Association Between Dementia Development and COVID-19 among Individuals Who Tested Negative for COVID-19 in South Korea: A Nationwide Cohort Study

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Abstract

We aim to assess whether the number of newly diagnosed dementia increases and whether comorbid psychiatric symptoms of patients with dementia worsen, in people who were tested for COVID-19. We used electronic medical records from a nationwide cohort consisting of people who tested positive (positive group), tested negative (negative group), and those who did not receive the test (control group) for COVID-19. For people with neither a history of dementia nor mild cognitive disorder (MCI), the negative group was more likely to develop dementia than the control group, and less likely to develop MCI than the positive group. For people who already had dementia, the negative group was more likely to develop comorbid psychiatric disorders than the control group, but less likely than the positive group. These findings suggest the necessity of managing mental health not only for patients with COVID-19 but also for people who tested negative for COVID-19.

Introduction

People infected with COVID-19 are known to suffer various mental illnesses such as depression and anxiety,[1] and even after recovering from COVID-19, psychiatric sequelae have been reported to occur.[2] In addition to studies on the effects of the pandemic with a focus on neuropsychiatric symptoms of the elderly, including dementia patients, are increasing.

However, studies to date on patients with dementia during the pandemic have several limitations. First, the participants of these studies were mainly patients infected with COVID-19, and the goals of the studies were primarily confined to finding out risk factors of adverse outcomes[3-5] or mortality rates.[3,6,7] Moreover, in the case of studies that targeted patients with dementia not infected with COVID-19, the number of participants was mostly small[8-13] and most of the evidence were empirical or anecdotal.[14-19] Therefore, more research, supported by strong evidences, on the influence of the pandemic in

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terms of changes in mental health undergone by patients with dementia not infected with COVID-19 is greatly required.

In this study, to see more clearly the impact of the pandemic on mental health of the elderly and of patients with dementia, we included as study participants not only those who tested positive for SARS-CoV-2, but also those who tested negative and as control group those who had not had the test at all. Our hypothesis is that those who have taken COVID-19 tests are likely to have more people infected with COVID-19 around them, implying that their experiences of COVID-19 are physically and psychologically closer than those who have not been tested. Therefore, we assumed that they received a greater adverse effect on mental health than those who had not been tested for COVID-19. As far as we know, this is the first study including people who tested negative as the participants for COVID-19 research.

The primary objective of this study is to assess whether, among those who had not been diagnosed with dementia before the pandemic, there is a difference between the three groups (those who tested positive, negative and the control group) in having newly diagnosed dementia during the pandemic. The secondary objective is to find out whether, among patients who had already been diagnosed with dementia but had no comorbid psychiatric diagnosis other than dementia before the pandemic, there is a difference between the three groups in having newly diagnosed psychiatric disorder or prescribed psychotropic medication during the pandemic. We used large electronic medical records of the national cohort consisting of the entire population in South Korea who have undergone SARS-CoV-2 RT-PCR test during the early period of the pandemic.

Methods

Study Design and Participants

The government of South Korea has created and managed a cohort that consists of all people who were tested for COVID-19, both those who tested negative, and also those who tested positive. This cohort was used in the present study and the participants are made up of three groups: those who tested positive for COVID-19 (positive group), those who tested negative (negative group), and those who did not receive the test (control group), during the 4 months between Feb 1, 2020 and May 31, 2020, the early period of COVID-19 outbreak in South Korea. The control group consisted of 15 times more numbers of participants of the positive group and their age and gender were matched to the positive group. We have created a new control group from the control group by selecting those who have visited a hospital more than once for any reason during the period between Feb 1, 2020 and May 31, 2020. In this study, only the new control group was used as the control group. Cases of self-referral were excluded from the negative group. All COVID-19 tests used real-time RT-PCR, and all COVID-19 tests and COVID-19 treatments were provided free-of-charge by the government. Data of sociodemographics, ICD codes, prescriptions and procedures were obtained through the claim database, the Health Insurance Review and Assessment Service of Korea (HIRA). The cohort data was provided by the government until July 31, 2021. Details of the database of the HIRA were presented in other studies.[20,21]

The first hypothesis of this study is that, from the day the positive group was diagnosed with COVID-19, and from the day the negative group was tested for COVID-19, distress will significantly worsen and social relations and activities will significantly decrease for both groups, therefore, during the pandemic, diagnosis of dementia will increase among those without a history of dementia. Second, diagnoses of comorbid psychiatric disorders or prescriptions of psychotropic medications will increase among those with a history of dementia but without a history of any psychiatric disorders other than dementia, compared to the control group.

All personal information were preprocessed into unidentifiable codes and written informed consent was waived by the ethics committee. This study protocol was exempted from review by the Institutional Review Board of The Armed Forces Medical Command (IRB number: AFMC-20087-IRB-20-087).

Variables of Interest

This study divided the study participants' residential areas into three categories: Daegu and Gyeongbuk area (Daegu/Gyeongbuk), where an epidemic outbreak occurred in the early period of COVID-19 in South Korea, the capital area including Seoul (capital), and all other areas (others). The positive and negative groups are more likely to live in group settings (e.g., nursing home, assisted living, and group home) compared to the control group. In order to reduce such selection bias, this study adjusted the data by including a variable indicating whether or not they were admitted to skilled nursing facilities during the period from Feb 1, 2020 to May 31, 2020. Economic statuses of the study participants were divided into three levels: the medical aids group who are unable to pay for health insurance and thus receive government assistance (low), the bottom 50% of those who pay for health insurance (middle) and the top 50% of those who pay for health insurance (high). The history of underlying diseases included hypertension, diabetes, chronic lower respiratory diseases, heart diseases, chronic kidney diseases, and malignant neoplasms. The following four ICD diagnoses of dementia were assessed: Alzheimer's disease (G30, F00), vascular dementia (F01), dementia in other diseases classified elsewhere (F02), and unspecified dementia (F03). We also included mild cognitive disorder (MCI) (F06.7). Risk factors for dementia included mood disorders including depression, hypertension, diabetes, obesity, traumatic brain injury, nicotine dependence (mental and behavioral disorders due to use of tobacco), and alcohol dependence (mental and behavioral

disorders due to use of alcohol) (corresponding ICD codes are reported in the supplementary Table 1).

Analysis of Newly Developed Dementia

We defined the index date as the date of the diagnosis of COVID-19 for the positive group and the date of RT-PCR test for COVID-19 for the negative group.

The first outcome is of those who have had neither a history of dementia nor MCI over the past five years (from Jan 1, 2015 to Jan 31, 2020), and we assessed whether there is any difference in the incidence rate of newly developed dementia between the three groups over the duration of 90 days after the index date. The analysis was conducted by 1:1 matching between the groups. Various sensitivity analyses were carried out to confirm the robustness of the study. We analyzed newly diagnosed cases of dementia since the index date; not only the cases where patients were diagnosed more than once but also more than twice. Since there is a possibility that depression caused by COVID-19 was misdiagnosed as dementia, we analyzed the cases which received the first diagnosis of newly developed dementia and also the diagnosis of depression at the same time. In addition, we also assessed that cases had MCI diagnosis more than once but no dementia diagnosis after the first diagnosis of MCI.

Furthermore, in order to adjust for pre-pandemic baseline cognitive function, data from the annual medical checkups supported by the National Health Insurance Services (NHIS) for entire citizens of South Korea was used. The Korean Dementia Screening Questionnaire-C (KDSQ-C) test included in the medical checkup is aimed at screening dementia for those over 66 years of age.[22] It is for those who want to get a medical checkup voluntarily. There are a total of 15 questions, possible points for each question being 0, 1, and 2. It mainly evaluates memory and daily activities that require complex cognitive functions, and a cut off score of 6 is used to diagnose dementia with 79% sensitivity and 80% specificity.[22] In this sub-analysis, among those who had the KDSQ-C test in 2018, only cases with no diagnosis of dementia in the past 5 years (MCI was not considered) and with less than 6 points of KDSQ-C score were included to adjust for baseline cognitive function. An additional analysis of participants with KDSQ-C ≥6 was also performed. English version of KDSQ-C is presented in the supplementary Table 2.

Analysis of Exacerbation of Comorbid Psychiatric Symptoms Among Patients With Dementia

The second outcome is of those with a history of dementia diagnosis during the past 5 years, but without any psychiatric diagnosis other than dementia in the previous year (from Feb 1, 2019 to Jan 31, 2020), and we aimed to assess whether any comorbid psychiatric symptom was newly developed or deteriorated. For this purpose, the three groups were compared for newly diagnosed cases of psychiatric disorders and for cases prescribed with psychometric medications, within 90 days after the index date. In addition, in order to examine the possibility that comorbid psychiatric symptoms of patients with dementia worsened because treatment was discontinued as study participants could not visit psychiatry clinics due to the pandemic, we examined whether there is a difference in the possibility of visiting psychiatry clinics between the three groups.

The list of diagnoses used to assess the history of psychiatric disorders other than dementia are as follows: psychotic disorders (F20–F29), mood disorders (F30–F39), anxiety disorders (F40–F48), insomnia (F51.0, G47.0), and mental and behavioral disorders due to psychoactive substance use (F10–F19). Delirium (F05) was added to this list of diagnoses used to assess the history of psychiatric disorders to make the list of newly developed psychiatric disorders. The types of psychotropic medications prescribed during the same period are antipsychotics, antidepressants, mood stabilizers, and benzodiazepines (a list of the psychometric medications are shown in supplementary Table 1). Lastly, the same analyses were repeated for those with a history of dementia diagnosis during the past 5 years and have had at least one psychiatric diagnosis other than dementia in the previous year.

Statistical Analysis

For analysis of newly developed dementia, we created a new cohort by adjusting baseline characteristics through propensity score matching. The propensity score was calculated through logistic regression analysis, and the greedy nearest neighbor algorithm was used for matching. Caliper widths of .1 of the pooled standard deviation of the logit of the propensity score was used. Variables used for matching were age, sex, region of residence, economic status, risk factors of dementia, underlying diseases, and admission to skilled nursing facilities. We used Kaplan–Meier estimator to estimate the incidence rate of newly developed dementia from the index date to 90 days. Log-rank test was used to compare the incidence rates between the groups. We calculated hazard ratio (HR) based on Cox proportional hazards model. Two-sided P<.05 was considered significant.

For analysis of exacerbation of comorbid psychiatric symptoms among patients with dementia, we did not perform 1:1 matching between the groups because the number of participants in the positive group was much smaller than the other groups and it led to large data loss of the other groups if they were matched 1:1 to the positive group. Because no matching was made, multiple testing occurred when comparing the three groups, and therefore, we used a Bonferroni correction and P<.017 was considered significant.

All HRs were adjusted for variables including age, sex, region of residence, economic status, types of dementia, underlying diseases, and admission to skilled nursing facilities. Statistical analyses were performed in SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC, USA).

Table 1. Baseline characteristics of study participants with neither a history of dementia nor MCI in the past 5 years.

		Positive group	Negative group	Control group
Total		7426 (100%)	199 252 (100%)	81 519 (100%)
Age				
	20-59	5778 (77.8%)	151 459 (76.0%)	57 209 (70.2%)
	60-69	1065 (14.3%)	22 914 (11.5%)	14 404 (17.7%)
	70-79	439 (5.9%)	15 268 (7.7%)	6708 (8.2%)
	≥80	144 (1.9%)	9611 (4.8%)	3198 (3.9%)
Sex				
	Female	4398 (59.2%)	103 005 (51.7%)	50 610 (62.1%)
	Male	3028 (40.8%)	96 247 (48.3%)	30 909 (37.9%)
Region of residence				
	Capital	966 (13.0%)	95 231 (47.8%)	9887 (12.1%)
	Daegu/Gyeongbuk	5645 (76.0%)	31 308 (15.7%)	63 222 (77.6%)
	Others	815 (11.0%)	72 713 (36.5%)	8410 (10.3%)
Economic status				
	Low	528 (7.1%)	8156 (4.1%)	2948 (3.6%)
	Middle	3153 (42.5%)	70 848 (35.6%)	33 680 (41.3%)
	High	3623 (48.8%)	116 431 (58.4%)	43 439 (53.3%)
Risk factors of dementia				
	Mood disorders	1000 (13.5%)	33 634 (16.9%)	11 967 (14.7%)
	Hypertension	1441 (19.4%)	52 720 (26.5%)	22 447 (27.5%)
	Diabetes	1125 (15.1%)	37 540 (18.8%)	15 699 (19.3%)
	Obesity	19 (.3%)	1030 (.5%)	299 (.4%)
	Traumatic brain injury	173 (2.3%)	7827 (3.9%)	2261 (2.7%)
	Nicotine dependence	2 (.0%)	187 (.1%)	39 (.0%)
	Alcohol dependence	87 (1.2%)	3192 (1.6%)	669 (.8%)
Underlying diseases				
	Chronic lower respiratory diseases	3524 (47.5%)	118 380 (59.4%)	41 769 (51.2%)
	Heart diseases	612 (8.2%)	29 143 (14.6%)	8509 (10.4%)
	Chronic kidney diseases	70 (.9%)	6953 (3.5%)	1110 (1.4%)
	Malignant neoplasms	421 (5.7%)	27 082 (13.6%)	6209 (7.6%)
Admission to skilled nursing facilities		139 (1.9%)	6362 (3.2%)	595 (.7%)
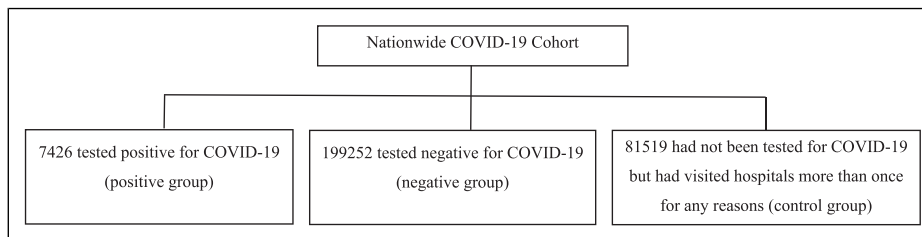
Figure 1. Study profile.

Results

Analysis of Newly Developed Dementia

Among those with neither a history of dementia nor MCI over the past five years, from Feb 1, 2020 to May 31, 2020, 7426 participants tested positive for COVID-19, 199 252 participants tested negative and 81 519 participants had not been tested but had visited hospitals more than once during the above period (Table 1, figure 1). For comparison between the groups, propensity score matching was performed (supplementary Table 3).

The outcomes of the analysis of newly developed dementia are presented in Table 2 and figure 2. At 90 days, the incidence rate of those who were diagnosed with dementia more than once in the positive group was higher than that of the control group. The results for the incidence rate of having diagnosis of dementia more than twice were also the same. The incidence rate of the first diagnosis of dementia accompanied by the

Table 2. Incidence rates and HRs of development of dementia from the index date to 90 days.

	Positive vs Control (1:1 matching, n = 7204)			Negative vs Control (1:1 matching, n = 47 514)			Positive vs Negative (1:1 matching, n = 7225)		
	Positive Incidence rate, % (95% CI)	Control Incidence rate, % (95% CI)	HR (95% CI)	Negative Incidence rate, % (95% CI)	Control Incidence rate, % (95% CI)	HR (95% CI)	Positive Incidence rate, % (95% CI)	Negative Incidence rate, % (95% CI)	HR (95% CI)
Diagnosed with dementia (once)[a]	.26*[b] (.16–.41)	.10 (.05–.20)	2.72*[c] (1.14–6.52)	.54*[d] (.48–.61)	.19 (.15–.23)	2.89*[c] (2.24–3.73)	.31 (.20–.46)	.41 (.28–.58)	.75 (.43–1.32)
Diagnosed with dementia (twice)[e]	.26*[b] (.16–.41)	.10 (.05–.20)	2.72*[c] (1.14–6.52)	.53*[d] (.47–.60)	.16 (.13–.20)	3.32*[c] (2.53–4.35)	.31 (.20–.46)	.38 (.26–.55)	.81 (.46–1.43)
Dementia with depression[f]	.09*[b] (.04–.19)	.01 (.00–.08)	6.35 (.76–52.7)	.11*[d] (.09–.15)	.03 (.02–.05)	3.56*[c] (1.94–6.55)	.07 (.02–.17)	.06 (.02–.14)	1.30 (.35–4.85)
Mild cognitive disorder[g]	.51*[b] (.37–.71)	.17 (.09–.29)	3.09*[c] (1.60–5.95)	.26 (.21–.30)	.23 (.19–.28)	1.09 (.84–1.43)	.54*[h] (.39–.74)	.32 (.21–.48)	1.68 (1.00–2.82)

aDiagnosed with dementia more than once;
bHigher incidence rate of the positive group compared to that of the control group;
cReference is the control group;
dHigher incidence rate of the negative group compared to that of the control group;
eDiagnosed with dementia more than twice;
fCases which received the first diagnosis of dementia and also the diagnosis of depression at the same time;
gDiagnosed with mild cognitive disorder more than once;
hHigher incidence rate of the positive group compared to that of the negative group.
*P<.05 was considered significant. P values for comparison between the incidence rates were calculated by log-rank test. P values for HRs were calculated by Cox proportional hazards regression analysis.
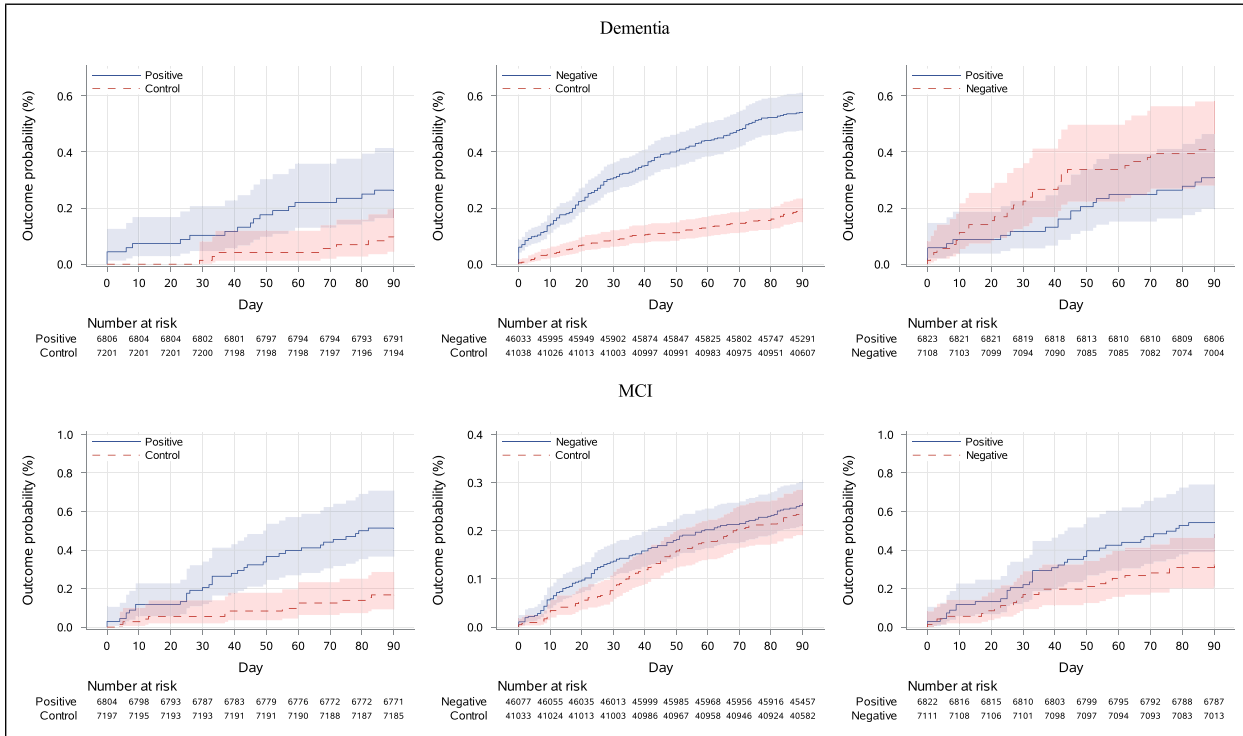
Figure 2. Kaplan–Meier curves for newly diagnosed dementia and MCI. Top graphs: newly diagnosed dementia more than once. Bottom graphs: newly diagnosed MCI more than once. Shaded areas for 95% CI. The number at risk is the number of people who have not yet had the outcome by the corresponding date.

Table 3. Incidence rates of dementia development from the index date to 90 days in the negative and control groups with KDSQ-C score <6.

	Negative group n=8004[a], n=1677[b]	Control group n=4293[a], n=1677[b]	
	Incidence rate, % (95% CI)		HR (95% CI)
Diagnosed with dementia (once)[c]	2.01*[d] (1.31–2.63)	.88 (.51–1.44)	2.30*[e] (1.23–4.30)
Diagnosed with dementia (twice)[f]	1.89*[d] (1.31–2.63)	.82 (.46–1.36)	2.32*[e] (1.22–4.44)
Dementia with depression[g]	.67 (.36–1.16)	.38 (.16–.79)	1.78 (.66–4.80)
Mild cognitive disorder[h]	2.45 (1.78–3.28)	4.41*[i] (3.48–5.50)	.55*[e] (.37–.81)

[a]Before matching;
[b]After matching;
[c]Diagnosed with dementia more than once;
[d]Higher incidence rate of the negative group compared to that of the control group;
[e]Reference is the control group;
[f]Diagnosed with dementia more than twice;
[g]Cases which received the first diagnosis of dementia and also the diagnosis of depression at the same time;
[h]Diagnosed with mild cognitive disorder more than once;
[i]Higher incidence rate of the control group compared to that of the negative group.
*P<.05 was considered significant.

diagnosis of depression was higher in the positive group than that of the control group. The incidence rate of having a diagnosis of MCI was also higher in the positive group than in the control group. In the negative vs control analysis, except for having a diagnosis of MCI, the negative group had higher incidence rates for being diagnosed with dementia for both more than once and also more than twice than the control group. In the positive vs negative analysis, there was no difference in the incidence rates of having a diagnosis of dementia. However, the incidence rate of having a diagnosis of

Table 4. Baseline characteristics of study participants with a history of dementia diagnosis in the past 5 years, but without a history of any psychiatric disorders other than dementia in the past 1 year.

		Positive group	Negative group	Control group
Total		194 (100%)	6474 (100%)	1610 (100%)
Age				
	20-59	17 (8.8%)	243 (3.8%)	83 (5.2%)
	60-69	23 (11.9%)	580 (9.0%)	153 (9.5%)
	70-79	45 (23.2%)	1710 (26.4%)	392 (24.3%)
	≥80	109 (56.2%)	3941 (60.9%)	982 (61.0%)
Sex				
	Female	137 (70.6%)	3659 (56.5%)	1106 (68.7%)
	Male	57 (29.4%)	2815 (43.5%)	504 (31.3%)
Region of residence				
	Capital	10 (5.2%)	2813 (43.5%)	112 (7.0%)
	Daegu/Gyeongbuk	164 (84.5%)	1071 (16.5%)	1361 (84.5%)
	Others	20 (10.3%)	2590 (40.0%)	137 (8.5%)
Economic status				
	Low	42 (21.6%)	916 (14.1%)	254 (15.8%)
	Middle	58 (29.9%)	1921 (29.7%)	493 (30.6%)
	High	92 (47.4%)	3565 (55.1%)	849 (52.7%)
Types of dementia				
	Alzheimer's disease	164 (84.5%)	5377 (83.1%)	1338 (83.1%)
	Vascular dementia	46 (23.7%)	1799 (27.8%)	343 (21.3%)
	Dementia in other diseases classified elsewhere	13 (6.7%)	174 (2.7%)	44 (2.7%)
	Unspecified dementia	50 (25.8%)	2049 (31.6%)	440 (27.4%)
Underlying diseases				
	Hypertension	144 (74.2%)	5417 (83.7%)	1218 (75.7%)
	Diabetes	96 (49.5%)	3572 (55.2%)	777 (48.3%)
	Chronic lower respiratory diseases	100 (51.5%)	4476 (69.1%)	968 (60.1%)
	Heart diseases	72 (37.1%)	3158 (48.8%)	597 (37.1%)
	Chronic kidney diseases	11 (5.7%)	912 (14.1%)	98 (6.1%)
	Malignant neoplasms	17 (8.8%)	1541 (23.8%)	179 (11.1%)
Admission to skilled nursing facilities		105 (54.1%)	2264 (35.0%)	429 (26.6%)

MCI was higher in the positive group than in the negative group, but only a tendency was observed in the HR analysis (P= .051).

For baseline cognitive function adjustment, we created and analyzed a cohort comprising participants with KDSQ-C score <6 and no history of being diagnosed with dementia for the past 5 years (Table 3). Those with KDSQ-C score <6 were 243 participants in the positive group, 8004 participants in the negative group and 4293 participants in the control group (Baseline characteristics in supplementary Table 4). The positive group was excluded from this analysis because the number of the positive group was small. After 1:1 matching between the negative and control group, there were 1677 participants each (matching results in supplementary Table 5). The incidence rates of both being diagnosed with dementia more than once and more than twice were still higher in the negative group than in the control group, but no difference was found in the incidence rate of having the first diagnosis of dementia accompanied by diagnosis of depression. However, the incidence rate of being diagnosed with MCI was lower in

the negative group than in the control group. Results showed that by matching the negative group and the control group 1:1 for people with KDSQ score ≥6, the incidence rate of being diagnosed with dementia more than once in the negative group was 2.7%, but there was no one in the control group (P = .015, supplementary Table 6).

Analysis of Exacerbation of Comorbid Psychiatric Symptoms Among Patients With Dementia

The number of participants who did have a history of dementia for the past 5 years but did not have any diagnosis of psychiatric disorders other than dementia for the past 1 year were, 194 in the positive group, 6474 in the negative group, and 1610 in the control group (Table 4). In Table 5, the incidence rates of the three groups and HRs between the groups are shown. The results of the statistical analysis of the incidence rate between the three groups are presented in supplementary Table 7. The positive group had higher HR of having a diagnosis of psychiatric disorder than the negative and the

Table 5. Incidence rates and HRs of newly diagnosed psychiatric disorders and prescribed psychotropic medications.

	Positive (n= 194)	Negative (n= 6474)	Control (n= 1610)	Positive vs Control (ref)	Negative vs Control (ref)	Positive vs Negative (ref)
	Incidence rate, % (95% CI)[d]			HR (95% CI)[e]		
Psychiatric disorder[a]	24.9 (18.7–31.5)	11.5 (10.7–12.3)	6.0 (4.9–7.2)	4.67* (3.17–6.86)	2.17* (1.69–2.80)	2.10* (1.49–2.96)
Psychotic disorders	.58 (.53–3.0)	.76 (.57–1.0)	.12 (.02–.43)	4.98 (.36–69.1)	11.29* (2.59–49.2)	.39 (.05–3.00)
Mood disorders	15.6 (10.6–21.4)	6.9 (6.3–7.5)	3.0 (2.2–3.9)	6.05* (3.65–10.05)	2.36* (1.67–3.35)	2.37* (1.53–3.65)
Anxiety disorders	8.7 (5.1–13.5)	3.6 (3.2–4.1)	2.1 (1.5–2.9)	5.11* (2.64–9.86)	2.06* (1.33–3.19)	2.29* (1.29–4.08)
Insomnia	7.5 (4.2–12.1)	2.1 (1.8–2.5)	1.2 (.74–1.8)	5.45* (2.51–11.8)	1.69 (.95–2.99)	3.23* (1.61–6.50)
Substance use disorder[b]	1.2 (.23–3.8)	.12 (.06–.24)	.06 (.00–.35)	–[f]	2.59 (.25–27.1)	7.21 (.99–52.2)
Delirium	2.9 (1.1–6.2)	2.6 (2.2–3.0)	.75 (.41–1.3)	4.47* (1.46–13.7)	3.11* (1.61–6.01)	1.10 (.43–2.82)
Visit psychiatry clinic	4.6 (2.2–8.5)	6.3 (5.7–6.9)	3.1 (2.4–4.1)	2.13 (.99–4.61)	1.89* (1.32–2.69)	.88 (.42–1.84)
Psychotropic medication[c]	60.0 (52.1–66.8)	45.7 (44.4–46.9)	24.0 (21.9–26.1)	1.53* (1.22–1.92)	1.69* (1.49–1.92)	1.31* (1.06–1.62)
Antipsychotics	35.8 (28.7–43.0)	22.1 (21.1–23.1)	11.7 (10.1–13.3)	1.66* (1.23–2.25)	1.52* (1.26–1.82)	1.52* (1.15–2.02)
Antidepressants	15.6 (10.6–21.4)	10.2 (9.5–11.0)	7.5 (6.3–8.9)	1.18 (.77–1.83)	1.08 (.85–1.38)	1.49 (.98–2.26)
Mood stabilizers	11.6 (7.3–16.8)	12.2 (11.3–13.0)	4.5 (3.6–5.6)	1.22 (.72–2.07)	2.15* (1.26–1.82)	.86 (.53–1.37)
Benzodiazepines	29.0 (22.4–36.0)	27.7 (26.6–28.8)	11.1 (9.6–12.7)	1.65* (1.19–2.31)	2.31* (1.93–2.76)	0.99 (0.53–1.37)

[a]One was categorized as having 'psychiatric disorder' if any of the following psychiatric disorders was diagnosed: psychotic disorders, mood disorders, anxiety disorders, insomnia, and mental and behavioural disorders due to psychoactive substance use;
[b]mental and behavioural disorders due to psychoactive substance use;
[c]One was categorized as having 'psychotropic medication' if any of the following medications was prescribed: antipsychotics, antidepressants, mood stabilizers, and benzodiazepines;
[d]The results of the statistical analysis of the incidence rate between the three groups is presented in supplementary table 7;
[e]All HRs are adjusted for variables including age, sex, region of residence, economic status, types of dementia, underlying diseases, admission to skilled nursing facilities;
[f]Couldn't be calculated because the HR was divided by 0 during the calculation.
*P < .017 was considered significant. (Bonferroni correction).

control groups, and the negative group also showed higher HR than the control group. As a result of the analysis of visiting psychiatry clinics, the positive group showed no difference from the control group, but the negative group showed higher HR than the control group.

The analysis of psychotropic medications showed that the positive group had higher HR than the negative and the control groups, and the negative group showed higher HR than the control group. The results of antipsychotics analysis also showed the same pattern, but in the case of antidepressants, no difference was found between the three groups.

According to the results of repeating the same analysis for cases with a history of dementia for the past 5 years and a history of diagnosis of psychiatric disorders other than dementia during the previous year, mixed results are shown but

in the case of antipsychotics, the positive group showed higher HR than the negative and control group, and the negative group had higher HR than the control group (supplementary Table 8).

Discussion

This study showed that cognitive functions and comorbid psychiatric symptoms were aggravated after testing positive for COVID-19, or after just being tested; the positive group showed worse results than the negative group (higher incidence rate of MCI, and comorbid psychiatric symptoms), and the negative group showed worse results than the control group (higher incidence rates of dementia, MCI and comorbid psychiatric symptoms).

What is most novel about this study compared to previous studies is that it included the negative group. The analysis of newly developed dementia showed that the negative group had a higher probability of developing dementia than the control group. Although we cannot totally rule out the possibility that neurodegenerative processes of the negative group rapidly accelerated over a short period of time, such cases are very unlikely, and a more probable explanation when considering the cause for such a result is that the negative group was psychologically and physically closer to COVID-19 than the control group, and thus, might have experienced more depressive mood, sleep rhythm disturbance, decrease in social relationships, decrease in outdoor activities, changes in lifestyle patterns, undernourishment, decrease in use of social support services, reduced frequency of use of higher cognitive function, and severe anxiety and agitation until the results of the COVID-19 test became available.

In this context, we can predict that the probability of having a diagnosis of dementia is in the order of the positive group > the negative group > the control group, according to the degree of mental distress and restrictions on daily life. The results showed that the positive and negative groups showed very large HR (2.7, 2.9, respectively) for dementia development compared to the control group. However, there was no difference in the incidence rate of dementia between the positive and the negative groups, although the positive group showed higher MCI incidence rate than the negative group. According to previous studies, it was reported that people infected with COVID-19 suffer from dementia symptoms.[2,23,24] Therefore, the results of the previous studies are not consistent with this study. Our explanation on this is as follows. It is likely that one of the reasons people in the negative group were tested for COVID-19 was due to contact with people in the positive group, which implies that they may share a similar environment or live in the same place. That means the positive vs negative group analysis in this study is more likely to be independent from a confounding variable related to living in group settings such as nursing homes, which was not controlled in the previous studies.[2,23,24] Accordingly, it is needed to consider the possibility that the results of the previous study may be due to selection bias.

If the reason for the development of dementia is that the cognitive function has temporarily deteriorated due to environmental factors as described above, it can be expected that it will recover reversibly. To answer this question, we analyzed the incidence rate of having a diagnosis of dementia more than twice, and as a result, it was found that there was little difference from the incidence rate of having it more than once. It is highly likely that the symptoms of dementia persisted until the next visit, and it also suggests that once diagnosed with dementia during the pandemic, they could not recover from the symptoms in a short time.

In the positive group, the result showed that one out of three to four dementia patients were having depressive symptoms, accounting for a high proportion. In addition, this proportion may be higher because there are cases in which a doctor interprets depressive symptoms of a person with dementia as apathy of dementia and does not add a diagnosis of depression.

For those who had already been diagnosed with dementia before the pandemic, the HRs for the development of mood disorder and anxiety disorder were in the order of the positive > negative > control group. Likewise, the probability of prescribing antipsychotics was also shown in the same order, which may be because an antipsychotic medication is the first drug to consider when patients with dementia show worsening of behavioral and psychological symptoms of dementia (BPSD).

We assessed whether there were differences between the groups in psychiatry clinic visits to investigate the possibility that dementia patients could not use medical services due to the pandemic. In South Korea, as of February 2020, compared to the same period last year, the number of patients in most departments other than psychiatry department decreased, but the number of patients in the psychiatry department increased by 8.5% for men and 9.9% for women, and the number of visits increased by 9.9%.[25] The results of this study show that the positive group did not differ in psychiatry clinic visits from the other two groups, and the negative group had more psychiatric visits than the control group. In other words, even if the positive group or the negative group had many restrictions in their lives due to COVID-19, their uses of psychiatric care services were not lower than that of the control group. In view of this, it is not convincing to say that the reason for the worsening of comorbid psychiatric symptoms in the positive and the negative groups, compared to the control group, is untimely suspension of dementia treatment.

This study has the following limitations that must be addressed. In South Korea, as of April 30, 2020, of deaths from COVID-19, 8.1% were infected at nursing homes, and 3.6% were infected at other social support facilities, amounting to a total of 11.7%.[26] This is very low compared to the 42% in the United States as of May 21, 2020, but accounts for a large percentage of total deaths in South Korea.[26] Among the elderly, those who have been tested for COVID-19 will be more likely to live in a group setting than those who have not been tested, leading to a selection bias for people living in group settings in this study. In order to take this into account as much as possible, "admission to skilled nursing facilities" was included as a variable, propensity score matching was performed, and efforts were made to adjust cognitive function through pre-pandemic dementia screening test KDSQ-C. This is the strength of this study. In South Korea, in the earliest stages of the COVID-19 outbreak, religious gatherings were identified as super-spreading events, but it is also a limitation of this study that the selection bias for this was not considered.[27] Second, the number of the positive group was small. Among the people in the positive group, too few had had the

KDSQ-C test, so they were excluded from the analysis, which hindered the verification of the research hypotheses. However, the number of the positive group was a fundamental limitation because it was the number of all confirmed COVID-19 cases in South Korea. Also, the inclusion of only voluntary participants in the KDSQ-C test can certainly act as a bias. Third, because variables including nicotine and alcohol dependences depend only on the ICD codes, we could not capture data of the real-world. Finally, there may be various confounding factors that have not been considered. One of them is levels of education, which takes up an important part in evaluating the risk factor of dementia, but it was not considered in our study.

In conclusion, our study showed increased risk of dementia and worsening of comorbid psychiatric symptoms in patients with dementia through various methods, not only in the positive group but also in the negative group. Especially, people in the negative group have received less attention from researchers and healthcare professionals. Furthermore, in future studies, finding out whether there are differences in outcomes analyzed in this study between residents of surge and non-surge areas of COVID-19 may help to supplement and expand the findings of this study.

Significance Statement

Increased risk of dementia development and worsening of comorbid psychiatric symptoms of dementia were found not only in people who tested positive for COVID-19 but also in those who tested negative compared to those who have not been tested at all.

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Supplemental Material

Supplemental material for this article is available online.

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