behavioral disturbances (13.6%). Geriatric outpatient appointments were arranged for 29.9% of the applicants, 14.2% were referred to the emergency department, and 23.0% were offered medical treatment. Outpatient examination and treatment were completed in 15% of the patients and 10.4% of them were hospitalized. The time series charts showed that e-mails were sent more frequently by patients with dementia than the others ($p = 0.03$).

Conclusions: Telemedicine, which enables many problems of patients to be solved in geriatric practice without face-to-face appointments, can also prevent infections and unnecessary hospitalizations, especially during these unusual pandemic days.

KEYWORDS

older adults, dementia, telemedicine, information technology, remote consultation

Introduction

COVID-19, which emerged in China in 2019, quickly spread all over the world and became a pandemic in a short time, creating a serious problem in terms of transmission to health personnel in health institutions and especially to patients in the risk group who go to the health institutions to receive health services (1). Elderly patients who are frail and whose cognitive functions are affected represent the group most associated with poor health outcomes of the pandemic. Quarantines, social isolation, and physical inactivity significantly affect physical and mental health (2). In particular, the restrictions implemented to maintain the social distance necessary to prevent the spread of the epidemic are some of the important changes that the epidemic brought to our lives. Elderly patients with multiple comorbidities may not show the typical symptoms of pulmonary infections such as fever, cough, and chest pain as younger people do. They may present with atypical presentations such as confusion, acute mental changes, frequent falls, movement disorder, loss of appetite, dysphagia, and incontinence (3). Due to the chronic changes caused by biological aging in elderly individuals, comorbidities are more common, and nutritional deficiencies, decreased effectiveness of the mucosal barrier, and atypical symptoms of infection make it difficult to understand and treat infections (4, 5). Due to the changes that occur in both the immune system and other physiological organ systems against pathogens with advancing age, infectious diseases are more common in geriatric patients and these diseases may progress more severely than in young people (5). The fact that the elderly population is at high risk for COVID-19 has brought along the search for regulations to protect elderly individuals. As in the whole world, there have been various restrictions applied more strictly to the elderly due to the COVID-19 pandemic in our country, and various disruptions have been experienced in the applications of patients to health institutions due to routine controls. Therefore, telemedicine, which reduces the risk of transmission by isolating patients during the pandemic period, and also provides service *via* technological communication tools (such as e-mail, and video conference) to maintain the continuity of health care, has come to the fore (6). Telemedicine is the rapid access to remote medical experience and information using telecommunication and information technologies (7). It involves the use of various types of information and communication technologies (ICTs), such as computers, the Internet, and cell phones according to the World Health Organization (WHO) definition (8). Telemedicine can also be applied as an appropriate, safe, effective, and new method in clinical care in health-related emergencies (9).

The extraordinary burden on the healthcare system due to the pandemic leads healthcare providers to use telemedicine so that patients without a diagnosis of COVID-19 may benefit from healthcare services. This practice, which has shown a striking development in recent years and helps to perform periodic health checks in patient groups with chronic diseases by using limited personnel and financial resources, has become one of the more commonly used methods for the maintenance of health services without disruption during the pandemic period (10). During the period when many polyclinics are closed to face-to-face visits due to the restriction rules, it is possible to reach the patients at home, ensure the safety of other patients by maintaining social distance, and maintain the quarantine through telemedicine. Teleisolation application improves palliative care and patient support services, contributes to personnel safety and reduces the psychological burden caused by isolation, increases patient comfort in patients who are placed in isolation in the emergency department (11). Telemedicine service is implemented in various ways, among which, e-mail application is one of the methods that provide communication between healthcare personnel and patients (12). This study aimed to investigate the contribution of e-mail, which is used as a telemedicine service in elderly patients, to the realization of health care effectively and efficiently.

Materials and methods

In our study, 374 e-mails were sent to the e-mail address of the Department of Geriatrics (geriatridanisma@deu.edu.tr) from a total of 213 patients between April 2020 and June 2021 and were evaluated retrospectively. The e-mail-based telemedicine service has been actively used for 4 years. Patients who were admitted to the outpatient clinics were informed about the e-mail service and suggested to contact the medical team in case of need. The e-mail account was checked every day by the geriatric fellow on-call. Each e-mail was replied to by the doctor's team within 48 h. Repetitive e-mails about the same patient within a week were not included in the study. The patients who utilized the e-mail technology by proxy were identified. The person who sent the e-mail, the complaint sent by e-mail, the referral given to the patient upon the e-mail response, the health condition that caused the patient to send the e-mail, the outpatient treatment or service hospitalization status of the patients who were summoned to the polyclinic control were recorded. The referrals given to the patients were determined as non-pharmacological intervention, drug regulation, geriatric outpatient control, emergency or another branch consultation deemed necessary. Other than these, appointment revision, drug refills, and control laboratory results evaluation were gathered under the "other" heading. After the evaluation of the patients who were hospitalized after their admission to the outpatient clinic, conditions that caused the need for inpatient treatment were grouped into disease progression, acute organ damage, COVID-19 or other infections, and adverse drug reactions. From the files of the patients included in the study, their demographic data, chronic diseases, diagnosis of dementia, and the drugs they used were examined.

Statistical analysis

Statistical evaluation of the data was carried out using the IBM SPSS 25 program. Descriptive statistics were presented as mean ± standard deviation for continuous variables and as % for categorical variables. E-mail frequencies were considered as monthly time series and time series charts were generated for e-mail frequencies from patients. The relationship between patients' recurrent applications to telemedicine and their complaints were evaluated by regression analysis.

Ethical approval

Ethical approval of the study was obtained on 08.09.2021 based on the decision numbered 2021/25-03 of the Non-Interventional Research Ethics Committee of our hospital. The study was conducted in accordance with the Declaration of Helsinki Principles.

Results

The total number of patients who sent e-mails was 213. Of these patients, 88 had repeated admissions. The mean age of the 213 patients who applied was 78.74 ±8.13 years, 59.2% were women, 53.1% were married, and the rate of those who completed at least 8 years of education was calculated as 32.9%.

According to the records, approximately 1,200 patients were regularly actively followed up in our department during these 2 years (2019–2021), and the rate of e-mail usage was found to be 17%. In patients who benefited from telemedicine, hypertension and dementia were the most common comorbidities, respectively. When the accompanying comorbidities and sociodemographic characteristics of single applicants and recurrent applicants were examined, it was determined that there was no statistically significant difference (Table 1).

TABLE 1 Sociodemographic data and comorbidities of the patients by admission status.

	Recurrent Application *n*: 88	**Single Application *n*: 125**	***p***
Age	79.08±7.78	78.44±8.34	0.34
Education (%)			0.68
Illiterate	9.6	6.4	
Primary school	42.5	36.4	
High school	13.7	20.9	
University	19.2	20.9	
Sex (Female) (%)	58.0	60.0	0.76
Marital status (%)			0.97
Married	61.5	60.0	
Widow	15.4	15.5	
Divorced	23.1	24.5	
Housing			0.09
Alone	7.3	16.2	
With spouse	52.5	55.9	
With family	31.7	24.3	
With caregiver	8.5	2.7	
In an institution	0	0.9	
Comorbidities (%)			
Hypertension	62.5	57.3	0.44
Coronary artery disease	30.7	21.0	0.10
Cerebrovascular disease	3.4	8.9	0.11
Diabetes Mellitus	30.7	36.3	0.39
Dementia	56.8	45.2	0.09

In the evaluation of 374 e-mails received, it was observed that the most common reason for the application was behavioral disorder due to dementia. Due to the cancellation of routine outpatient clinic appointments in line with the restrictions proposed during the pandemic period, new appointment requests were in the second rank. These were followed by urinary system complaints, balance disorder, high blood pressure, pain, glycemic dysregulation, sleep and nutrition disorders, COVID-19 recommendations, acute mental change, cough, fever, and falls (Table 2). The recommendations given for the applications made by the patients were gathered under four main headings and others. The most common referral was geriatrics outpatient control recommendation (29.9%). Medication revisions were made by e-mail in 23% of all applications, 14.2% were referred to the emergency service or another related branch, and non-pharmacological recommendations were made to 19%. Outpatient examination and treatment were completed in 15% of the patients who were referred to the geriatric outpatient clinic, but 10.4% were hospitalized. It was observed that the most common disease progression (50%) was in the final diagnosis of the patients in the inpatient service. Infection, especially pneumonia, acute organ damage, and drug side effects were found to be other common causes of hospitalization (Table 2).

No statistically significant finding was found in the regression analysis performed to show whether there is a relationship between recurrent admissions and the reasons for admission (Table 3). When the monthly number of e-mail applications was evaluated, it was found that dementia patients applied more frequently and the applications were mostly in April-May and October-November, when the pandemic peaked in our country (Figure 1).

TABLE 2 Reasons for application.

Applications *N*: 374	%
By proxy	97,6
Causes	
Fever	1.6
Pain	5.3
Cough	1.9
Acute mental status change	2.1
Imbalance	6.1
Sleep disturbance	4.8
Behavioral disturbances	13.6
Nutritional impairment	4.3
Urinary system complaints	6.4
Falls	1.3
Glycemic dysregulation	5.1
Blood pressure increase	5.3
Appointment cancellation	11.2
Others	27.8
COVID-19 information request	2.9
Hospitalization	10.4
Referral	
Non-pharmacological intervention	19.0
Drug regulation	23.0
Geriatric outpatient clinic appointment	29.9
Emergency referral	14.2
Others	13.9
Outpatient application	15.0
Hospitalization	10.4
Infection	22.2
COVID-19	2.8
Disease progression	50.0
Acute organ injury	13.9
Adverse drug reaction	11.1

TABLE 3 The relationship between the reasons for application and the recurrent application.

Variable	Beta	OR (CI)	*p*-value
Fever	0.138	1.148 (0.205–6.437)	0.875
Pain	−0.150	0.861 (0.335–2.214)	0.861
Cough	0.361	1.435 (0.271–7.603)	0.671
Gait and balance problems	−0.113	0.893 (0.366–2.175)	0.803
Sleep disturbance	−0.332	0.717 (0.270–1.907)	0.506
Behavioral disturbances	0.517	1.678 (0.834–3.374)	0.147
Urinary system complaints	1.054	2.870 (0.941–8.754)	0.064
Falls	−1.942	0.143 (0.016–1.311)	0.085
Glycemic dysregulation	0.474	1.607 (0.554–4.662)	0.383
Blood pressure increase	0.831	2.296 (0.737–7.154)	0.152

Discussion

In this study investigating the frequency and effectiveness of telemedicine use *via* e-mail in the geriatric clinic, it was seen that the rate of telemedicine use among the patients followed up was approximately 17%, and patients commonly used this method because of dementia-related behavioral disorders. Because of the suggestions made to 55.9% of the incoming e-mails, it was observed that the existing medical problems of the patients were resolved before they came to the hospital during the peak times of COVID-19 and that the patients in need of acute care were directed to the inpatient service or the emergency room. Considering the recurrent applications, the most common reason for admission was behavioral disorder, appointment cancellation, and urinary system infection, as in single applications. It was remarkable that the majority of the applicants by e-mail belonged to dementia patients.

Thanks to telemedicine applications, which have become popular especially with the pandemic, for the increasing elderly population, the quality of life of individuals with chronic disease is improved by monitoring of the elderly at home, and the rate of admission to the hospital of the elderly is reduced by the use of information and communication technologies (13). The popularity of telemedicine applications increased gradually during the COVID-19 pandemic period, and many studies on the use of telemedicine in this process have been added to the literature (14). Especially in this period, telemedicine provided the possibility of maintaining social distance and reducing the risk of exposure to infection, namely for the high-risk population, while providing the opportunity for chronic disease management (15). Chronic diseases represent a major public health problem worldwide and are the leading cause of death among older adults (16). It has been shown that e-health services, which are used as communication technology, are both helpful and cost-effective in the diagnosis and management of chronic diseases such as congestive heart failure, stroke, chronic obstructive pulmonary disorder (COPD), diabetes mellitus (DM), hypertension, asthma, dementia and depression (17). As in our clinic, elderly patients with follow-up should be evaluated closely due to their accompanying comorbidities, multiple drug treatments, and geriatric syndromes (18). In the present study, it was observed that 59.2% of 213 patients who applied by e-mail had hypertension and 33.3% had DM. Of the total e-mail applications, 5.1% were for blood pressure and 5.3% for glycemic regulation. This supports the view that the dramatic improvement in telemedicine patient groups with chronic diseases helps to perform periodic health checks by using limited personnel and financial resources (10). In the period when many polyclinics are closed to face-to-face visits due to the restriction rules of patients, the continuity of health

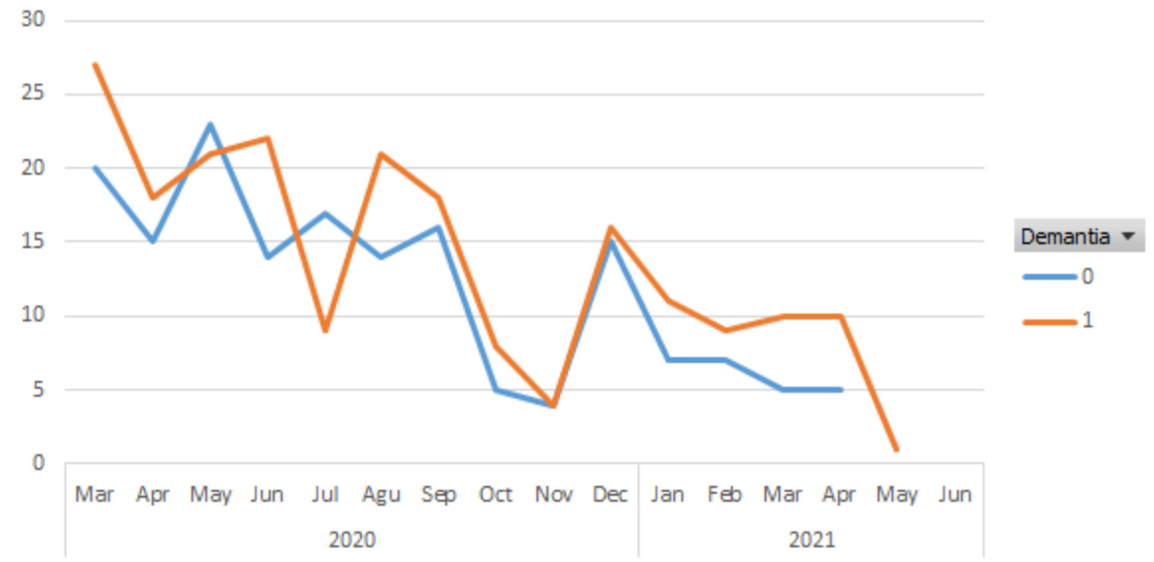

FIGURE 1
The time series plot of e-mails according to the months.

services is possible with telemedicine facilities by maintaining social distance, ensuring the safety of patients, and maintaining isolation (19). In our study, although geriatric outpatient control was recommended most frequently in the referrals given to the patients by e-mail, the continuation of the isolation was ensured by the home treatment arrangement of 23% of the patients. Non-pharmacological recommendations were made to 19% of the patients, 14.2% of whom were directed to related branches or emergencies, thus contributing to the prevention of unnecessary patient admissions and economic burden. There is research showing that quality virtual visits can improve the outcome of home care patients at a lower cost than traditional face-to-face home health visits, supporting the results in our clinic (20).

In the literature review in which telehealth and digital care types and applications are compiled for the current policies for COVID-19; health officials and policymakers are urged to consider social, organizational, and technological determinants to encourage the adoption of these practices for the current pandemic and future disasters (21). It was reported that the reasons for using telemedicine during the COVID-19 epidemic differ between studies, and common uses include clinical care, follow-up, medical education, diagnosis, rehabilitation, triage, research, surveillance, and contact tracing. Most of the studies in this field have been done on internal diseases and branches (14). Follow-up of the patients can be done *via* phone calls, video chat, and e-mail. In a retrospective cohort study conducted by Ramasmawy et al., the response status of healthcare providers in New York, which is considered to be the international epicenter of the COVID-19 pandemic, was evaluated with video consultations without face-to-face meetings, and it was concluded that telemedicine application as an alternative method to traditional clinical evaluation and patient satisfaction was high (22). Our study showed how effectively the e-mail system, which has been used for about 4 years in our geriatrics department to reduce the frequency of patients visiting the health center and to provide guidance in emergencies, is used especially during the pandemic period. When the monthly number of e-mail applications was evaluated, it was found that patients with dementia applied more frequently and the applications were mostly in April-May and October-November, when the pandemic peaked in our country. Organizing the appointments of the dementia patient and supporting basic and instrumental life activities are both a burden and a source of stress for the caregiver. It was determined that 49.8% of the 213 patients who applied and 56.8% of the 88 patients who applied recurrently had a diagnosis of dementia. Among the total e-mails, it was indicated that the most common reason for referral was behavioral disorder in dementia patients (13.6%). This result was similar when recurrent applicants were evaluated separately. However, no statistically significant finding was found in the regression analysis performed to show whether there is a relationship between recurrent admissions and the reasons for admission. The behavioral disorder occurring in dementia patients is characterized by rapid cognitive decline, low quality of life, and increased caregiver burden (23). Telemedicine caregiver assessment can reach caregivers where they are, providing needed support and guidance. Caregiver burden assessment scales may be applied face-to-face as well as in telemedicine visits by verbal and screen sharing methods (24). Rapidly adapting the telemedicine program, which has been carried out with 36 nursing homes since 2018 and introducing new protocols for COVID-19, Cormi et al. stated that hospitals in France, received 15 times more teleconsultation on March 1–28, 2020 compared to February, were prevented from becoming more crowded due to the applications (25). In the University of Rochester Specialized Oncology Care and Research in the Elderly clinic, telemedicine consultancy service has been implemented as the fastest and most efficient way of intervention to reduce the exposure of elderly and oncological patients to COVID-19 due to hospital admission. This application was evaluated as promising, but the inability to make eye contact during telephone visits, the absence of face-to-face interaction, and the inability to evaluate objective physical function were shown as disadvantages (26).

This has led healthcare providers to more advanced methods such as video conferencing. Thus, it has been stated that remote consultation by a trained health worker can be provided for a detailed geriatric evaluation (27).

Similarly, in our study, the inability to perform a physical examination, which is the cornerstone of detailed geriatric evaluation in our patients, and the accompanying physical problems such as vision-hearing impairment in many of our patients were the main difficulties we encountered in the practice of telemedicine. The fact that the elderly do not prefer to use the internet or cannot gain experience because they do not use technology, causes them to be deprived of digital services (28). In the study evaluating the relationship between telemedicine use and sociodemographic characteristics, participants classified as ready for telemedicine use were shown as married women, individuals younger than 80 years of age, Non-Hispanic Caucasians, those with at least a university degree, and those without myocardial infarction, DM, cancer, anxiety, and depressive states (28). Lam et al., in their study investigating the reasons why 4,525 adults with an average age of 79.6 were unprepared for telemedicine, stated that 38% were not ready for video visits due to their technological inexperience (29). Similarly, the fact that our patients are not a group that actively uses the internet and technology is a fundamental limiting factor in our country. However; In the period when the pandemic peaked in our country and quarantine measures were increased, the rate of the e-mail was found to be significantly higher than in other months. Considering that dementia patients constituted the most e-mailed group in this period, the benefit of the application is understood more clearly.

As far as we are concerned, our unit is one of the few centers where telemedicine is used effectively in elderly patients in our country. Follow-up of patients *via* e-mail has been carried out actively for about 4 years. In this respect, our study shows the characteristics of a pilot study. The limitation of the study is that it is retrospective. In addition, in this study, which was performed in a memory clinic with a reference center, the fact that patients may have a higher incidence of dementia may affect the generalizability of the study results.

Conclusion

In terms of mortality and morbidity, due to COVID-19, older patients in the high-risk group can contact the clinic *via* their e-mail address for reasons such as their current clinical status and treatment recommendations, it is possible to guide patients, to ensure the safety of our patients by maintaining social distance, to comply with the isolation recommendations and to contribute to the protection of public health. Findings from this study reveal the importance of a practical telemedicine method with applicability and adoption during the pandemic in older adults. Telemedicine also enables regular follow-up to patients living in remote/rural areas not only during the pandemic period but also in ordinary circumstances. At the same time, this study's results encourage the healthcare personnel about the potential of digital technologies that provide clinical and psychological support during the pandemic and beyond. In addition to being a method that can be used effectively in elderly patients during the pandemic period, telemedicine also provides health services for patients who live far from health care or who have mobility/transport limitations. More studies are needed on the factors affecting the application of telemedicine in the provision of clinical services, its importance, and its replacement with clinical evaluation.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

Ethical approval of the study was obtained on 08.09.2021 based on the decision numbered 2021/25-03 of the Non-Interventional Research Ethics Committee of Dokuz Eylul University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ATI and EAB made the study concept and design. KAS and HK helped in acquisition of data. IY performed analysis and interpretation of data. KAS and DK drafted the manuscript. ATI established critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Long-covid cognitive impairment: Cognitive assessment and apolipoprotein E (APOE) genotyping correlation in a Brazilian cohort

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Introduction: Few studies have objectively evaluated cognitive deficits after the acute phase of COVID-19 disease. Moreover, the role of apolipoprotein E (APOE) genotypes in cognitive decline in patients with COVID-19 has not been evaluated yet.

Methods: This cross-sectional study was conducted in confirmed cases of COVID-19 patients with neurological symptoms that persisted for more than 3 months from the onset. We determined APOE genotypes.

Results: The final sample consisted of 141 patients. The most frequent APOE genotype was E3/E3 ($N = 95$; 67.3%). In total, 93 patients (65.9%) had memory impairment symptoms as the main complaint, objectively confirmed through screening tests in 25 patients (17.7%). Patients with cognitive impairment had a lower frequency of anosmia than the normal and subjective cognitive decline (SCD) groups ($p = 0.005$). In addition, depression was recurrent in the cognitive impairment group and the SCD group ($p = 0.046$). Cognitive impairment was significantly more frequent in hospitalized patients and those with a lower education level. Cognitive status was not associated with APOE genotypes.

Discussion: Hospitalized patients had more severe infection with a greater possibility of systemic complications, greater inflammatory response, and prolonged hospitalization, which could impact cognitive performance. Cognitive impairment in patients with COVID-19 does not necessarily involve specific APOE polymorphisms. However, psychiatric disorders may also be responsible for cognitive complaints. Cognitive complaints are frequent in patients with COVID-19, even after the acute phase of the disease and in mild cases. Hospitalized participants and depressed patients may have a higher risk of cognitive impairment. APOE genotypes or haplotypes may not significantly play a role in COVID-19 cognitive impairment.

KEYWORDS

COVID-19, cognitive impairment, SARS-CoV-2 infection, dementia, risk factor

Introduction

The COVID-19 outbreak started in Wuhan, China and was declared a pandemic by the World Health Organization (WHO) on 11 March 2020, with high infection and mortality levels worldwide.[1] COVID-19 has a wide range of clinical manifestations, such as neurological manifestations (1, 2). In a study conducted in Wuhan, 36.4% of the patients had some neurological manifestation, with central or peripheral neurological involvement, such as dizziness, headache, altered level of consciousness, stroke, ataxia, and epilepsy (3).

Aside from general neurological manifestations, cognitive impairment was evaluated in different COVID-19 phases. A Chinese study evaluated the cognition of 29 patients with COVID-19, correlating cognitive complaints to high C-reactive protein (CRP) levels during the disease's acute phase (4). Another study evaluated cognitive impairment in outpatients using the Montreal Cognitive Assessment (MoCA), finding cognitive impairment in patients with mild symptomatic COVID-19 after 12 weeks of COVID-19 onset (5). Moreover, different cognitive presentations have been described in acute patients, such as encephalopathy associated with severe conditions and akinetic mutism associated with frontal hypometabolism in brain fluorodeoxyglucose (FDG)-PET (6, 7).

More severe COVID-19 manifestations in patients have been correlated with the APOE-4 allele of the apolipoprotein E (APOE) gene (8). This association is significant since the same allele confers a higher risk of sporadic Alzheimer's disease (AD) (9). Furthermore, a previous study showed that single nucleotide polymorphisms (SNPs) rs429358 and rs7412 of the APOE gene are associated with ischemic cerebral infarction, which is essential given the contribution of cerebrovascular diseases in the pathophysiology of many dementia cases (10, 11). As far as we know, no publications have evaluated cognitive manifestations after COVID-19 and correlated them with APOE polymorphisms. Similarly, we observed a limited number of studies in the literature evaluating cognitive manifestations in patients after the COVID-19 acute phase.

This study aimed to determine the relationship between COVID-19 and cognitive impairment and APOE gene polymorphisms in an outpatient public university hospital in Northeast Brazil.

Methods

Patients and clinical assessment

This cross-sectional study was conducted with COVID-19 outpatients at the Walter Cantídio University Hospital in Fortaleza, Northeast Brazil. Patients were recruited from July to August 2020 from an ongoing prospective longitudinal study by our research group.

We included patients with a diagnosis of COVID-19 confirmed in the past 12 months by nasal swab reverse transcription (RT)-polymerase chain reaction (PCR) or serological test, with any neurological symptom that persisted for more than 3 months from the onset. We excluded patients who did not undergo confirmatory testing for COVID-19 and those without neurological complaints (e.g., headaches, cognitive complaints, and others). Evaluations were performed in the neurology outpatient clinic of the Walter Cantídio University Hospital of the Federal University of Ceará, Brazil.

Patients were clinically evaluated by two independent neurologists (JWLTJ and DNO). The same clinical evaluation and identification form was applied to all patients. Age, gender, schooling, initial neurological symptoms, hospitalization, COVID-19 test type, complementary tests, comorbidities, alcohol abuse, and tobacco history were questioned. Moreover, the Medical Research Council (MRC) dyspnea scale was applied to assess dyspnea before and after COVID-19 (12).

Cognitive assessment

Participants were submitted to Addenbrooke's Cognitive Examination-Revised (ACE-R), the Mini-Mental State Examination (MMSE), and the Clinical Dementia Rating (CDR). Pfeffer's instrumental activities of the daily living scale were applied to assess functionality, and the Geriatric Depression Scale (GDS) was applied to assess mood, or the Beck Inventory, depending on the age of the patient (13–18). Furthermore, the Prospective and Retrospective Memory Questionnaire (PRMQ) scale was applied for retrospective memory assessment (19). The values of 58, 76, and 83 were used as the cutoff points for the ACE-R, respectively, for <4, 4–8, and > 8 schooling years (20, 21). Concerning the MMSE, we employed the cutoff points of 19 and 24, respectively, for 0 and up to 4 schooling years (22, 23). In addition, patients

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[1] https://www.who.int/emergencies/diseases/novelcoronavirus-2019 (accessed August 17, 2021).

were defined as healthy if CDR = 0 and cognitively impaired if CDR = 0.5 (15). Functional impairment was defined by a score of 3 on the Pfeffer scale (24). Regarding psychiatric evaluation, we used a cutoff point of 3 on the GDS and 10 on the Beck inventory to diagnose depression (18, 25). In this study, cognitive impairment was defined when a cognitive complaint was confirmed by screening tests, regardless of functional impairment. Patients with cognitive complaints without objective impairment in the tests performed were characterized as subjective cognitive decline (SCD) (26).

APOE genotyping analysis

According to the manufacturer's instructions, the patient's blood samples were collected in EDTA tubes, and subsequently, genomic DNA was extracted from peripheral blood leukocytes with the commercial PureLink™ Genomic DNA Mini Kit® (Invitrogen) (25). APOE genotypes were determined by real-time PCR (qPCR) using the TaqMan® allelic discrimination system (TaqMan® SNP Genotyping Assay, ThermoFisher®) (26). To this end, we used probes per sequences provided by the manufacturer: C___3084793_20 (rs429358) and C____904973_10 (rs7412), observing the information contained in the catalog number: 4351379, and similar protocols were used, described in the literature, for performing the technique. All analyses were performed in the QuantStudio® 5 qPCR platform (Applied Biosystems®, Foster City, CA, USA) (27).[2, 3, 4, 5]

Statistical analysis

Categorical data were expressed as absolute counts and percentages. Chi-square tests were used to evaluate the association among categorical data. Continuous data were first evaluated for normal distribution using the Kolmogorov–Smirnov test (28). Normal data were expressed as mean ± standard deviation (SD) and non-normal data as the median and interquartile range (IQR). Continuous data were compared among three groups per cognitive impairment (normal or cognitive unimpaired [CU] vs. cognitive impairment vs. subjective cognitive decline [SCD]). We compared normal data using one-way ANOVA with Tukey's *post hoc test*, and we adopted the Kruskal–Wallis test with Dunn's *post hoc test* for non-normal data (29). We analyzed data using SPSS software for Macintosh, version 23 (Armonk, NY: IBM Corp.). Values of $p <$ 0.05 were considered statistically significant.

Ethical aspects

The Research Ethics Committee of the Walter Cantídio University Hospital approved the study project under the number 4.092.933. All patients signed an Informed Consent Form with the right to privacy and confidentiality of the information obtained and could refuse to participate in the proposed activities and questions.

Results

In total, 207 individuals were screened, of which 66 were excluded (48 for not having performed blood collection, 10 for not showing neurological symptoms, and 8 for not having tested positive for COVID-19 through tests) (Figure 1). The final number of patients included in this study was 141, and all the following analyses were conducted on them. Patients were evaluated, on average, 4.5 months after COVID-19.

Table 1 presents a descriptive summary of the patients' characteristics. There was a female predominance (63.1%). The mean age was 48 years (16–90; SD = 14), with most patients having schooling >12 years (54.6%) (Figure 2). Most patients were not hospitalized in the acute phase of the disease (65.2%), and a minority had a severe clinical condition requiring admission to the intensive care unit (ICU) (3.5%). The most frequent APOE genotype was E3/E3 with 67.3% of cases, with a predominance of the E3 allele (96.5%); the second was the genotype E3/E4, corresponding to 23.4% of all cases, and the E4 allele (26.2%). In addition, 93 of the 141 patients (65.9%) had memory impairment symptoms as the main complaint. However, such complaint was objectively confirmed through screening tests in 25 patients (17.7%). In patients with cognitive impairment, we detected new dementia or deteriorated previous dementia in 2.8% of the total sample.

Regarding ACE-R and its sub-items evaluation, the cognitive impairment group showed a worse profile in total ACE-R and all sub-items (Tables 2, 3). The cognitive impairment group had decreased total ACE-R and sub-items than the normal and SCD groups ($p < 0.001$) (Figure 3).

Furthermore, other tests showed alterations in the cognitive impairment group. The MEEM score decreased in the cognitive impairment group compared with the normal and SCD groups (median of 23.5 [IQR of 17.5–26.5] vs. 29 [28–30] vs. 29 [28–30], respectively, $p < 0.001$). Concerning Beck's depression inventory, a statistical difference was only observed between the SCD group and the normal group, where SCD had increased levels ($p = 0.030$). Regarding Pfeffer's score, cognitive impairment had increased levels compared with the normal and SCD groups (Table 4; Figure 4). Before and after, there was no

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[2] https://www.thermofisher.com/order/catalog/product/K182002#/K182002

[3] https://www.thermofisher.com/order/catalog/product/4351379#/4351379

[4] https://www.thermofisher.com/order/genome-database/details/genotyping/C___3084793_20?CID=&ICID=&subtype=

[5] https://www.thermofisher.com/order/genome-database/details/genotyping/C____904973_10?CID=&ICID=&subtype=

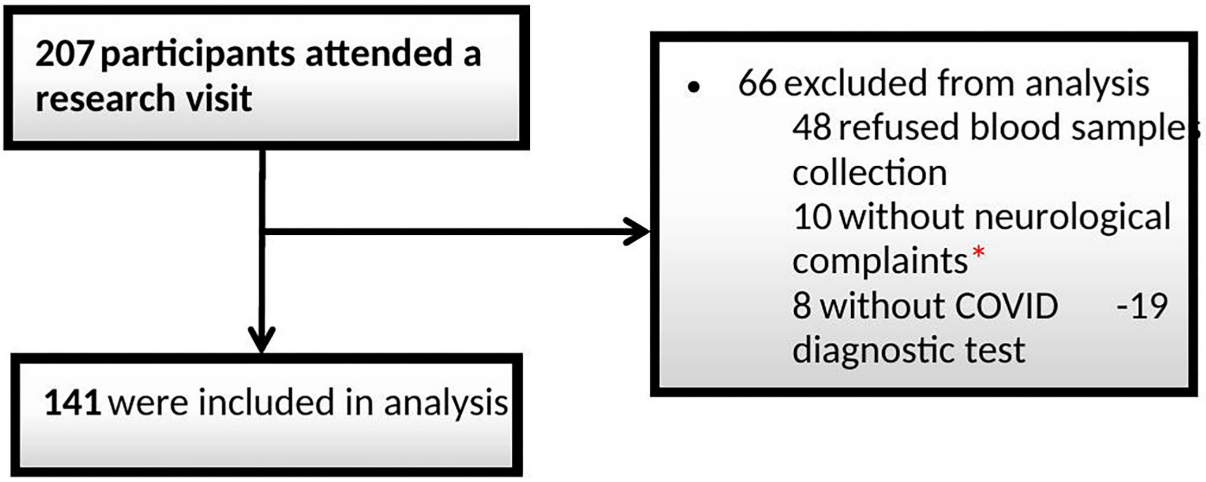

FIGURE 1
Flow diagram of participants. *E.g., headache, anosmia, cognitive complaints and others.

TABLE 1 Participant demographics, clinical characteristics, APOE genotype and cognition impairment.

Variables	n	%
Gender		
Male	52	36.9%
Female	89	63.1%
Scholarity (years)		
0	4	2.8%
1–4	6	4.3%
5–8	17	12.1%
9–12	37	26.2%
>12	77	54.6%
Hospitalization		
No	92	65.2%
Yes	36	25.5%
APOE genotype		
E2/E2	1	0.7%
E2/E3	8	5.7%
E2/E4	1	0.7%
E3/E3	95	67.3%
E3/E4	33	23.4%
E4/E4	3	2.1%
APOE allele		
E2	10	7.1%
E3	136	96.5%
E4	37	26.2%
Cognition		
Normal	48	34,0%
CI	25	17.7%
SCD	68	48.2%

CI, cognitive impaired; SCD, Subjective cognitive decline.

statistical significance between the groups for evaluations with other scores, such as PRMQ, GDS, and MRC.

Table 5 shows the correlation between patients' cognitive impairment and other symptoms (anosmia, depression, and headache). The cognitive impairment group had a lower frequency of anosmia than the normal and SCD groups (4 vs. 40 vs. 34%, respectively, $p = 0.005$). Depression was more frequent in the SCD and cognitive impairment groups than in the normal group (50 vs. 40 vs. 27%, respectively, $p = 0.046$). A total of 48 patients developed depression after COVID-19. In total, nine patients were hospitalized in the acute phase of the disease. Moreover, they had a mean ACER score of 85.7 [62–99], 63% were women, and the mean age was 43.4 years.

Table 6 shows patients' demographics and APOE genotyping with cognitive status correlation. Cognitive status had no association with APOE genotypes ($p = 0.840$) or alleles (Table 6). Conversely, the cognitive impairment was significantly more frequent in hospitalized patients and those with a lower education level (Table 6). Table 7 describes age comparisons concerning patients' cognitive status. The cognitive impairment group was significantly older than the SCD and normal groups (Table 7; Figure 2).

Discussion

Cognitive complaints are common during and after COVID-19, but few studies have objectively evaluated such complaints, especially after the acute phase of the disease (5). Furthermore, the literature has not yet reported the assessment of specific APOE haplotypes or genotypes with such cognitive complaints after COVID-19. In this study, we evaluated an outpatient population. Cognitive changes were the main complaints, even

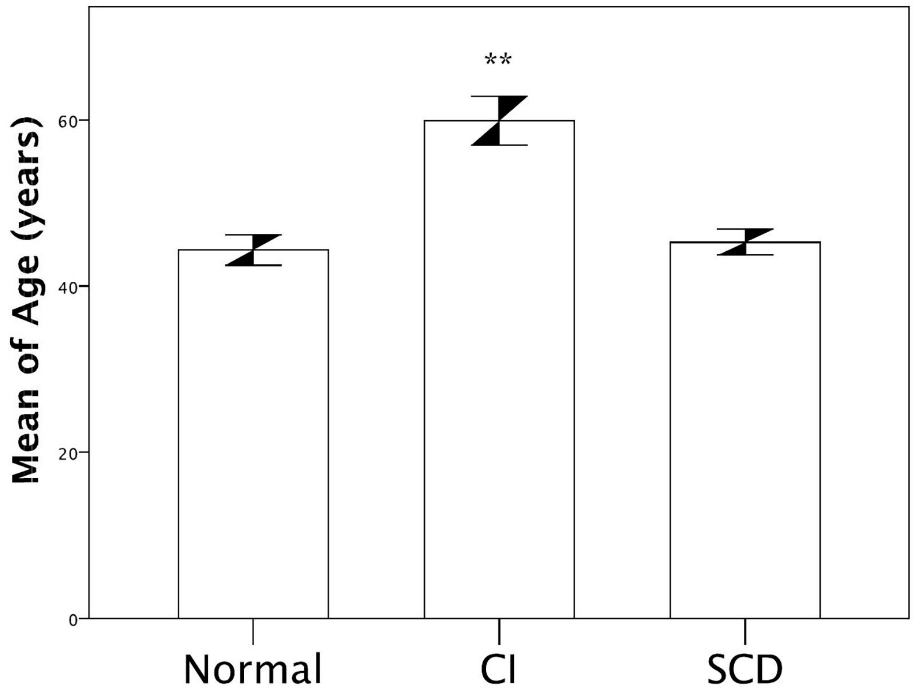

FIGURE 2
Comparison of age according cognitive status. ANOVA test was applied with Tukey post-test. ** $p < 0.05$ between CI vs. SCD and Normal in multiple using Tukey's test.

TABLE 2 Total ACER, ACER subitens, MMSE, PRMQ, Beck, GDS, Pfeffer, and MRC scores.

Instruments	Mean	Minimum	Maximum	Standard deviation	Median	Mean (95%CI)	
						LL	UL
Total ACE-R	82.5	12.0	100.0	15.1	87.0	80.0	85.1
Attention and orientation	16.5	4.0	18.0	2.6	18.0	16.1	17.0
Memory	19.4	0.0	26.0	5.1	20.0	18.6	20.3
Fluency	9.6	0.0	14.0	3.1	10.0	9.1	10.1
Language	23.5	4.0	26.0	4.3	25.0	22.7	24.2
Visuospatial	13.6	0.0	20.0	2.9	14.0	13.1	14.0
MMSE	27.4	10.0	30.0	3.7	29.0	26.8	28.0
PRMQ	7.0	5.0	25.0	4.0	5.0	6.3	7.7
Beck	5.2	0.0	21.0	6.6	0.0	4.0	6.4
GDS	3.7	0.0	12.0	3.6	3.0	2.1	5.3
Pfeffer	1.7	0.0	30.0	6.7	0.0	0.6	2.8
MRC before	0.0	0.0	2.0	0.2	0.0	0.0	0.1
MRC after	0.6	0.0	3.0	0.9	0.0	0.4	0.7

LL, Lower limit; UL, Upper limit; ACE-R, Addenbrooke's Cognitive Examination-Revised; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; MRC, Medical Research Council; GDS, Geriatric Depression Scale; PRMQ, Prospective and Retrospective Memory Questionnaire's scale.

in mild cases with a low mean age of 48 years and an average assessment of 4 months after the COVID-19 diagnosis. Analyzed by a cognitive screening instrument, we confirmed objective cognitive deficits in some subjects. Furthermore, depression was more common in subjects with SCD compared to the normal group.

Other studies have evaluated the association between cognitive impairment and COVID-19, both in the acute/subacute phase (<12 weeks) or after this period (>12 weeks) of the disease (30, 31). This differentiation is crucial since other factors can contribute to cognitive complaints, such as hospitalization, hypoxemia, and delirium in the acute phase of the disease (32–34). Our study, for example, found a significantly higher number of subjects with cognitive complaints and cognitive impairment hospitalized during the acute phase of the disease. Possible explanations could be that hospitalized patients had more severe infection with a greater possibility of systemic complications, more significant inflammatory response, and prolonged hospitalization, all related to worse cognitive performance (33, 34). Negrini et al. evaluated cognitive impairment in discharged patients and demonstrated that cognitive malfunctioning appears to be linearly associated with the length of stay in the intensive care unit (35). Furthermore, two recent systematic reviews, one with meta-analysis, found a lower general cognition in patients with COVID-19 (36, 37). The meta-analysis with the Montreal Cognitive Assessment (MoCA) showed lower scores for patients with COVID-19 compared to healthy controls (37). Conversely, other factors may account for the symptoms after the acute phase, such as inflammatory markers (4). This last finding is important, as previous evidence shows a possible causal role of microglial inflammation and Alzheimer's disease (38).

TABLE 3 Total ACE-R and subitens scores comparison in relation of patients cognitive status.

	Cognitive status			
	Normal ($n = 48$)	**CI ($n = 25$)**	**SCD ($n = 68$)**	***P*-value***
Total ACE-R	89 (81–93)	65.5 (46.5–76)	89 (84–92)	**<0.001** ^{A}
Attention and orientation	18 (17–18)	14 (10–17.5)	18 (17–18)	**<0.001** ^{A}
Memory	22 (19–24)	12.5 (10–15.5)	21 (19–23)	**<0.001**^{A}
Fluency	11 (8–12)	6.5 (3.5–8)	11 (9–12)	**<0.001**^{A}
Language	25 (24–26)	21 (15–22.5)	25 (24–26)	**<0.001**^{A}
Visuospatial	14 (13–16)	11 (8–13)	15 (14–16)	**<0.001**^{A}

Continuous data expressed as median and interquartile range between parenthesis.
*Kruskal-Wallis test was applied with Dunn post-test. A: $p < 0.001$ between CI vs. SCD, and $p < 0.001$ between CI vs. Normal.
CI, cognitive impaired; SCD, Subjective cognitive decline.

To correlate a possible genetical predisposition and a significant risk of developing cognitive impairment, we performed an APOE genotyping for SNPs rs429358 and rs7412 in those patients, which are widely discussed in the literature as responsible for increasing the risk of dementia and cognitive impairment (39–42). APOEs play a vital role in lipid transport and metabolism, thus influencing the risk of cardiovascular disease (10). They also have neuroprotective functions, including the E4 haplotype associated with an

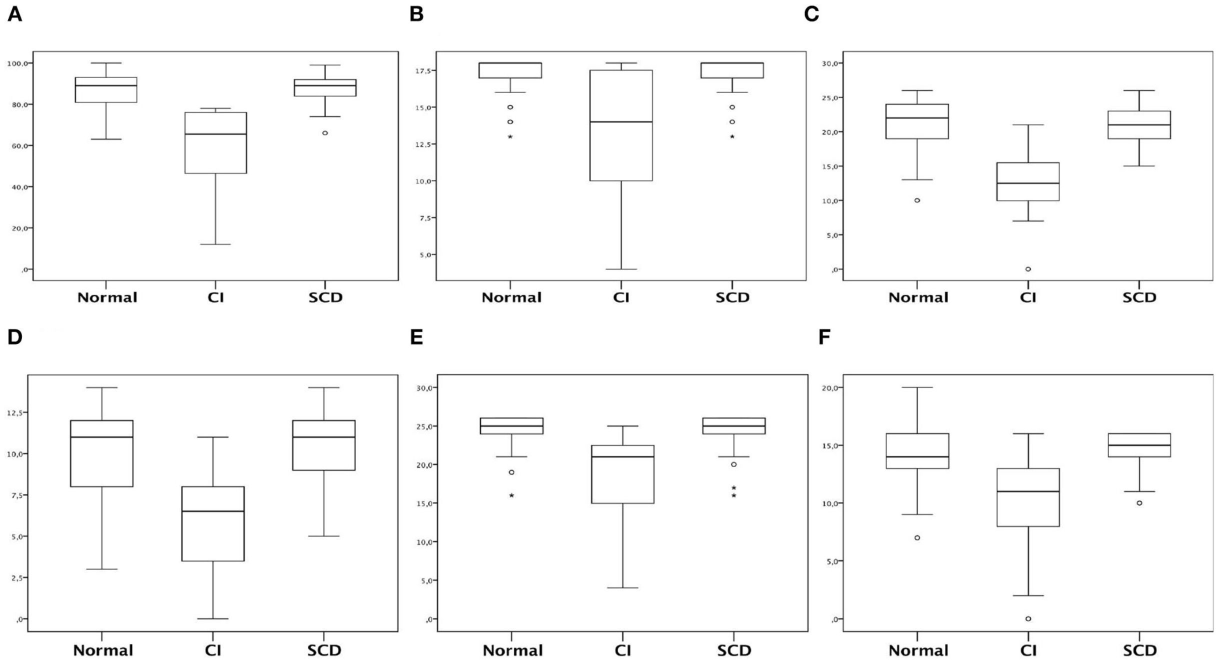

FIGURE 3
Box-plot representing total ACE-R and subitens scores comparison in relation of patients cognitive status. **(A)** Total ACE-R; **(B)** Attention and orientation; **(C)** Memory; **(D)** Fluency; **(E)** Language; **(F)** Visuospatial. *Kruskal-Wallis test was applied with Dunn post-test. **(A)** $p < 0.05$ between CI vs. SCD and Normal. CI, coginitve impaired; SCD, subjective cognitive decline.

increased risk of Alzheimer's disease (9). The E3 allele, in turn, does not display a greater or lesser risk of developing Alzheimer's disease. Most of our sample had E3/E3 genotype (67.3%), and the E4 allele was detected in 26.2% of the cases, similar to previous studies in the Brazilian population where the E3/E3 genotype was predominant (43). Our study did not evidence significant difference between groups regarding genotypes found or specific alleles, perhaps due to a low number of participants, mainly in the cognitive impairment group, despite a trend of a direct correlation between the cognitive impairment/SCD groups and the E4 allele, the same implicated in an increased risk of sporadic Alzheimer's disease (9). However, other factors could trigger cognitive impairment and do not necessarily involve specific APOE polymorphisms, such as inflammation, cerebral ischemia, and hypoxemia. To the best of our knowledge, no study has evaluated this association of post-COVID cognitive impairment with APOE polymorphism to date.

TABLE 4 MEEM, PRMQ, Beck, GDS, Pfeffer, and MRC scores comparison in relation of patients cognitive status.

	Cognitive status			
	Normal ($n = 48$)	**CI ($n = 25$)**	**SCD ($n = 68$)**	***P*-value***
MEEM	29 (28–30)	23.5 (17.5–26.5)	29 (28–30)	**<0.001**^{A}
PRMQ	5 (5–5.5)	5 (5–13)	5 (5–7)	0.079
Beck	0 (0–5)	1.5 (0–14.5)	4 (0–12)	0.030^{B}
GDS	3 (0–4)	3 (2–11)	1.5 (0–6)	0.407
Pfeffer	0 (0–0)	0 (0–22)	0 (0–0)	**<0.001**^{A}
MRC before	0 (0–0)	0 (0–0)	0 (0–0)	0.885
MRC after	0 (0–1)	0 (0–1)	0 (0–1)	0.333

Continuous data expressed as median and interquartile range between parenthesis. The bold values indicate the statistically significant signaled values.

*Kruskal-Wallis test was applied with Dunn post-test.

A: $p < 0.001$ between CI vs. SCD and $p < 0.001$ between CI vs. Normal.

B: $p = 0.024$ between Normal vs. SCD.

CI, cognitive impaired; SCD, Subjective cognitive decline.

After the acute disease phase of COVID-19 infection, some patients have described some persistent symptoms, such as memory complaints, receiving the name "long-haulers" by some authors (44). This clinical picture is similar to that of myalgic encephalomyelitis/chronic fatigue syndrome and the symptoms described after influenza (45, 46). However, post-COVID-19 symptoms occur at a higher frequency than influenza (46).

In this study, memory complaints without objective evidence were common and found in 65.9% of patients. Similarly, objective cognitive impairment detected through screening tests occurred in 17.7% of patients. These two backdrops refer to subjective cognitive decline and mild cognitive impairment conditions, whose gold standard for the diagnosis lies in extensive neuropsychological assessment not

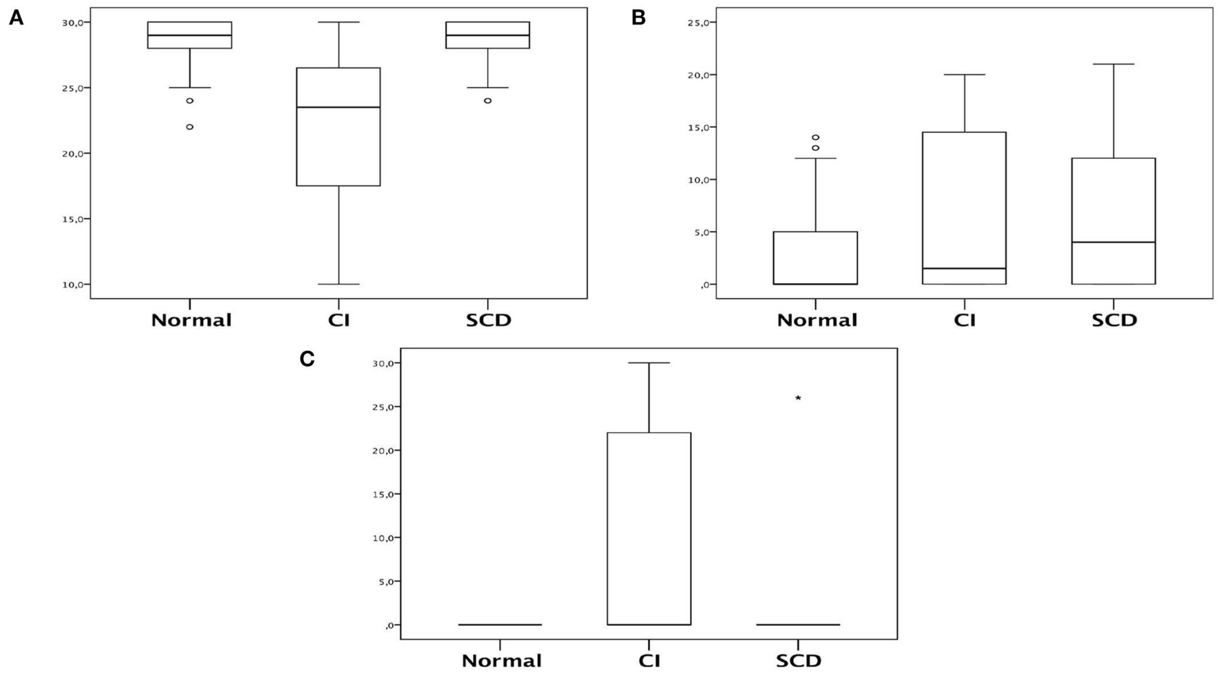

FIGURE 4
Box-plot representing MEEM, Beck and Pfeffer comparison in relation of patients cognitive status. **(A)** MMSE; **(B)** Beck; **(C)** Pfeffer. The asterisk symbol used to indicate the type of statistical test used to calculate *p*.

TABLE 5 Comparison between cognitive impairment in relation to other symptoms.

	Cognitive status			
	Normal = 48 *n* (%)	CI = 25 *n* (%)	SCD = 68 *n* (%)	*P*-value*
Anosmia				**0.005**
No	29 (60.4)	24 (96)	45 (66.2)	
Yes	19 (39.6)	1 (4)	23 (33.8)	
Depression				**0.046**
No	35 (72.9)	15 (60)	34 (50)	
Yes	13 (27.1)	10 (40)	34 (50)	
Headache				0.291
No	37 (77.1)	19 (76)	44 (64.7)	
Yes	11 (22.9)	6 (24)	24 (35.3)	

Categorical data expressed as absolute count and percentages between parenthesis. The bold values indicate the statistically significant signaled values.
*Chi-square test was used.
CI, cognitive impaired; SCD, Subjective cognitive decline.

TABLE 6 Comparison between patients demographics and APOE genotype in relation to cognitive status.

	Cognitive status			
	Normal = 48 *n* (%)	CI = 25 *n* (%)	SCD = 68 *n* (%)	*P*-value*
Gender				0.104
Female	22 (45.8)	11 (44)	19 (27.9)	
Male	26 (54.2)	14 (56)	49 (72.1)	
Scholarity (years)				**<0.001**
Until 8 years	5 (10.4)	12 (48)	10 (14.7)	
9 years or more	43 (89.6)	13 (52)	58 (85.3)	
Hospitalization				**<0.001**
No	34 (79.1)	9 (36)	49 (81.7)	
Yes	9 (20.9)	16 (64)	11 (18.3)	
APOE genotype				0.840
E2/E2	0 (0)	0 (0)	1 (1.5)	
E2/E3	2 (4.2)	2 (8)	4 (5.9)	
E2/E4	0 (0)	0 (0)	1 (1.5)	
E3/E3	37 (77.1)	16 (64)	42 (61.8)	
E3/E4	8 (16.7)	6 (24)	19 (27.9)	
E4/E4	1 (2.1)	1 (4)	1 (1.5)	
APOE allele				
E2	2 (4.2)	2 (8)	6 (8.8)	0.618
E3	47 (97.9)	24 (96)	65 (95.6)	0.793
E4	9 (18.8)	7 (28)	21 (30.9)	0.335

Categorical data expressed as absolute count and percentages between parenthesis. The bold values indicate the statistically significant signaled values.
*Chi-square test was used.
CI, cognitive impaired; SCD, Subjective cognitive decline.

TABLE 7 Total sample age and according cognitive status.

	Age (years)				
	Mean	Standard deviation	Minimum	Maximum	*P*-value*
Total sample	48	14	16	90	-
Cognitive status					<0.001
Normal	44	13	17	69	
CI	60	15	23	90	
SCD	45	13	16	74	

*ANOVA test was applied with Tukey post-test for multiple comparisons: $p < 0.001$ between CI vs. SCD and $p < 0.001$ between CI vs. Normal.

performed in these patients (26, 47). These conditions are essential given the possible progression to Alzheimer's disease (48, 49).

Psychiatric disorders may also be responsible for cognitive complaints (50). In our study, subjects with SCD had significantly higher scores on Beck's depression inventory than the normal group, which is relevant since patients with SCD had more depressive symptoms (26). Furthermore, Ismael et al. evaluated patients with mild COVID-19 and showed that 26.2% of patients had depressive symptoms 2 months after infection (51). Moreover, the impact on patients' lives also contributes to depressive symptoms (52).

In addition, our study found an inverse correlation between cognitive impairment and anosmia, which was in disagreement with other studies. Cristillo et al. found a direct association between cognitive impairment and olfactory dysfunction in patients after COVID-19 but in an old sample, making it possible as a brain aging marker (53). Previous studies demonstrated that olfactory dysfunction occurred in elderly patients along with cognitive impairment as brain aging markers (54). Finally, our study did not find associations between cognitive impairment and headache. Notwithstanding this, this association between headache and cognitive impairment can be found in patients after the acute phase of COVID-19 (55).

The most affected cognitive impairment group domain in ACE-R sub-items was the memory, as found in other studies (56, 57), which is relevant because limbic structures may suffer from inflammation (58). Hosp et al. evaluated brain PET-FDG in patients with acute phase COVID-19 and showed limbic involvement besides other brain structures (30). There was also a worse performance in the other ACE-R sub-items of attention, fluency, language, and visuospatial functions, but it was lighter than the memory sub-item.

Our study has some significant limitations. First, there was no control group. Additionally, our study has a selection bias, as we selected patients with neurological symptoms. We also did not perform a broader neuropsychological assessment to determine which cognitive domains were more affected and objectively assess other patients with subjective memory complaints without objective evidence in screening tests. Furthermore, a neuropsychological assessment is part of the diagnostic criteria for cognitive impairment and SCD; as it was not performed, the diagnosis of these conditions was impaired.

Moreover, despite differences found between cognitive impairment and normal/SCD groups' ACE-R scores, we should mention that there were essential differences between these groups regarding age and schooling, respectively, lower and higher in the normal/SCD groups, which may explain these differences found in ACE-R. Furthermore, selecting patients whose symptoms persisted for more than 3 months created a noteworthy bias since those whose symptoms disappeared before this period did not seek care. Furthermore, as the number of dementia cases found was low, we did not adjust for the total sample, and this study may achieve only a moderate effect if it exists since the total sample size should be $n = 1,283$ to achieve a small effect ($w = 0.3$) with a power of 80% for an association between APOE status and cognition on independence tests (59). Finally, there was no neuroimaging evaluation, precluding analysis of associations between complaints and radiological correlations. Nonetheless, this study is the most extensive series of patients so far, emphasizing cognitive complaints in an outpatient setting after the disease's acute phase. Furthermore, our sample consisted of patients with mild forms of the disease and after the acute and subacute phases of the disease, allowing us to show the persistent symptoms even in this population. Finally, APOE polymorphism analysis and possible associations with other symptoms strengthen our study.

In conclusion, our study helps to build knowledge about patients with post-COVID-19 cognitive manifestations. Our study reveals that cognitive complaints are common in patients with COVID-19, even after the acute disease phase and in mild cases, similar to other studies in the literature (36, 37). Hospitalized participants may have a higher risk of cognitive impairment. Moreover, APOE genotypes or haplotypes may not significantly play a role in the COVID-19 cognitive impairment. Longitudinal follow-up of these patients is critical to determine whether this cognitive impairment persists after a certain period. Furthermore, a neuropsychological assessment of these patients is crucial for better characterization of SCD or MCI and determining the most affected cognitive domains. Finally, it would be necessary for those with cognitive impairment to evaluate biomarkers of neurodegenerative diseases in cerebrospinal fluid or plasma, such as amyloid Beta 1–42, phosphorylated tau, and light chain neurofilament, thus bringing a link between COVID-19 and the onset or worsening of neurodegenerative diseases (60, 61).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of the Walter Cantídio University Hospital under the number 4.092.933. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design of work: JT-J, MS-N, and PB-N. Acquisition, analysis, or interpretation of data and work and drafting the work: JT-J and PB-N. All authors were involved in the critical review of the manuscript for important intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Common mental disorders during the COVID-19 pandemic in Hong Kong: Age-related differences and implications for dementia risk

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Background: The COVID-19 pandemic has imposed a profound negative impact on the mental health and wellbeing of societies and individuals worldwide. Older adults may be more vulnerable to the mental health effects of the pandemic, either directly from the infection itself or indirectly through the preventive measures. However, the existing literature on mental health in the older age groups has not been consistent so far. The aim of this study was therefore to assess the prevalence of common mental disorders (CMD; including depression and anxiety disorders) given their association with dementia risk, and to further examine age-related differences between older ($\geq$60 years old) and younger (18–59 years old) adult's psychological status during the COVID-19 pandemic.

Method: This was a secondary analysis of a cross-sectional survey-study conducted during the second wave of COVID-19 pandemic in Hong Kong. The survey was disseminated through different social media platforms to the general population and included sociodemographic questions, self-reported physical health, and previous encounter with SARS or COVID-19. CMD was the primary outcome and was assessed using the 6-item Kessler Scale. A total of 1030 adults fulfilled inclusion criteria.

Results: The prevalence of CMD during the pandemic was 16.1%. Compared to younger adults, older adults were significantly less likely to have a CMD (unadjusted OR = 0.07, 95% CI = 0.02–0.30, $p < 0.001$), with 18.1% of younger adults having CMD compared to 1.6% in the older cohort. Age differences remained significant after controlling for sociodemographic factors, physical health, and previous encounter with SARS or COVID-19 (adjusted OR = 0.12, 95% CI = 0.02–0.57, $p = 0.008$).

Conclusion: Common mental disorders are highly prevalent during the COVID-19 pandemic in Hong Kong, though older adults appeared to be less affected mentally. Present findings highlight the urgent need to implement measures and strategies to mitigate the mental health problems, with particular attention to the younger cohort. Given their association with higher dementia risk, early detection and treatment of depression and anxiety disorders will be of critical importance in providing some relief to the already pressurized dementia burden in the longer term.

KEYWORDS

COVID-19, mental health, depression, anxiety, age, dementia

Introduction

The outbreak of the COVID-19 pandemic has led to a mental health crisis globally (1, 2). The direct effects of the pandemic (i.e., the coronavirus infection itself) and the secondary impact (i.e., fear of getting infected, fear of death, social distancing, and quarantine) have inevitably created an environment in which many determinants of mental health are affected (3–5). Based on the data published so far, the early stages of pandemic have often found to be associated with increased levels of stress, anxiety, depression, and insomnia in the general population (6–9), with some preliminary findings even suggesting these effects may persist (10) or worsen (11) in the longer term. Such changes in mental health status can have a significant impact on the psychological risk factors that serve as important predictors of dementia (12, 13). Dementia represents one of the most significant public health challenges. Due to the irreversible nature of the disease and the lack of effective treatments, intervention of modifiable risk factors is of great clinical importance in slowing or preventing dementia onset (14). Depression is recognized as one of the modifiable risk factors for dementia (14, 15), whilst other neuropsychiatric symptoms such as anxiety have also been suggested to act as a prodromal symptom (16) as well as a risk factor for cognitive decline (17, 18). With the emerging evidence pointing to detrimental changes in psychological health during the COVID-19 pandemic and that such symptoms are amenable to treatment (19), monitoring the prevalence of common mental disorders (CMD; including depression and anxiety disorders) and identifying vulnerable groups for timely targeted assistance and intervention is therefore a public health priority (20).

Older adults have typically been considered as one of the most vulnerable groups to the consequences of the COVID-19 pandemic (21, 22). This population was not only perceived to be at the greatest risk of severe complications and mortality (23) but also predicted to be more susceptible to the negative psychological impacts of isolation and loss of access to social and health care (24–26). As a response, much concern has risen about the mental health of older adults, and numerous studies have since been conducted. Contrary to expectations however, the postulation that older adult's mental health would be disproportionately affected by the pandemic has not been uniformly supported by the available literature so far. To date, a number of cross-sectional surveys conducted in the first wave of the pandemic have reported that older adults are at most risk for significant deteriorations in their mental health, with elevated levels of anxiety and/or depressive symptoms (27–30). Similar results were also revealed in a study which compared population-based surveys data before and during the pandemic in Hong Kong, elevated rates of stress, anxiety and depression symptoms were prominent during the COVID-19 outbreak, and such increases were particularly evident amongst the older population as compared to the younger population (31). Moreover, a study conducted in China also found the emotional response of older adults aged 60 years and above was more apparent as compared to the other age groups (32).

In contrast, despite all the challenges that the older population may face during the pandemic, lower rates of mental distress in this population compared to younger age groups have been reported, with older adults faring better than younger adults in multiple metrics of mental health (33). Several large representative surveys of adults in the US (34), UK (35), Denmark (36), Slovenia (37) and China (38) have also found an inverse relationship between age and mental health symptoms. Compared to younger adults, older adults seem to respond to the pandemic with a more positive emotional response and reported lower rates of anxiety and depression. To further complicate the findings, however, some studies have even found that mental health symptoms (i.e., the prevalence and severity of depression and anxiety symptoms) were not differentiated based on age (7, 39–41). Such inconsistencies emphasize the need for further research to explore age differences in the psychological impact of COVID-19, whilst taking into consideration of the potential confounding effects of various social determinants of mental health changes during the COVID-19 pandemic such as female, lower socioeconomic status as well as subjective poorer physical health (42–44). Moreover, it is worth noting that most of the studies outlined above (except Pedersen et al. (36) and Prelog et al. (37)) provided only a snapshot of the immediate and the early months of the mental health responses following the COVID-19 outbreak, which may evolve with the development of the pandemic, public health interventions, and repeated exposure to social distancing regulations.

In this context, this study aimed to (i) evaluate the prevalence of CMD during the second wave of the COVID-19 pandemic in Hong Kong, given their high prevalence during the early stages as well as prior to the COVID-19 pandemic (13.3%, see Lam et al. (45)) and (ii) to further examine whether mental health differs amongst the older and younger population in response to the pandemic.

Methods

Study setting, design and participants

This study was a secondary analysis of a cross-sectional survey conducted in Hong Kong during the COVID-19 pandemic (46). This planned secondary analysis specifically concerned age differences and prevalence of mental health problems of the same cohort.

Participant recruitment was conducted between 17 June and 31 July 2020, during the outbreak of the second wave of the COVID-19 pandemic in Hong Kong. The survey was disseminated using the university mass email system and various social media platforms (including Facebook, WhatsApp and WeChat) to the general population and the community cohorts from our ongoing government-commissioned studies, where the households were randomly selected based on the addresses from all 18 districts of Hong Kong generated from the Census and Statistics Department of the Government of Hong Kong. Participants were included if they were Hong Kong residents aged 18 years and over with internet access. Those who were younger than 18, non-local residents, or having significant impairments in communication or understanding instructions were excluded. Completion of the whole survey took about 5 min, and participants only needed to choose the answers that best reflected themselves rather than what they hoped they should be. Participants were free to participate or withdraw anytime from the survey, with no negative consequences associated in those who did not complete or submit their responses online. As there was no direct contact with participant or data collection of personal identifiers, informal consent was sought from participants (i.e., those who successfully completed and submitted a response online was deemed as giving their implied consent).

Ethics approval was obtained from the Survey and Behavioral Research Ethics Committee at the University and study registration was completed (ChiCTR 2000033936) before commencement of the survey. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Assessment of mental health problems

The 6-item Kessler scale (K6) was used in the present study. The K6 is a simple and quick self-administered rating scale developed to assess psychological distress and screen for CMD in the general population (47). The scale has been validated locally with good psychometric properties reported (48). Participants were asked to rate how often they felt (1) nervous, (2) hopeless (3) restless or fidgety, (4) so depressed that nothing could cheer them up, (5) that everything was an effort, and (6) worthless in the last 30 days. Each item codes from 0 to 4, yielding a total K6 score that ranges from 0 to 24. Higher scores are indicative of greater symptom severity. A cut-off score of 13 was used to define CMD, as previously suggested as indicative of severe mental distress (47).

Assessment of covariates

The following potential confounding factors were examined: basic sociodemographics (sex, educational level, employment status and retirement), self-reported physical health status (assessed by the 5-point Likert scale of self-rated assessment used in the World Health Survey (49), possible choices were "very good," "good," "moderate," "bad" or "very bad"), and previous personal or close encounter with severe acute respiratory syndrome (SARS) in 2003 or COVID-19 (participants, their family members, or people with whom they had close contact diagnosed with SARS or COVID-19 before).

Statistical analysis

As this was a secondary analysis of an earlier published study, the sample size was predetermined (46). Statistical analysis was performed using the IBM SPSS Statistics, Version-26.0 (IBM Corp). In this study, age was used both as a continuous and binary variable, with a cut-off of 60 years old as a separation between older ($\geq$60 years) and younger adults (18–59 years). First, comparisons of variables between older and younger participants were analyzed using the independent t-test or the χ^2, as appropriate. The level of statistical significance was set at $p < 0.05$ (two-tailed). We analyzed self-rated physical health as a dichotomous measure, with "bad" and "very bad" as poor. To determine the relationship between age (continuous variable) and K6 total score, Spearman's correlation coefficient was used. Where a significant correlation was found, linear regression further analyzed the relationship, first unadjusted and then adjusting for covariates including sex, educational level, employment status, retirement, physical health, and previous encounter with SARS or COVID-19. Finally, logistic regression analysis was employed to examine the association between age (categorical variable) and CMD, with the former treated as the independent variable and the latter as the dependent variable. Model 1 was unadjusted, whereas Model 2 was adjusted for the same potential confounding factors. The odds ratios (ORs) were computed to yield point estimates with 95% confidence intervals (CI). The younger population served as the reference group.

Results

Prevalence and characteristics of participants by age group

A total of 1036 individuals responded to the online survey. Of these, six were excluded as they did not meet the inclusion criteria. Hence the final analysis included 1,030 participants. The cohort consisted of 905 younger adults and 125 older adults respectively. Compared to the younger adults, older adults were more likely to have lower educational level, retirement, and a lower K6 total score. 18.1% of younger adults reported having CMD compared to 1.6% in the older cohort. There was no significant difference in sex, unemployment rate, self-perceived physical health, or previous encounter with SARS or COVID-19 between the two groups (Table 1).

Association between age and K6 total score

Correlation analyses revealed a statistically significant inverse relationship between age and total K6 score ($r = -0.378$, $p < 0.001$). The likelihood of having a higher K6 total score, thus poorer mental health appears to decrease with age (Figure 1). Consistent with such findings, linear regression analysis also found that age was associated with K6 total score. For each 1-year increase in age the expected decrease in K6 total score was 0.11 points ($B = -0.11$, 95% CI $= -0.13$ to -0.10, $p < 0.001$). This association remained significant after adjusting for sex, educational level, employment status, retirement, physical health and previous encounter with SARS or COVID-19 ($B = -0.13$, 95% CI $= -0.15$ to -0.11, $p < 0.001$; Table 2).

Association between age group and CMD

Logistic regression analyses revealed that the odds of reporting CMD was significantly lower in the older adult population than in the younger population (unadjusted OR $= 0.07$, 95% CI $= 0.02$ to 0.30, $p < 0.001$). This association remained statistical significance after adjusting for covariates including sex, educational level, employment status, retirement, physical health, and previous encounter with SARS or COVID-19 (adjusted OR $= 0.12$, 95% CI $= 0.02$ to 0.57, $p = 0.008$; Table 3). Apart from younger age, poor physical health (adjusted OR $= 2.58$, 95% CI $= 1.74$ to 3.82, $p < 0.001$) and higher educational level (adjusted OR $= 1.56$, 95% CI $= 1.03$ to 2.36, $p = 0.04$) appeared to independently increase the odds of having CMD during the pandemic.

Discussion

The present study sought to examine the prevalence of CMD and to explore age-related differences in mental health during the COVID-19 pandemic in Hong Kong. Findings from this cross-sectional survey extend previous research (7, 31, 38) and demonstrate a high prevalence of depression and anxiety disorders in the general population, and such symptoms may persist over time, even into the subsequent waves of the pandemic. In this study, we found that 16.1% of our cohort were living with CMD during the second wave of COVID-19 pandemic. This was higher than the prevalence of CMD that we found before the pandemic, which was 13.3% (45). Similar findings have also been documented in studies concerning the Hong Kong population in which the authors also reported a marked elevation of 30.6% (31) and 33.8% (50) in anxiety and depression during the first wave of the pandemic. Whilst these numbers may only provide rough comparison estimates, given the variation in the timeframe and measures used to assess mental health problems, but such consistent, marked increases are worthy of attention. So far, much emphasis has been placed on the precautionary measures and medical resources to minimize the spread of the COVID-19 infection and to reduce mortality, but the psychosocial/mental health consequences associated with these measures and the virus itself have largely been neglected (51). From a clinical perspective, present findings

TABLE 1 Comparison of characteristics between younger and older adults ($n = 1,030$).

Characteristics	Younger adults (18–59 years) $n = 905$	Older adults (≥60 years) $n = 125$	P-value
Female, *n* (%)	634 (70.1)	79 (63.2)	0.12
Tertiary educational level, *n* (%)	663 (73.3)	43 (34.4)	<0.001
Unemployment, *n* (%)	37 (4.1)	5 (4.0)	0.96
Retirement, *n* (%)	14 (1.5)	72 (57.6)	<0.001
Poor physical health, *n* (%)	156 (17.2)	25 (20.0)	0.45
Previous encounter with SARS or COVID-19, *n* (%)	26 (2.9)	5 (4.0)	0.49
K6 total score, mean (SD)	8.1 (4.7)	4.7 (3.3)	<0.001
Common mental disorders (*n*, %)	164 (18.1)	2 (1.6)	<0.001

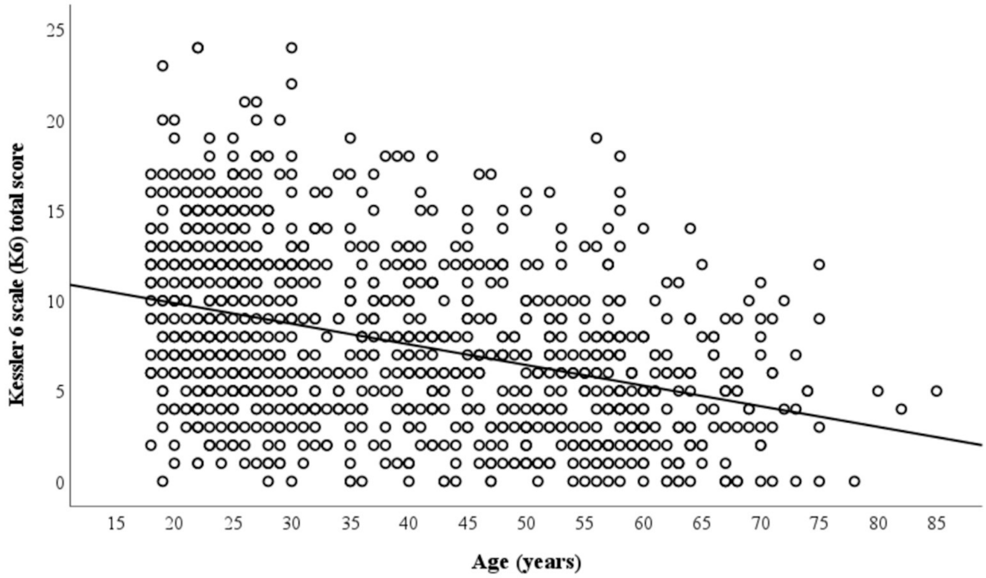

FIGURE 1
Correlation between participant age and K6 total score.

TABLE 2 Linear regression analysis of associations between age and K6 total score.

	B	SE	Standard β	95% CI	P-value
Unadjusted regression model (adjusted $R^2 = 0.14$)					
Age	−0.11	0.01	−0.38	−0.13 to −0.10	<0.001
Adjusted regression model (adjusted $R^2 = 0.18$)					
Age	−0.13	0.01	−0.42	−0.15 to −0.11	<0.001
Female	0.30	0.29	0.03	−0.28 to 0.87	0.31
Tertiary educational level	−0.70	0.33	−0.07	−1.34 to −0.05	0.04
Unemployment	0.30	0.68	0.01	−1.03 to 1.63	0.66
Retirement	0.08	0.56	0.01	−1.02 to 1.19	0.88
Poor physical health	2.28	0.35	0.18	1.59 to 2.97	<0.001
Previous encounter with SARS or COVID-19	1.07	0.78	0.04	−4.72 to 2.60	0.17

CI, confidence interval; SE, standard error; SARS, severe acute respiratory syndrome.

highlight the urgent need to implement and reconsider public mental health measures and responses in order to meet the added demand for mental health services.

The increased prevalence of CMD imposes significant public health implications, and one of the most concerning and debilitating longer-term impact concerns dementia, which already constitutes a public health emergency (52). Depression represents a risk factor for cognitive decline and dementia (53), with studies consistently associating depression (or depressive symptoms) with a more than two-fold increase in dementia risk (54, 55). Additional studies have also shown that depression accelerates the progression and conversion from a cognitively normal state to mild cognitive impairment and dementia (56–58), and those with persistent symptoms exhibit more rapid pathological brain aging (59) and are at greater risk of cognitive decline (15). Moreover, longer durations of untreated depression are correlated with hippocampal atrophy (60) indicating progressive neurodegeneration and dementia is involved in depression symptomatology. Although relatively less studied, recent evidence suggests anxiety may confer an additional risk for incident cognitive decline and dementia (17). Among mid-life and older community adults, increased anxiety was found to predict verbal memory deterioration over a 12-year follow-up period (18). Likewise, midlife anxiety symptoms have been associated with an increased risk for the development of dementia, where the mean interval between

TABLE 3 Regression analysis of determinants of common mental disorders (CMD).

Variable	Model 1		Model 2	
	OR (95%CI)	P-value	OR (95%CI)	P-value
18–59 years (younger adults)	Reference group			
≥60 years (older adults)	0.07 (0.02–0.30)	<0.001	0.12 (0.02–0.57)	0.008
Female	1.33 (0.91–1.93)	0.14	1.33 (0.90–1.97)	0.15
Tertiary education level	1.81 (1.22–2.68)	0.003	1.56 (1.03–2.36)	0.04
Unemployment	1.24 (0.56–2.72)	0.60	1.29 (0.57–2.94)	0.55
Retirement	0.11 (0.03–0.47)	0.003	0.52 (0.10–2.61)	0.43
Poor physical health	2.42 (1.65–3.53)	<0.001	2.58 (1.74–3.82)	<0.001
Previous encounter with SARS or COVID-19	1.54 (0.65–3.64)	0.32	1.74 (0.71–4.28)	0.22

Model 1: unadjusted.
Model 2: adjusted for all factors.

anxiety assessment and dementia diagnosis was more than 10 years (61). Adding to the evidence base, a recent meta-analysis also identifies anxiety as associated with a 24% higher risk of developing all-cause dementia (62). More recently, asymmetric atrophy of the hippocampus has also been demonstrated in humans with Alzheimer's disease (AD) and was found to increase with social isolation in a study using animal models for AD (63). More importantly, isolation was associated with an increased and worsening of neuropsychiatric symptoms, and such symptoms may function as the underlying mechanisms responsible for such an association between COVID-19 related isolation and worsening of AD-brain hippocampal asymmetry (63). Taken together the evidence, although mental health effects on dementia incidence was not directly assessed in the present study, the increased prevalence of depression and anxiety disorders during the COVID-19 pandemic has the potential to increase the risk for subsequent dementia, as well as worsen its symptoms. Early identification and timely treatment of this increasing CMD is thus crucial in preventing another public health crisis in the near future and extend the quality of life in old age.

The awareness that increased age is a risk factor for COVID-19-related mortality, together with the restrictions on social interactions inducing loneliness and isolation, had a psychological impact on older adults during the pandemic. However, in this study, we did not observe such an effect amongst the older population. In fact, results showed that age is negatively associated with K6 score. In particular, compared to our cohort of younger adults, older adults were less likely to report poor mental health, with 18.1% of younger adults reported having depression and anxiety disorders, compared to only 1.6% of those in the older population. Importantly, age differences in mental health remained significant after accounting for socioeconomic factors and participants' previous encounter with SARS or COVID-19. The present findings are consistent with existing studies suggesting that older adults may be less negatively affected by COVID-19 related mental health problems, report fewer negative emotions (64), and experience less anxiety and depression compared to their younger counterparts (36, 65). Although research is still ongoing, these studies seem to suggest that at least a sub-population of older adults is emotionally resilient, potentially owing to their complex experiences and adaptive coping skills/strategies built during their previous lives. Indeed, their resilience has been found to be less influenced by stressful life events (66) and associated with meaning in life (67), which may in part explain the better mental health outcomes observed in the older age groups.

Self-perceived physical health was in the lower interests of researchers during the COVID-19 pandemic. Interestingly, in this study we found that physical health status mediated the relationship between age and mental health outcomes, such that older adults who perceived their physical health as poor were more likely to report CMD than their counterparts who perceived their physical health as good. Similar findings have also been reported elsewhere, in which the authors found that anxiety and depressive symptoms were more frequent amongst adults who subjectively assessed their physical health as poor (68). The present findings may be of clinical importance and suggests that better self-perceived health may serve as a relative protecting factor for the impact of the COVID-19 pandemic on mental health but further investigation is warranted before conclusions can be drawn.

Limitations

Despite its interesting results, the study has important limitations. First, as this was a cross-sectional observational study, it is difficult to elucidate a causal relationship between the COVID-19 pandemic and mental health problems. As the pandemic continues to evolve, continuous efforts are needed to monitor the wellbeing of the general population. Second, the present findings might not be generalizable to other populations. Different countries are characterized by different COVID-19 incidence and death rates, and there are wide variations in governmental restrictions which in turn is likely to have differential impacts on mental health. Third, assessment of mental health problems relied on self-rated measures, and health records were not reviewed, so the diagnosis, onset and duration of depression and anxiety disorders could not be confirmed. Thus, it cannot be ruled out that study results may have reflected, at least partially pre-existing psychiatric disorders/psychological symptoms. Fourth, due to the strict restriction measures in place, the study was conducted through an online survey distributed by the university mass email system and various social media platforms. Recruitment using several platforms was made in an attempt to optimize response rate, however the underrepresentation of older adults in our sample is evident. It must be mentioned that whilst the university mass email system targeted different populations including students, alumni, staff members, as well as retirees, the exact number of people from different age groups in the mass email system was not known. Furthermore, online recruitment potentially skews the participants toward more digitally experienced and skilled users, resulting in a bias toward representativeness especially of the older and vulnerable populations. Lastly, as the current data were collected anonymously through an online survey, participants' responses and identity such as their sociodemographics could not be verified.

Conclusion

To conclude, the COVID-19 pandemic has lasted and created a significant negative impact on mental health worldwide. Findings from this study suggests the COVID-19 pandemic was associated with an elevated risk for CMD (depression and anxiety disorders) especially for the younger population. Whilst continuous efforts have focused on the preventive measures, present findings highlight the urgent need for implementation of resources to reduce the COVID-19 related mental health problems. Timely identification and treatment of depression and anxiety disorders will be of critical importance, given their association with dementia risk, prompt tackling may thus provide the opportunity to offer some relief to the already pressurized dementia burden in the longer term.

Data availability statement

The data that support the findings of this study are available from the corresponding authors AL and LL upon reasonable request.

Ethics statement

Ethics approval was obtained from the Survey and Behavioural Research Ethics Committee at the Chinese University of Hong Kong before commencement of the survey.

Author contributions

SC, AL, and LL conceived of and designed the study. JK, RY, and CK searched the literature. GC, CL, and BW designed the online questionnaire and collected the data. JK analyzed and interpreted the data and wrote the paper. AL and LL supervised the study, has full access to all the data in the study, and has the final responsibility for the decision to submit for publication. All authors critically edited, revised the work, and read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of the COVID-19 pandemic on some modifiable risk factors of dementia in an aging, rural Indian population

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Introduction: The impact of the COVID-19 pandemic and associated lockdowns is likely to have caused adverse changes in lifestyle-related/cardiovascular risk factors and other such modifiable risk factors of dementia. We aimed to examine the pandemic's impact on some modifiable risk factors of dementia among rural Indians belonging to a large, prospective aging cohort—Srinivaspura Aging, NeuoSenescence, and COGnition (SANSCOG).

Methods: This was a cross-sectional study among adults aged≥45years (n=3,148; 1,492 males and 1,656 females) residing in the villages of Srinivaspura in Karnataka state, India. SANSCOG study data (clinical and biochemical assessments) of these participants were obtained from three distinct periods: (i) the "pre-COVID period"—before India's nationwide lockdown on 24 March 2020, (ii) the "COVID period"—during the first and second waves of the pandemic, wherein the social restrictions were prominent (25 March 2020 to 30 September 2021), and (iii) the "post-COVID period"—after easing of restrictions (from 1 October 2021 onward). Proportions of participants with diabetes, hypertension, obesity, dyslipidemia (diagnosed using standard criteria), and depression (diagnosed using the Geriatric Depression Scale) were compared between the above three periods.

Results: The odds of having obesity, abnormal triglycerides, and depression among individuals in the COVID period were 1.42 times, 1.38 times, and 2.65 times more than the odds in the pre-COVID period, respectively. The odds of having hypertension, obesity, abnormal total cholesterol, abnormal triglycerides, abnormal LDL, and depression among individuals in the post-COVID period were 1.27 times, 1.32 times, 1.58 times, 1.95, 1.23, and 3.05 times more than the odds in the pre-COVID period, respectively. The odds of diabetes did not differ between any of the three periods.

Discussion: We found significantly higher odds of some of the studied risk factors in the COVID and post-COVID periods compared to the pre-COVID period, suggesting that the pandemic adversely impacted the physical and psychological health of this marginalized, rural Indian population. We call for urgent public health measures, such as multimodal, lifestyle-based, and psychosocial interventions, to mitigate this negative impact and reduce the future risk of dementia.

KEYWORDS

pandemic (COVID-19), COVID-19, rural India, dementia, elderly, cardiovascular risk factors

1. Introduction

The COVID-19 pandemic resulted in a global public health emergency and upended the lives of millions of persons worldwide. During the first wave of the pandemic, India underwent one of the world's biggest nationwide lockdowns from 25 March to 31 May 2020 (1). These lockdowns strictly prohibited individuals from leaving their homes except in emergencies, shut down public transport systems, and closed all offices, businesses, and institutions, barring essential services. After the total lockdown period, there were phased reductions in restrictions that extended till the onset of the second wave.

The second wave that started in February 2021 was associated with relatively milder, state-wise lockdowns, implemented entirely or partially according to the prevailing situations in localized areas. In Karnataka (where our study was conducted), containment measures, such as movement and transport restrictions, including night curfews, continued till May/June 2021, after which there were relaxations in inter-state, intra-state transport, economic activities, and work-related activities. By the end of October 2021, social gatherings, including cinema halls, auditoriums, and similar places, were permitted to function at 100% occupancy (2). The third wave in early 2022 did not entail any prominent lockdowns, and control measures were sporadic. So, it can be said that significant social restrictions in Karnataka due to the COVID-19 pandemic lasted till the end of September 2021. Though these public health measures were undoubtedly essential to control the disease spread and reduce mortality, the stringent lockdowns, particularly during the first wave, had prominent socioeconomic and health-related implications (3–7).

The pandemic and associated restrictions also resulted in substantial lifestyle changes. Studies worldwide have reported reduced physical activity (8, 9), altered dietary behaviors (10–12), and diminished psychosocial functioning (13, 14). Similar changes were also observed among Indians, with studies from different parts of the country reporting an increase in unhealthy eating habits, decreased physical activity, and weight gain (10, 15–17). Thus, it is possible that the pandemic had an impact on the prevalence of lifestyle-related disorders, such as diabetes, hypertension, dyslipidemia, obesity, etc. Further, it overburdened India's healthcare system, and therefore, people's access to routine healthcare was considerably hindered (18–21). These challenges, in turn, adversely affected the management of individuals with chronic diseases (22, 23). In addition, the pandemic led to increased stress, and some studies from India have revealed a negative impact on psychological health (14, 24–26).

Though the impact of the pandemic was wide-ranging, vulnerable populations, such as older adults, had disproportionately higher adverse effects. This impact was seen not only in direct effects, such as increased susceptibility to infection, more severe symptoms, and worse outcomes, including higher mortality (27), but also in indirect effects, such as social isolation, disruption in routine lifestyle, and poor access to healthcare (28, 29).

India's older population is growing rapidly and will reach 353 million by 2050 (30). This demographic transition will be accompanied by an increase in the prevalence of dementia. Therefore, it is essential to examine the adverse effects of the COVID-19 pandemic on the aging Indian population, specifically on lifestyle-related disorders, such as diabetes, hypertension, obesity, dyslipidemia, and psychological disorders, such as depression, since they are recognized modifiable risk factors of dementia (31–33). As such, the prevalence of the above risk factors is generally on the rise among Indians owing to rapid urbanization and its associated lifestyle changes. The pandemic's potential adverse effects could precipitate this situation, which, in turn, would further worsen the burden of dementia in the country.

We are conducting a large-scale, population-based, prospective cohort study on aging in rural Indians, namely Srinivaspura Aging, NeuoSenescence, and COGnition (SANSCOG) study (34). This cohort study aims to understand the differential trajectories of aging and identify risk and protective factors for dementia. SANSCOG cohort includes cognitively healthy aging individuals who undergo multimodal (clinical, cognitive, biochemical, genetic, and neuroimaging) assessments and are periodically followed up over a long term (at least 10 years).

SANSCOG cohort participants, who hail from a rural area in Karnataka in southern India, were substantially impacted by both waves of the pandemic. The first wave lockdowns entailed a prominently adverse financial impact for our predominantly agriculture-dependent participants due to hampering harvest, transport, and sale of their farm produce (35, 36). During the second wave, there was a severe healthcare crisis when the infections rapidly spread among these rural areas. The already fragile rural healthcare infrastructure in these areas was overwhelmed with the massive load of COVID cases. Therefore, the pandemic considerably disrupted our study participants' everyday lives and significantly impacted their lifestyles.

In the current study, we aimed to examine the impact of the COVID-19 pandemic on specific modifiable risk factors of dementia, namely diabetes, hypertension, obesity, dyslipidemia, and depression in aging Indians from the SANSCOG study cohort. We hypothesized that there would be an increase in the prevalence of one or more of the risk factors mentioned above in the post-COVID period compared to the pre-COVID period. However, since these risk factors are potentially modifiable, prompt identification and appropriate mitigative measures can be put in place, which is why this study is important in the purview of dementia risk reduction.

2. Methods

2.1. Study design

A cross-sectional study design was employed for this study, wherein baseline clinical and biochemical assessment data of SANSCOG cohort participants were utilized.

2.2. Setting

SANSCOG cohort study is being conducted in a community-based setting in the villages of Srinivaspura 'taluk' (sub-district) in Kolar district, Karnataka state, India.

2.3. Recruitment

SANSCOG cohort study employs an area sampling strategy, a non-probabilistic sampling technique, wherein eligible and consenting participants are recruited from the villages of Srinivaspura.

2.4. Participants

SANSCOG cohort recruits rural-dwelling, cognitively healthy individuals (males and females) aged 45 years and above from the Srinivaspura area. Individuals with a known diagnosis of dementia (additional dementia screening was also done at the community before recruitment), psychosis, bipolar disorder, substance dependence (except nicotine), and any severe medical illness or significant hearing or vision impairment likely to limit the study evaluation are excluded. Further details of SANSCOG study recruitment and assessments are published elsewhere (34).

This study included 3,148 SANSCOG cohort participants (males: 1492, females: 1656) who had completed their baseline clinical and blood biochemical assessments. These participants underwent their assessments from 1 January 2018 to 30 April 2022. They were then divided into three mutually exclusive groups based on the timing of their baseline assessment. The three groups of participants were as follows:

(i) Participants who had completed their baseline assessments in the "pre-COVID period" (1 January 2018 to 24 March 2020).
(ii) Participants who had completed their baseline assessments in the "COVID period" (25 March 2020 to 30 September 2021).
(iii) Participants who had completed their baseline assessments in the "post-COVID period" (1 October 2021 to 30 April 2022).

2.5. Ethics clearance and informed consent

SANSCOG study has obtained ethics clearance from the Institutional Ethics Committee (Institutional Review Board) of the Centre for Brain Research, Indian Institute of Science, Bangalore, India. Written, informed consent was obtained from all participants before recruitment.

2.6. Measurements

(i) *Clinical assessments*: Clinical assessments were conducted by trained clinicians or nurses, and data were collected using handheld digital devices. Data on self-reported physician diagnoses of diabetes and hypertension and relevant treatment details were obtained. Systolic and diastolic blood pressure (BP) was measured to the nearest 2 mm Hg using a mercurial sphygmomanometer (Diamond Deluxe BP apparatus, Industrial Electronic and Allied Products) in the right arm supine position.
(ii) *Anthropometric measurements*: Height was measured in centimeters using a standard stadiometer with the participant standing. Weight was measured in kilograms using a body composition monitor (Tanita InterScan BC-601). Body Mass Index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters).
(iv) *Depression assessment*: Depression was assessed using the Geriatric Depression Scale (GDS-30) (37), administered in the local language by trained clinicians or nurses well-versed in the local language and culture. GDS-30 is a self-reported scale that has been validated extensively. It comprises 30 'yes or no' questions; for questions 1, 5, 7, 9, 15, 19, 21, 27, 29, and 30, a 'no' response is scored as one point, and for other questions, a 'yes' answer is scored as one. The total score is the sum of the scores of individual questions (maximum score of 30).
(v) *Blood biochemical tests*: Periodic blood collection camps were organized in the respective villages where the participants were recruited from (given the difficulty in participants coming to the laboratory due to poor public transport facilities in the area). A total volume of 15 ml of peripheral venous blood was collected from each participant under overnight fasting conditions by trained phlebotomists for a detailed panel of biochemical tests that included glucose, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Glucose estimation was done using the hexokinase method, whereas the enzymatic method was used for lipid parameters.
(vi) *Diagnostic criteria for risk factors*: Diagnoses of the studied conditions/risk factors, namely diabetes, hypertension, obesity, abnormal lipid profile, and depression, were made using the criteria listed in Table 1.

TABLE 1 Diagnostic criteria for risk factors.

Risk factor	Criteria for diagnosis
Hypertension	• Self-reported past diagnosis of hypertension
	• In participants who did not have/were not aware of a past diagnosis, systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg
Diabetes	• Self-reported past diagnosis of diabetes
	• In participants who did not have/were not aware of a past diagnosis, fasting blood glucose ≥ 126 mg/dl
Obesity	• BMI ≥ 25 kg/m2 (Asia-Pacific classification)
Abnormal total cholesterol	• Fasting serum total cholesterol > 200 mg/dl
Abnormal triglycerides	• Fasting serum triglycerides ≥ 150 mg/dl
Abnormal HDL	• Fasting serum HDL < 40 mg/dl
Abnormal LDL	• Fasting serum LDL > 100 mg/dl
Depression	• Geriatric Depression Scale (GDS-30) score ≥ 10

This table describes the diagnostic criteria for all the risk factors studied in this manuscript. BP = blood pressure, BMI = body mass index, HbA1c = hemoglobin A1c (indicates average blood sugar level over the last 3 months), HDL = high-density lipoprotein, and LDL = low-density lipoprotein.

2.7. Statistical analysis

All variables were compared between the three periods, namely, the pre-COVID, the COVID, and the post-COVID periods. Categorical variables were checked for statistical association using a Chi-squared test, and the continuous variables were first checked for normality using the Shapiro–Wilk test. Then, as appropriate, an analysis of variance (ANOVA) or Kruskal–Wallis *H*-test was used. A value of $p < 0.05$ was considered statistically significant. A binary logistic regression model for the dichotomous outcome variable (normal = 0, modifiable risk factor present = 1) was adopted to obtain odds ratios (OR) and its 95% confidence interval (CI) for the COVID period and the post-COVID period when compared with the pre-COVID period. The odds ratios were adjusted for marital status, occupation, income, and years of education. All analyses for data were computed using the Statistical Package for Social Sciences (SPSS) software version 26 (IBM Corp, NY, United States).

3. Results

Out of the total of 3,148 participants, 1,658 (males: 776; 46.8%, females: 882; 53.2%) belonged to the pre-COVID period, 840 (males: 408; 48.6%, females: 432; 51.4%) belonged to the COVID period, and 650 (males: 308; 47.4%, females: 342; 52.6%) belonged to the post-COVID period, as shown in Table 2. This gender distribution across the three COVID periods was not statistically significant (value of $p = 0.705$). The mean (standard deviation, SD) age of participants in pre-COVID, COVID, and post-COVID periods was 58.3 (10.3) years, 59.0 (9.6) years, and 58.3 (9.4) years, respectively, and this age difference between the three periods was not statistically significant (value of $p = 0.099$). However, the mean (SD) years of education (formal education) was statistically significant (value of $p < 0.001$) between pre-COVID [3.9 (4.6) years], COVID [4.7 (4.6) years], and post-COVID [4.8 (4.8) years] periods. The majority of the study participants were currently married (pre-COVID 77.2%, COVID 81.5%, and post-COVID 84.0%), had an annual income of less than 1 lakh (pre-COVID 96.3%, COVID 93.4%, and post-COVID 97.8%), and were agricultural laborers (pre-COVID 61.7%, COVID 71.8%, post-COVID 71.9%).

A few variables used in this study had some missing data. A detailed description of missing values of the variables used in this analysis is shown in Table 3. The reason for missing values included participants' refusal due to time constraints, data entry errors, and technical problems with equipment. For most of the variables the percentage of missing values was under 10%, and hence, we used pair-wise deletion in the analyses.

The results of binary logistic regression show that though the odds of hypertension among individuals in the COVID period did not change when compared to the pre-COVID period [OR 0.91, 95% CI (0.75, 1.10)], it increased significantly in the post-COVID period by 1.27 times [OR 1.27, 95% CI (1.04, 1.55)], as shown in Table 4. The odds of diabetes did not differ significantly in COVID [OR 1.22, 95% CI (0.97, 1.52)] and post-COVID period [OR 0.80, 95% CI (0.62, 1.05)].

The odds of obesity among individuals in the COVID period were 1.42 times [OR 1.42; 95% (CI 1.17–1.73)] more than in the pre-COVID period. Similarly, the odds of obesity in the post-COVID period were 1.32 times [OR 1.32; 95% CI (1.07–1.63)] more than in the pre-COVID period.

Further, the odds of abnormal triglycerides were 1.38 times [OR 1.38; 95% (CI 1.15, 1.66)] more among individuals in the COVID period and 1.23 times [OR 1.32; 95% CI (1.00, 1.50)] more in the post-COVID period as compared to the pre-COVID period. The odds of abnormal total cholesterol [OR 0.98; 95% CI (0.799, 1.20)] in the COVID period did not differ statistically when compared to the pre-COVID period; however, in the post-COVID period, it increased by 1.58 times [OR 1.58; 95% CI (1.28, 1.96)] in comparison with the pre-COVID period. A similar trend was observed for abnormal LDL,

TABLE 2 Sociodemographic characteristics of the study participants.

Characteristics	Pre-COVID period (*n* =1,658)	COVID period (*n* =840)	Post-COVID period (*n* =650)	Value of *p*
Age in years, mean (SD)	58.3 (10.3)	59.0 (9.6)	58.3 (9.4)	0.099
Age-group, *n* (%)				
< 65 years	1,142 (68.9)	558 (66.4)	454 (69.8)	0.314
≥ 65 years	516 (31.1)	282 (33.6)	196 (30.2)	
Gender, *n* (%)				
Male	776 (46.8)	408 (48.6)	308 (47.4)	0.705
Female	882 (53.2)	432 (51.4)	342 (52.6)	
Marital status, *n* (%)				
Currently married	1,278 (77.2)	685 (81.5)	546 (84.0)	< 0.001
Others	378 (22.8)	155 (18.5)	104 (16.0)	
Years of education, mean (SD)	3.9 (4.6)	4.7 (4.6)	4.8 (4.8)	< 0.001
Annual income, *n* (%)				
< 1 lakh	1,579 (96.3)	783 (93.4)	630 (97.8)	< 0.001
≥ 1 lakh	60 (3.7)	55 (6.6)	14 (2.2)	
Occupation, *n* (%)				
Agriculture	1,023 (61.7)	587 (71.8)	456 (71.9)	< 0.001
Non-agriculture	634 (38.3)	230 (28.2)	178 (28.1)	

SD, standard deviation.

TABLE 3 Numbers and percentages of participants with missing data.

Variables	Number	Percentage
Age	0	0
Gender	0	0
Marital status	0	0
Years of Education	245	7.8
Income	27	0.9
Occupation	40	1.3
Hypertension	0	0
Diabetes	0	0
Obesity	412	13.1
Abnormal total cholesterol	251	8.0
Abnormal triglycerides	252	8.0
Abnormal LDL	286	9.1
Abnormal HDL	251	8.0
Depression	326	10.4

This table depicts the numbers and percentages of participants with missing data for all the variables studied in this study.
HDL = high-density lipoprotein and LDL = low-density lipoprotein.

wherein the odds in the COVID period did not differ statistically [OR 0.92; 95% CI (0.77, 1.11)] but significantly increased by 1.95 times [OR 1.95; 95% CI (1.57, 2.42)] when compared to the pre-COVID period. Interestingly, concerning abnormal HDL, though the odds among individuals in the COVID period did not differ when compared to the pre-COVID period [OR 0.98, 95% CI (0.81, 1.18)], it decreased in the post-COVID period by 0.72 times [OR 0.72, 95% CI (0.59, 0.88)].

The odds of depression among individuals in the COVID period were 2.65 times [OR 2.65; 95% CI (2.05 to 3.44)] more, and that in the post-COVID period were 3.05 times [OR 3.05; 95% CI (2.33 to 3.99)] more than the odds in the pre-COVID period.

In summary, the odds of the having hypertension, abnormal total cholesterol, abnormal LDL, depression, abnormal triglycerides, and obesity increased in the COVID/post-COVID period as compared to pre-COVID period. However, it should be noted that for hypertension, abnormal total cholesterol and abnormal LDL the odds ratio of the post-COVID period is outside the 95% CI of the OR for the COVID period, suggesting an increase in the post-COIVD period compared to the COVID period.

4. Discussion

In this study, we aimed to understand the effect of the COVID-19 pandemic on certain modifiable risk factors of dementia, namely, diabetes, hypertension, obesity, dyslipidemia, and depression in a population of rural individuals aged ≥45 years, belonging to a prospective, aging cohort from southern India. We observed that the odds of having obesity, abnormal triglycerides, and depression among individuals in the COVID period and the post-COVID period were higher when compared to that in the pre-COVID period. On the other hand, there were higher odds of having hypertension, abnormal total cholesterol, and abnormal LDL only in the post-COVID period and not in the COVID period; there was no significant difference in the odds of having diabetes between any of the three periods.

Worsening obesity and depression during the COVID and post-COVID periods in our study population could be attributed to a variety of reasons, namely increased stress, decreased physical activity during the lockdown, and unhealthy eating habits (19). In addition, we speculate that the pandemic placed a substantial financial strain on the rural participants from Srinivaspura due to the hampering of transport and sale of their agricultural produce. For the other studied risk factors (hypertension, abnormal total cholesterol, and LDL) that seem to have worsened only during the post-COVID period compared to the pre-COVID period, we speculate that this trend could be due to the delayed effect of the COVID-related restrictions on these parameters.

Prior studies across the world (mainly from urban settings) have shown conflicting evidence on the impact of the pandemic on blood pressure (38–43). This ambiguity could be due to methodological issues such as including participants with wide age ranges (18–60 years), different sampling strategies, and robustness of blood pressure monitoring.

Our finding that there was no change in the proportion of diabetes with respect to the pandemic is in line with the results of a recent multicentric study from Italy—the Glycalock study (44). Conversely, several studies from different countries have reported that persons with type 2 diabetes had worsening glycemic control (45–50). Studies from India have shown both worsening (51, 52) and improvement (53) in glycemic control among persons with diabetes during the lockdown period. However, most of these studies have assessed the effect of COVID lockdowns on glycemic control in the short term, unlike our study, wherein the defined COVID period was relatively more extended (the entire period from the start of the first wave to the end of the second wave), which could be one of the possible reasons why we did not see a significant change in the proportions of persons with diabetes in our subjects. We also need to remember that earlier studies from other parts of the world have shown that the pandemic positively affected lifestyle behaviors in certain groups of individuals (54, 55). The varying effects of the pandemic on different population groups are likely due to socio-cultural factors.

Our finding of an increased proportion of obesity in both the COVID and post-COVID periods could be due to a substantial decrease in physical activity and an increase in sedentary behavior in our rural study population due to the pandemic-related movement and social restrictions. A meta-analysis of 61 studies conducted across American, European, and Asian populations showed that COVID-19 was linked with significant decreases in mobility, walking, and physical activity and increases in sedentary activity (56). The majority of our SANSCOG cohort participants are usually engaged in intensive manual labor as part of their agricultural work. Therefore, the movement restrictions due to the lockdown likely resulted in a considerable decrease in their normal/pre-pandemic level of physical activity. Furthermore, the pandemic could have also limited their intake of healthier foods due to restricted access or the severe economic impact, thus resulting in an increase in the proportion of the readily available and cheaper carbohydrates in their diet. A recent study from a

TABLE 4 Results of binary logistics regression: comparison between the pre-COVID, COVID, and the post-COVID periods.

Outcome variables	Factor	Adjusted ORs (95% CI)	Value of *p*
Hypertension	Pre-COVID period®	1	
	COVID period	0.91 (0.75, 1.10)	0.333
	Post-COVID period	1.27 (1.04, 1.55)	0.022
Diabetes	Pre-COVID period®	1	
	COVID period	1.22 (0.97, 1.52)	0.088
	Post-COVID period	0.80 (0.62, 1.05)	0.102
Abnormal total cholesterol	Pre-COVID period®	1	
	COVID period	0.98 (0.799, 1.20)	0.846
	Post-COVID period	1.58 (1.28, 1.96)	< 0.001
Abnormal triglycerides	Pre-COVID period®	1	
	COVID period	1.38 (1.15, 1.66)	0.001
	Post-COVID period	1.23 (1.00, 1.50)	0.050
Abnormal HDL	Pre-COVID period®	1	
	COVID period	0.98 (0.81, 1.18)	0.803
	Post-COVID period	0.72 (0.59, 0.88)	0.002
Abnormal LDL	Pre-COVID period®	1	
	COVID period	0.92 (0.77, 1.11)	0.371
	Post-COVID period	1.95 (1.57, 2.42)	< 0.001
Obesity	Pre-COVID period®	1	
	COVID period	1.42 (1.17, 1.73)	< 0.001
	Post-COVID period	1.32 (1.07, 1.63)	0.010
Depression	Pre-COVID period®	1	
	COVID period	2.65 (2.05, 3.44)	< 0.001
	Post-COVID period	3.05 (2.33, 3.99)	< 0.001

This table shows the binary logistic regression model results for the dichotomous outcome variable (normal = 0, modifiable risk factor present = 1) for the COVID and post-COVID periods compared with the pre-COVID period, adjusted with marital status, occupation, income, and years of education.
® = reference group; OR – Odds ratio; CI – Confidence interval.

metropolitan city in northern India by Ghosh et al. (17) reported carbohydrate consumption increased by 21% among diabetic patients during the lockdown period. It is also a possibility that the increase in psychological stress and depression (as evidenced in this study) was a factor contributing to increased obesity. Studies from several countries (47, 57–59) have clearly shown that BMI / obesity increased during or after the pandemic, and this phenomenon is referred to as "covibesity" or "double pandemic" (60–62).

In line with our study findings, the negative effect of the pandemic on lipid parameters has been demonstrated by previous studies in other countries (49, 63) as well as India (64); changes in lifestyle and stress during the lockdown are likely explanations for this trend. However, an intriguing finding in our study is that there was a worsening of all serum lipid parameters except HDL in the COVID or post-COVID periods. Interestingly, a previous study from eastern India among urban-dwelling males (64) reported a significant deterioration in total cholesterol and triglycerides after the lockdown. However, HDL did not show any significant change; the same pattern was also seen in another study from Slovenia (65). Further, a systematic review by Ojo et al. (47) on 11 studies, predominantly from urban populations worldwide, showed inconsistent effects of the COVID-19 lockdown on lipid parameters. There could be several reasons for such inconsistent findings, such as variations in dietary patterns (a carbohydrate-rich diet is known to increase triglyceride levels and reduce HDL levels (66)) or levels of physical activity and associated medical comorbidities, such as diabetes mellitus and metabolic syndrome.

Lastly, our finding that depression significantly increased during COVID and post-COVID times is expected since our rural cohort underwent tremendous distress due to the severe economic impact of the pandemic in this rural area. A number of studies from India (24, 67–69) and other parts of the world (67, 70) have demonstrated the negative psychological impact of this pandemic, including the rise in depression. Also, this adverse impact has been reported to be higher in older adults than in the general population (71).

Now, it is crucial to take into consideration that all the above-studied risk factors potentially have a bidirectional relationship with COVID-19, (i) the pandemic appears to have an adverse effect on them, as demonstrated by our findings; and (ii) these risk factors have an adverse influence on COVID-19 susceptibility, morbidity, and mortality (72). Therefore, prompt recognition of the worsening of the above risk factors and early intervention measures can be helpful not only in the short term while the pandemic is ongoing but also in the long term in terms of reducing morbidity due to cardiovascular disease, cerebrovascular disease, and of course, dementia.

Our findings are significant since the studied risk factors for dementia are preventable with increased health awareness, simple lifestyle changes, and community-level public health measures, not only in the pandemic but also beyond that. For example, the *India Hypertension Control Initiative*—a partnership initiative between the Ministry of Health and Family Welfare of the Indian central government, state governments, the Indian Council of Medical Research, and the World Health Organization implemented an adaptive strategy in five Indian states during the COVID-19 lockdown to improve access to anti-hypertensive medication for patients with hypertension by means community-based drug distribution at the primary care level and home delivery through frontline workers.

Strengths of our study include a large sample size and a relatively homogenous population. Such studies from India, particularly on aging adults from rural areas, are scarce. Further, using trained clinicians to conduct in-person medical examinations and the objective measurements for all the studied parameters made the assessments robust. This contrasts with many prior studies, which have relied on self-reported measures using web-based or telephonic surveys. Further, we calculated adjusted odds ratios controlling for occupation, income, marital status, and years of formal education, thus partialing out the potential effect of socio-cultural factors.

Our study has some limitations. Due to the study's cross-sectional design, we could not compare risk factors in the same group of individuals in the pre-COVID, COVID, and post-COVID periods. This, along with non-random sampling, could have resulted in potential confounders when comparing the three groups of individuals. Additionally, the findings in our rural cohort may not be generalizable to other populations worldwide or other parts of India due to the vast socio-cultural diversity. We did not have reliable data on the COVID infection status of these participants (due to their poor awareness and hesitation in testing). So, the direct effects of the pandemic on these risk factors could not be delineated from its indirect effects. Finally, we limited our study to only specific modifiable risk factors as we had objective and robust data on these parameters.

We advocate the need to plan and implement urgent lifestyle-based intervention measures, such as the FINGERS model (73) as well as psychosocial interventions to mitigate this pandemic's adverse impact and put preventive measures in place to handle similar situations in the future. However, it is essential that these interventions should be tailored according to the needs and acceptability of the Indian population and should also be easily implementable through cost-effective public health measures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Ethics Committee, Centre for Brain Research. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JS, AM, PM and VR have made a substantial intellectual contribution to the conception, design, or conduct of the study, and had full access to all the data in the study. JS and AM: acquisition of data. JS, AM, PM and VR: analysis and interpretation of data. JS, AM, PM and VR: drafting and reviewing the manuscript. All authors approved the final version of the manuscript for publication and accept responsibility to submit for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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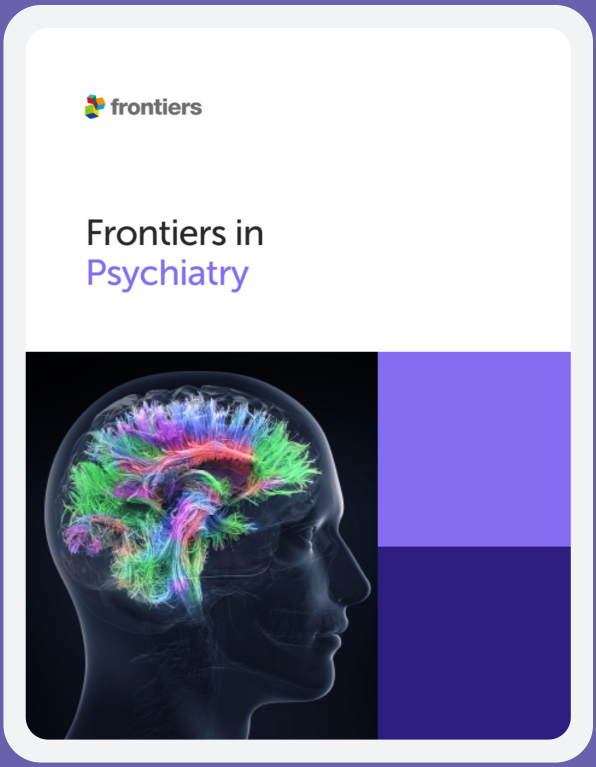

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