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Original Article

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A potential association between COVID-19 vaccination and development of Alzheimer's disease

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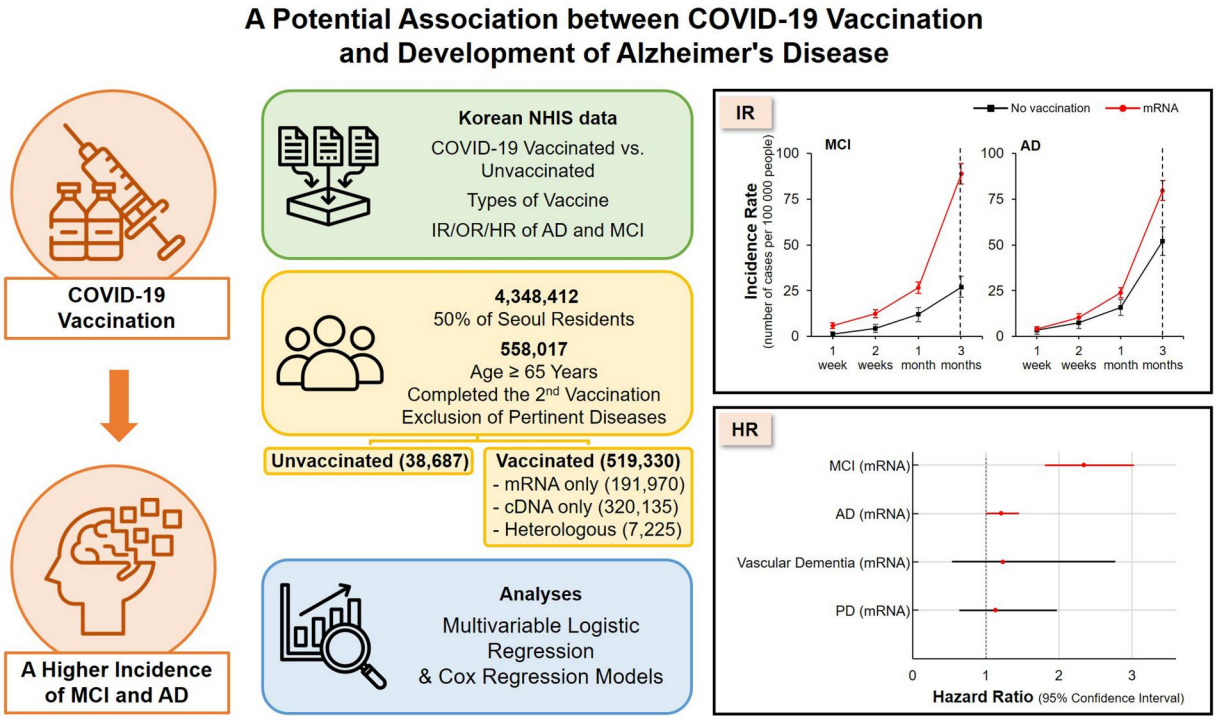
Graphical Abstract



COVID-19, Coronavirus Disease 2019; NHIS, Natuonal Health Insurance Service; AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; PD, Parkinson's Disease; IR, Incidence Rrate; OR, Odds Ratio; HR, Hazard ratio.

Abstract

Background: The challenges of the COVID-19 pandemic extend to concerns about vaccine side effects, particularly potential links to neurodegenerative diseases such as Alzheimer's disease (AD).

Aim: This study investigates the association between COVID-19 vaccination and the onset of AD and its prodromal state, mild cognitive impairment (MCI).

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Design: A nationwide, retrospective cohort study leveraging data from the Korean National Health Insurance Service was conducted.

Methods: The study, conducted in Seoul, South Korea, analyzed data from a random 50% sample of city residents aged 65 and above, totaling 558 017 individuals. Participants were divided into vaccinated and unvaccinated groups, with vaccinations including mRNA and cDNA vaccines. The study focused on AD and MCI incidences post-vaccination, identified *via* ICD-10 codes, using multivariable logistic and Cox regression analyses. Patients with vascular dementia or Parkinson's disease served as controls.

Results: Findings showed an increased incidence of MCI and AD in vaccinated individuals, particularly those receiving mRNA vaccines, within three months post-vaccination. The mRNA vaccine group exhibited a significantly higher incidence of AD (odds ratio [OR]: 1.225; 95% confidence interval [CI]: 1.025–1.464; $P = 0.026$) and MCI (OR: 2.377; CI: 1.845–3.064; $P < 0.001$) compared to the unvaccinated group. No significant relationship was found with vascular dementia or Parkinson's disease.

Conclusions: Preliminary evidence suggests a potential link between COVID-19 vaccination, particularly mRNA vaccines, and increased incidences of AD and MCI. This warrants the need for further research to elucidate the relationship between vaccine-induced immune responses and neurodegenerative processes, advocating for continuous monitoring and investigation into the vaccines' long-term neurological impacts.

Introduction

The emergence of coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, swiftly necessitated the development of effective vaccines, leading to an unprecedented global vaccination campaign.[1] The rapid pace of these vaccines' development and their critical role in controlling the virus spread and reducing disease severity have been remarkable.[2–4] Despite the demonstrated efficacy of COVID-19 vaccinations in preventing severe illness, hospitalizations and deaths associated with COVID-19,[5] concerns about potential long-term side effects remain a subject of ongoing research and public concern.[6]

Alzheimer's disease (AD), a progressive neurodegenerative disorder, represents a significant public health concern, especially with an aging global population.[7] The complex etiology of AD, influenced by genetic, environmental and lifestyle factors,[8] makes understanding any potential links between widely administered COVID-19 vaccines and the development or progression of AD crucial. Yet, to date, there is a scarcity of data on this potential association.[9] Given the potential association between long-COVID syndrome and neurodegenerative disorders, it would also be important to assess subjects who received vaccinations but do not yet have long-COVID syndrome to better understand the association between COVID-19 vaccination and the development of the AD continuum.[10,11]

This report aims to explore the potential association between COVID-19 vaccination and the development of AD and its prodromal state, mild cognitive impairment (MCI), by examining National Health Insurance Service (NHIS) data from Seoul, South Korea. The study's strength lies in its large sample size and the use of the comprehensive NHIS database and the early assessment of subjects before the Omicron pandemic to better describe the nature of COVID-19 vaccinations beyond or before the effect of long-COVID syndrome on AD development.

Methods

Data source

This retrospective cohort study analyzed data from the Korean NHIS, selecting a random 50% sample of Seoul's population residing in the city as of 1 January 2021, to assess the incidence of AD and MCI following COVID-19 vaccination. The dataset, detailed with medical records from 2020 to 2021, adhered to the International Classification of Diseases, 10th Revision (ICD-10), for consistent disease categorization.[12] This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, and was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, enabling a detailed population-based cohort analysis by utilizing the extensive medical claims and diagnostic data from the NHIS.[13]

Study population

This study encompassed 4 348 412 Seoul residents, randomly selected from the NHIS, amounting to half of the city's population as of 1 January 2021. After excluding individuals under 20 years, 4 203 887 people remained for analysis. As of 30 September 2021, 3 839 014 were identified as vaccinated and 364 873 as non-vaccinated. Inclusion criteria were limited to individuals who had received both doses of the COVID-19 vaccine by 30 September 2021; those who did not receive their second dose by this deadline were omitted. Consequently, 2 154 389 vaccinated and 350 953 non-vaccinated individuals were left after further excluding deceased subjects. The index date for vaccinated individuals was the date of their second dose received by 30 September 2021, while for non-vaccinated individuals, it was established as 1 October 2021. Ultimately, 558 017 individuals aged 65 or older (519 330 vaccinated; 38 687 unvaccinated) were included in the analysis (Figure S1 in the Supporting Information, Table 1).

To assess the link between vaccination and the onset of specific diseases, medical records from a year prior to the index date were reviewed and participants with any record of the pertinent diseases during this period were excluded (Figure S1 in the Supporting Information). The onset of the diseases was marked by a primary or secondary diagnosis after the index date. Diseases were identified using ICD-10 codes, covering a range of conditions including MCI, AD, vascular dementia, other forms of dementia, Parkinson's disease (PD), neurodegenerative disorders, cranial neuropathy, autonomic dysfunction, insomnia and obesity.[14] Detailed definitions of each ICD-10 code are provided in Table S1 in the Supporting Information. Briefly, AD was defined when the diagnostic code of F00 (dementia in Alzheimer disease) or G30 (Alzheimer disease) was registered; MCI was defined when the diagnostic code F06.7 (mild cognitive disorder) was registered.

Outcome measurements

The incidence of AD and MCI in the vaccinated population was compared with that in the unvaccinated population after controlling for potential confounders. Multivariable logistic regression and Cox regression models were employed to assess the association between COVID-19 vaccination and subsequent MCI and AD development. We also investigated the incidence of post-

Table 1. Baseline characteristics of the participants stratified by COVID-19 vaccination.

	Total	Vaccination		P
		No	Yes	
	(*n* = 558 017)	(*n* = 38 687)	(*n* = 519 330)	
Gender, *n* (%)				<0.001
Male	265 718 (47.62)	15 746 (40.70)	249 972 (48.13)	
Female	292 299 (52.38)	22 941 (59.30)	269 358 (51.87)	
Age, mean (SD), years	72.90 (6.57)	75.23 (8.67)	72.73 (6.35)	<0.001
60–69 years, *n* (%)	220 084 (39.44)	13 297 (34.37)	206 787 (39.82)	
70–79 years, *n* (%)	244 137 (43.75)	14 169 (36.62)	229 968 (44.28)	
≥80 years, *n* (%)	93 796 (16.81)	11 221 (29.00)	82 575 (15.90)	
Insurance level, *n* (%)				<0.001
Low	154 979 (27.77)	12 402 (32.06)	142 577 (27.45)	
Middle	123 290 (22.09)	9389 (24.27)	113 901 (21.93)	
High	279 748 (50.13)	16 896 (43.67)	262 852 (50.61)	
CCI, *n* (%)				<0.001
0	243 918 (43.71)	22 614 (58.45)	221 304 (42.61)	
1	144 394 (25.88)	6411 (16.57)	137 983 (26.57)	
≥2	169 705 (30.41)	9662 (24.97)	160 043 (30.82)	
Comorbidity, *n* (%)				
Diabetes mellitus	42 315 (7.58)	2463 (6.37)	39 852 (7.67)	<0.001
Hyperlipidemia	169 336 (30.35)	8286 (21.42)	161 050 (31.01)	<0.001
Hypertension	313 681 (56.21)	13 336 (34.47)	300 345 (57.83)	<0.001
COPD	309 643 (55.49)	15 131 (39.11)	294 512 (56.71)	<0.001
Prior COVID-19 infection, *n* (%)	3905 (0.70)	510 (1.32)	3395 (0.65)	<0.001
First vaccination product, *n* (%)				
AZD1222	327 358 (63.03)	NA	327 358 (63.03)	NA
BNT162b2	191 601 (36.89)		191 601 (36.89)	
mRNA-1273	371 (0.07)		371 (0.07)	
Second vaccination product, *n* (%)				
AZD1222	320 137 (61.64)	NA	320 137 (61.64)	NA
BNT162b2	198 820 (38.28)		198 820 (38.28)	
mRNA-1273	372 (0.07)		372 (0.07)	
JNJ-78436735	1 (0.00)		1 (0.00)	
First to second vaccination product, *n* (%)				
AZD1222–AZD1222	320 135 (61.64)	NA	320 135 (61.64)	NA
AZD1222–BNT162b2	7222 (1.39)		7222 (1.39)	
AZD1222–JNJ-78436735	1 (0.00)		1 (0.00)	
BNT162b2–AZD1222	2 (0.00)		2 (0.00)	
BNT162b2–BNT162b2	191 598 (36.89)		191 598 (36.89)	
BNT162b2–mRNA-1273	1 (0.00)		1 (0.00)	
mRNA-1273–mRNA-1273	371 (0.07)		371 (0.07)	
First to second vaccination type, *n* (%)				
No vaccination	38 687 (6.93)	38 687 (100.00)	0	NA
mRNA vaccination only	191 970 (34.40)	0	191 970 (36 96)	
cDNA vaccination only	320 135 (57.37)	0	320 135 (61.64)	
Heterologous vaccination	7225 (1.29)	0	7225 (1.39)	
Vaccination interval, months, mean (SD)	56.76 (26.57)	0 (0)	56.76 (26.57)	NA

COVID-19, coronavirus disease 2019; *n*, number; SD, standard deviation; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary diseases; AZD1222, AstraZeneca ChAdOx1-S recombinant vaccine; BNT162b2, Pfizer-BioNTech Comirnaty; mRNA-1273, Moderna Spikevax; JNJ-78436735, Janssen/Johnson and Johnson COVID-19 vaccine; NA, not applicable or not available.

vaccination vascular dementia and PD as control groups for AD to better understand the potential causes underlying abnormal protein aggregation after the vaccination.

The study measured the cumulative incidence rates of MCI or AD per 10 000 individuals, comparing vaccinated and non-vaccinated groups at intervals of one week, two weeks, one month and three months post-vaccination. The covariates included were gender, age, insurance level, Charlson comorbidity index (CCI),[14] diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease and a history of previous COVID-19 infection. The identification of comorbidities and previous COVID-19 infections was based on primary or secondary diagnoses recorded at least twice within the year preceding the index date.

Participants were categorized into four groups according to their vaccination status: unvaccinated, mRNA vaccine only, cDNA vaccine only and a combination of the two. The mRNA vaccine-only group received the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines for both doses, while the cDNA vaccine-only group completed the Oxford-AstraZeneca (ChAdOx1 nCoV-19) or Johnson & Johnson (Ad26.COV2-S) vaccines. A heterologous vaccine group consisted of individuals vaccinated with both mRNA and cDNA vaccines. The National Health Insurance (NHI) premium, reflecting monthly income levels including earnings and capital gains, was used as a proxy for income. The study categorized participants into three income groups: low, middle and high, based on medical aid enrollees and percentiles (0–33%, 34–66%, 67–100%) among NHI enrollees. The CCI diseases were monitored, and participants were classified as having a CCI score of 0, 1 or ≥2 based on primary or secondary diagnoses.

Statistical analysis

Statistical evaluations in this study were conducted using SAS Enterprise Guide (version 8.3, SAS Institute, Cary, NC, USA). The distribution normality of the data was verified using the

Table 2. Odds ratio (OR) of mild cognitive impairment (MCI) and Alzheimer's disease (AD) following COVID-19 vaccination.

Disease	Variable	One week			Two weeks			One month			Three months		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
MCI	1st–2nd vaccination type												
	No vaccination	1	Ref		1	Ref		1	Ref		1	Ref	
	mRNA vaccination only	2.363	0.851–6.563	0.099	1.815	0.972–3.389	0.061	1.395	0.965–2.016	0.076	2.377	1.845–3.064	<0.001
	cDNA vaccination only	2.185	0.739–6.464	0.158	1.627	0.832–3.182	0.155	1.118	0.746–1.675	0.590	1.763	1.348–2.306	<0.001
	Heterologous vaccination	1.778	0.191–16.565	0.613	1.354	0.292–6.274	0.699	1.389	0.570–3.387	0.470	2.114	1.267–3.525	0.004
	Gender												
	Female	1.255	0.862–1.828	0.236	1.169	0.902–1.514	0.238	1.473	1.227–1.769	<0.001	1.617	1.460–1.792	<0.001
	Age	1.048	1.009–1.087	0.015	1.046	1.020–1.073	0.001	1.047	1.029–1.064	<0.001	1.036	1.026–1.047	<0.001
	Insurance level												
	Low	1	Ref		1	Ref		1	Ref		1	Ref	
	Middle	0.528	0.277–1.006	0.052	0.666	0.435–1.021	0.062	0.820	0.620–1.086	0.166	0.963	0.828–1.121	0.628
	High	1.122	0.736–1.708	0.593	1.214	0.901–1.637	0.203	1.208	0.980–1.490	0.076	1.228	1.092–1.382	0.001
	CCI												
	0	1	Ref		1	Ref		1	Ref		1	Ref	
	1	1.382	0.834–2.292	0.209	1.325	0.936–1.876	0.113	1.251	0.982–1.594	0.070	1.143	0.998–1.309	0.054
	≥2	1.763	1.039–2.992	0.036	1.394	0.954–2.035	0.086	1.370	1.054–1.781	0.019	1.172	1.009–1.361	0.038
	Comorbidity												
	Diabetes mellitus	0.454	0.277–0.746	0.002	0.636	0.452–0.894	0.009	0.680	0.535–0.863	0.002	0.819	0.717–0.935	0.003
	Hypertension	0.853	0.564–1.290	0.452	0.940	0.704–1.254	0.673	0.819	0.672–0.999	0.049	0.760	0.681–0.848	<0.001
	Hyperlipidemia	1.399	0.902–2.169	0.134	1.194	0.882–1.618	0.251	1.124	0.912–1.386	0.273	1.175	1.045–1.320	0.007
	COPD	1.383	0.776–2.464	0.272	1.053	0.669–1.657	0.823	0.959	0.690–1.332	0.801	1.088	0.909–1.301	0.357
	COVID19	NA	NA	NA	0.609	0.085–4.345	0.621	0.873	0.280–2.721	0.815	1.566	0.970–2.531	0.067
AD	1st–2nd vaccination type												
	No vaccination	1	Ref		1	Ref		1	Ref		1	Ref	
	mRNA vaccination only	1.071	0.519–2.206	0.853	1.263	0.772–2.065	0.353	1.254	0.904–1.740	0.175	1.225	1.025–1.464	0.026
	cDNA vaccination only	0.690	0.253–1.886	0.470	0.664	0.335–1.320	0.243	0.856	0.547–1.339	0.495	0.823	0.645–1.049	0.116
	Heterologous vaccination	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.346	0.085–1.406	0.138
	Gender												
	Female	1.373	0.826–2.282	0.221	1.296	0.933–1.801	0.122	1.310	1.055–1.627	0.014	1.256	1.117–1.413	<0.001
	Age	1.135	1.095–1.175	<0.001	1.133	1.107–1.159	<0.001	1.145	1.128–1.163	<0.001	1.141	1.132–1.151	<0.001
	Insurance level												
	Low	1	Ref		1	Ref		1	Ref		1	Ref	
	Middle	0.907	0.481–1.709	0.762	0.825	0.531–1.282	0.392	1.034	0.776–1.376	0.822	1.044	0.893–1.222	0.588
	High	0.576	0.332–1.002	0.051	0.715	0.501–1.020	0.064	0.828	0.652–1.052	0.123	0.838	0.735–0.956	0.009
	CCI												
	0	1	Ref		1	Ref		1	Ref		1	Ref	
	1	1.274	0.606–2.675	0.523	1.048	0.664–1.653	0.841	1.091	0.812–1.464	0.563	1.038	0.882–1.222	0.653
	≥2	2.101	0.985–4.484	0.055	1.152	0.702–1.893	0.575	1.141	0.826–1.577	0.424	1.077	0.900–1.289	0.417
	Comorbidity												
	Diabetes mellitus	1.427	0.758–2.687	0.270	1.212	0.787–1.865	0.382	1.074	0.814–1.417	0.615	1.205	1.032–1.406	0.018
	Hypertension	0.829	0.476–1.444	0.508	0.829	0.577–1.190	0.308	0.866	0.683–1.100	0.238	0.871	0.764–0.991	0.037
	Hyperlipidemia	0.437	0.246–0.777	0.005	0.733	0.502–1.071	0.108	0.904	0.706–1.157	0.422	0.762	0.665–0.872	<0.001
	COPD	1.555	0.775–3.121	0.214	0.847	0.466–1.539	0.585	1.009	0.700–1.453	0.963	1.021	0.834–1.250	0.844
	COVID19	NA	NA	NA	0.890	0.124–6.379	0.908	1.116	0.357–3.489	0.850	0.896	0.445–1.803	0.758

COVID-19, coronavirus disease 2019; CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary diseases; NA, not applicable or not available.

Table 3. Hazard ratio (HR) of mild cognitive impairment (MCI) and Alzheimer's disease (AD) following COVID-19 vaccination.

Disease	Variables	Value	HR	95% CI	P
MCI	1st–2nd vaccination type	No vaccination	1	Ref	
		mRNA vaccination only	2.342	1.818–3.018	<0.001
		cDNA vaccination only	1.742	1.332–2.278	<0.001
		Heterologous vaccination	2.088	1.253–3.481	0.005
	Gender	Female	1.615	1.457–1.789	<0.001
	Age	Year	1.037	1.026–1.047	<0.001
	Insurance level	Low	1	Ref	
		Middle	0.963	0.828–1.120	0.628
		High	1.228	1.091–1.381	0.001
	CCI	0	1	Ref	
		1	1.143	0.998–1.308	0.053
		≥2	1.173	1.010–1.362	0.036
	Comorbidity	Diabetes mellitus	0.820	0.718–0.936	0.003
		Hypertension	0.760	0.681–0.848	<0.001
		Hyperlipidemia	1.174	1.045–1.319	0.007
		COPD	1.089	0.910–1.301	0.352
		COVID19	1.570	0.973–2.532	0.065
AD	1st–2nd vaccination type	No vaccination	1	Ref	
		mRNA vaccination only	1.209	1.013–1.444	0.036
		cDNA vaccination only	0.806	0.633–1.027	0.081
		Heterologous vaccination	0.337	0.083–1.373	0.129
	Gender	Female	1.253	1.115–1.409	<0.001
	Age	Year	1.140	1.131–1.149	<0.001
	Insurance level	Low	1	Ref	
		Middle	1.044	0.893–1.220	0.591
		High	0.838	0.735–0.956	0.008
	CCI	0	1	Ref	
		1	1.042	0.886–1.225	0.623
		≥2	1.082	0.905–1.294	0.386
	Comorbidity	Diabetes mellitus	1.203	1.032–1.403	0.018
		Hypertension	0.874	0.768–0.995	0.042
		Hyperlipidemia	0.761	0.665–0.871	<0.001
		COPD	1.024	0.837–1.253	0.816
		COVID19	0.907	0.452–1.818	0.782

COVID-19, coronavirus disease 2019; CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary diseases; NA, not applicable or not available.

Kolmogorov–Smirnov test. We presented baseline characteristics as means ± standard deviation for continuous metrics and as frequency (percentages) for categorical factors. The impact of COVID-19 vaccination on the occurrence of MCI or AD was analyzed using Student's *t*-test for continuous variables, and chi-square or Fisher's exact tests for categorical variables. The cumulative incidence rates were calculated as occurrences per 10 000 individuals. Multiple logistic regression was employed to determine odds ratios (ORs) and their 95% confidence intervals (CIs) for the association between COVID-19 vaccination and MCI or AD development. Cox proportional hazards models were utilized to compute hazard ratios (HRs) and their 95% CIs. A *P*-values threshold of <0.05 (two-sided) was set for determining statistical significance.

Ethical approval

The study was approved by the Institutional Review Board of the Ewha Women's University Hospital (IRB No. EUMC 2022-07-003) and the requirement for informed consent was waived by the IRB. All data were anonymized before retrieval.

Results

Baseline characteristics of the participants stratified by COVID-19 vaccination status are provided in Table 1. In individuals with mRNA vaccination only, the three-month post-vaccination incidence was significantly higher for MCI (OR: 2.377; 95% CI: 1.845–3.064; $P < 0.001$) and AD (OR: 1.225; CI: 1.025–1.464; $P = 0.026$) compared to those unvaccinated. Individuals who received cDNA vaccines only (OR: 1.763; CI: 1.348–2.306; $P < 0.001$) and cross-vaccination (OR: 2.114; CI: 1.267–3.525; $P = 0.004$) also exhibited a significant increase in MCI incidence compared to those unvaccinated (Table 2). The risk of developing MCI and AD after the vaccination remained unchanged, particularly in the mRNA vaccination group, compared to the unvaccinated groups. The HR for MCI in individuals vaccinated only with mRNA vaccines was 2.342 (95% CI: 1.818–3.018, $P < 0.001$), with cDNA vaccines only was 1.742 (95% CI: 1.332–2.278, $P < 0.001$) and with heterologous vaccination was 2.088 (95% CI: 1.253–3.481, $P = 0.005$). For AD, the HR in individuals vaccinated only with mRNA vaccines was 1.209 (95% CI: 1.013–1.444, $P = 0.036$; Table 3). The study found no significant association between COVID-19 vaccination and the development of vascular dementia and PD (Table 4).

Discussion

This nationwide, population-based study explored the incidence rates of AD and MCI following COVID-19 vaccination in Seoul, Republic of Korea, revealing a higher incidence in the vaccinated group compared to the unvaccinated group. Notably, this increase was observed as early as 12 weeks post-mRNA vaccination, suggesting its potential temporal association with the onset of AD continuum.

The observed trend raises questions about the role of vaccine-induced immune responses in neurodegenerative processes. COVID-19 vaccines, particularly mRNA types, are designed to elicit robust immune response.[15] This response could potentially influence the pathogenesis of AD, characterized by abnormal

Table 4. Hazard ratio (HR) of vascular dementia and Parkinson's disease following COVID-19 vaccination.

Disease	Variables	Value	HR	95% CI	P
Vascular dementia	1st–2nd vaccination type	No vaccination	1	Ref	
		mRNA vaccination only	1.230	0.548–2.761	0.616
		cDNA vaccination only	0.786	0.287–2.147	0.638
		Heterologous vaccination	NA	NA	NA
	Gender	Female	0.846	0.539–1.329	0.468
	Age	Year	1.100	1.059–1.142	<0.001
	Insurance level	Low	1	Ref	
		Middle	0.694	0.345–1.395	0.305
		High	0.915	0.550–1.522	0.733
	CCI	0	1	Ref	
		1	1.524	0.781–2.974	0.217
		≥2	2.149	1.084–4.261	0.029
	Comorbidity	Diabetes mellitus	0.944	0.539–1.651	0.839
		Hypertension	0.824	0.494–1.375	0.459
		Hyperlipidemia	0.886	0.519–1.512	0.656
		COPD	1.247	0.635–2.446	0.522
		COVID19	NA	NA	NA
Parkinson's disease	1st–2nd vaccination type	No vaccination	1	Ref	
		mRNA vaccination only	1.129	0.649–1.963	0.668
		cDNA vaccination only	0.830	0.450–1.532	0.552
		Heterologous vaccination	0.495	0.064–3.824	0.500
	Gender	Female	0.768	0.576–1.024	0.072
	Age	Year	1.045	1.017–1.074	0.002
	Insurance level	Low	1	Ref	
		Middle	0.750	0.494–1.139	0.177
		High	0.824	0.596–1.139	0.241
	CCI	0	1	Ref	
		1	1.415	0.948–2.112	0.089
		≥2	1.803	1.189–2.736	0.006
	Comorbidity	Diabetes mellitus	0.638	0.437–0.932	0.020
		Hypertension	0.994	0.718–1.376	0.969
		Hyperlipidemia	0.912	0.650–1.278	0.592
		COPD	0.960	0.583–1.579	0.871
		COVID19	0.714	0.100–5.101	0.737

COVID-19, coronavirus disease 2019; CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary diseases; NA, not applicable or not available.

protein aggregation, namely amyloid-beta plaques and tau tangles.[16] As the mRNA encoded in the SARS-CoV-2 vaccine is known to cross the blood–brain barrier, or at least disrupt the barrier, the SARS-CoV-2 spike protein might interact with amyloid-beta proteins, affecting their aggregation and influencing microglial activation.[17] This interaction may potentially exacerbate the cognitive decline associated with AD by promoting an environment conducive to inflammation and protein misfolding.[17] Additionally, lipid nanoparticles in mRNA vaccines can activate Toll-like receptors, leading to inflammatory reactions that might exacerbate neuroinflammatory pathways associated with AD pathogenesis.[17] Such inflammatory reactions may trigger a cytokine storm involving interleukin-1 beta and tumor necrosis factor-alpha, which have been implicated in both acute and chronic neuroinflammatory responses that accelerate the progression of AD.[18] Furthermore, N1-methylpseudouridine in mRNA vaccines may cause ribosomal frameshifting during translation, resulting in aberrant protein products that could contribute to neurodegenerative processes.[19] These aberrant proteins could disrupt normal cellular functions, including autophagic processes, and thereby lead to the accumulation of neurotoxic protein aggregates that are hallmark features of AD.[20] Albeit not confirmed, the molecular mimicry related to S-protein formed by SARS-CoV-2 vaccine should also be considered as a source of autoimmune responses potentially exacerbating AD pathology.[21] Moreover, vaccines could induce a cascade of low level neuroinflammatory responses, known contributors to the development and progression of neurodegeneration.[9] Further exploration of these mechanisms could provide additional insights into the long-term effects of mRNA vaccines on the central nervous system and their potential link to neurodegenerative diseases, including AD.

The higher incidence of AD post-vaccination in older individuals and females might reflect demographic differences in AD as well as in immune response to vaccines. Older adults often exhibit a heightened inflammatory response, which could predispose them to faster progression of neurodegenerative diseases.[22] Similarly, sex differences in immune system functioning could account for the increased susceptibility observed in females.[23]

The distinct post-vaccination effects were not observed in the development of vascular dementia compared to the results from MCI and AD. This lack of association suggests that the observed increase in AD continuum incidence post-vaccination might be specific to Alzheimer's pathology and not to the vascular etiologies of dementia (Table 4). No increase in the incidence and risk of PD after the vaccination, in line with a previous report,[9] may indicate a potential link between COVID-19 vaccination and abnormal aggregation in specific proteins, which findings need to be verified in long-term follow-up studies (Table 4).

We excluded participants with prior diagnoses of pertinent diseases, including MCI and AD from our study to reduce the risk of reverse causation. The absence of an increase in HRs in PD and vascular dementia also supports the strong association between COVID-19 vaccination and AD continuum. If reverse causation was at play, we would expect to see similar effects in other neurodegenerative or acute neurological conditions like PD and

vascular dementia. However, despite these efforts and findings, the potential for reverse causation cannot be entirely ruled out. The early increase in the incidence of AD continuum may have also contributed to the initial vaccinating policy of the country, such that the elderly or those with illness, who may have a higher risk of AD or MCI, were more likely to be vaccinated at the beginning.

The study's strength lies in its large sample size and the use of the comprehensive NHIS database. However, there are limitations that need to be addressed in future studies. First, the major limitation is the short duration of follow-up up to 3 months, given that AD is a chronic neurodegenerative disorder. The low prevalence of COVID-19 infection in the cohort, coupled with the study's timing before the omicron pandemic, also limits the assessment of long-COVID effects on AD. In the meantime, from a different perspective, it is worth noting that this cohort can be a platform to better describe the nature of COVID-19 vaccinations beyond or before the effect of long-COVID syndrome on AD development. It is also notable that the incidence and risk of development of MCI and AD after mRNA vaccination became more prominent by 12 weeks, which warrants future studies with longer follow-up periods. Especially, datasets including post-omicron wave will be crucial to understanding the long-term impact of COVID-19 and vaccinations on development and progression of the AD continuum. Second, this study focused on specific population (Seoul residents, aged ≥65); thus, the findings may not be generalizable to other populations or age groups and warrant further investigation in both domestic and international cohort with a broader range of ages. Third, while this study explored the implications of COVID-19 vaccinations on AD, it is also essential to consider the findings from studies that indicate the protective effects of other vaccinations, such as flu and shingles vaccines, against AD development.[24,25] This aspect highlights the need for comprehensive research into how various types of vaccinations might influence AD risk. Fourth, the diagnostic accuracy of MCI and AD based on records from a nationwide database such as NHIS may be less precise than diagnoses derived from detailed neuropsychological tests, brain imaging and additional biomarkers that assess neurodegenerative changes. A recent literature on the AD diagnostic accuracy by comparing diagnostic codes alone versus diagnostic codes plus medication history revealed that the latter underestimates the actual prevalence of the disease.[26] Conversely, diagnosis based solely on codes closely approximates the real prevalence of AD, a method we have adopted to assess the development of MCI and AD in this study.[26]

Overall, the beneficial effects of COVID-19 vaccination, which have clearly improved mortality and morbidity associated with COVID-19, cannot be overlooked.[2–4] This study provides preliminary evidence of a potential association between COVID-19 vaccination and increased incidence of MCI and AD. While the findings highlight a need for cautious interpretation, they demonstrate the importance of ongoing surveillance and research into the long-term effects of COVID-19 vaccines on AD continuum. Further research will also need to include prospective human studies and preclinical investigations into the underlying biological mechanisms, especially those involving abnormal protein aggregation and neuroinflammation. This comprehensive approach will enhance our understanding of the risk–benefit balance of COVID-19 vaccinations, particularly in populations at risk for neurodegenerative disorders.

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Author contributions

Jee Hoon Roh (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [lead], Investigation [equal], Methodology [equal], Project administration [lead], Resources [equal], Software [equal], Supervision [lead], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review and editing [lead]), Inha Jung (Formal analysis [equal], Investigation [equal], Visualization [equal], Writing—original draft [equal]), Yunsun Suh (Data curation [equal], Investigation [equal], Methodology [equal], Writing—original draft [equal]) and Min-Ho Kim (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Resources [equal], Software [equal], Validation [equal], Writing—original draft [equal]).

Supplementary material

Supplementary material is available at *QJMED* online.

Conflict of interest

None declared.

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