

COVID-19 Vaccination by APOE4 Status: Impact on Health-Related Risk Factors for Alzheimer's Disease



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Take-Home Message: COVID-19 vaccination may confer health benefits beyond protection against COVID-19 itself by lowering the odds of health-related AD risk factors, such as hypertension, depression, and sleep disorders. Repeated vaccination may reduce AD risk by decreasing the overall burden of these risk factors, which requires confirmation in studies with longer follow-up. The protective effects of vaccination appeared more pronounced in APOE4 non-carriers.

INTRODUCTION	METHODS	RESULTS	RESULTS	DISCUSSION																																																												
COVID-19 infection, especially when it requires hospitalization, has been associated with an increased risk of dementia. COVID-19 vaccines reduce the likelihood of hospitalization, suggesting that they may be protective against dementia, including Alzheimer’s disease (AD). Because AD develops over many years, detecting a reduction in its risk few years after vaccination may be challenging. An alternative approach is to examine the effects of COVID-19 vaccination on health-related AD risk factors, assuming that reduction in burden of these factors may translate into lower AD risk. Here, we used UK Biobank data to investigate how the number of COVID-19 vaccine doses received before age 65 influences subsequent onsets of AD-related health traits, such as hypertension, depression, and sleep disorders, in carriers and non-carriers of APOE4, the strongest genetic risk factor for AD.	We used UK Biobank (UKB) data sample of 201,789 participants with COVID-19 vaccination information; among them, 117,891 received one dose, and 77,430 received two vaccine doses. Multivariable logistic regression models were used. Binary outcomes were defined as 1, if disease occurred after age 65, and 0, if individual remained event-free while surviving age 65. Vaccination <i>count</i> was a primary predictor of AD-related health traits. Propensity-score weights based on major preexisting conditions (stroke, cancer, renal failure, severe infections) were applied to reduce confounding. Covariates included sex, education, smoking, and age at first assessment. Analyses were also stratified by APOE4 carrier status.	Table. Associations between COVID-19 vaccinations received before age 65 and the later onset of diseases that are also AD risk factors (hypertension, depression, sleep disorders) using logistic regression model. <table><tr><th>Health-related AD risk factors</th><th>Sample</th><th>Coefficient</th><th>SE</th><th>OR (95%CI)</th><th>P-Value</th></tr><tr><td colspan="6">UK Biobank</td></tr><tr><td rowspan="3">Depression</td><td>All</td><td>-0.73</td><td>0.24</td><td>0.48 (0.29,0.76)</td><td>0.003</td></tr><tr><td>APOE4 carriers</td><td>0.15</td><td>0.37</td><td>1.16 (0.54,2.30)</td><td>0.687</td></tr><tr><td>APOE4 non-carriers</td><td>-1.24</td><td>0.33</td><td>0.29 (0.15,0.53)</td><td><0.001</td></tr><tr><td rowspan="3">Hypertension</td><td>All</td><td>-0.94</td><td>0.11</td><td>0.39 (0.31,0.48)</td><td><0.001</td></tr><tr><td>APOE4 carriers</td><td>-0.90</td><td>0.22</td><td>0.41 (0.26,0.62)</td><td><0.001</td></tr><tr><td>APOE4 non-carriers</td><td>-0.97</td><td>0.13</td><td>0.38 (0.29,0.49)</td><td><0.001</td></tr><tr><td rowspan="3">Sleep disorder</td><td>All</td><td>-1.17</td><td>0.15</td><td>0.31 (0.23,0.41)</td><td><0.001</td></tr><tr><td>APOE4 carriers</td><td>-0.97</td><td>0.27</td><td>0.38 (0.22,0.63)</td><td><0.001</td></tr><tr><td>APOE4 non-carriers</td><td>-1.26</td><td>0.18</td><td>0.28 (0.19,0.40)</td><td><0.001</td></tr></table>	Health-related AD risk factors	Sample	Coefficient	SE	OR (95%CI)	P-Value	UK Biobank						Depression	All	-0.73	0.24	0.48 (0.29,0.76)	0.003	APOE4 carriers	0.15	0.37	1.16 (0.54,2.30)	0.687	APOE4 non-carriers	-1.24	0.33	0.29 (0.15,0.53)	<0.001	Hypertension	All	-0.94	0.11	0.39 (0.31,0.48)	<0.001	APOE4 carriers	-0.90	0.22	0.41 (0.26,0.62)	<0.001	APOE4 non-carriers	-0.97	0.13	0.38 (0.29,0.49)	<0.001	Sleep disorder	All	-1.17	0.15	0.31 (0.23,0.41)	<0.001	APOE4 carriers	-0.97	0.27	0.38 (0.22,0.63)	<0.001	APOE4 non-carriers	-1.26	0.18	0.28 (0.19,0.40)	<0.001	A greater count of COVID-19 vaccinations received before age 65 was associated with significantly (p-values <0.01) lower odds of the health-related AD risk factors: <u>depression</u> (OR=0.48 in the total sample; OR=0.29 in APOE4 non-carriers); <u>hypertension</u> (OR=0.39 in the total sample; OR=0.38 in APOE4 carriers); <u>sleep disorders</u> (OR=0.31 in the total sample; OR=0.28 in APOE4 non-carriers, OR=0.38 in carriers). Effect sizes were overall larger in APOE4 non-carriers (Table). CONCLUSION Our study found that COVID-19 vaccination may confer health benefits beyond protection against COVID-19 itself by <u>lowering the odds of health-related AD risk factors, such as hypertension, depression, and sleep disorders.</u>	Our findings imply that COVID-19 vaccinations may reduce the overall burden of AD risk factors and, through this, potentially lower AD risk. Evaluating direct protective effects of repeated COVID-19 vaccinations on AD risk will require longer follow-up. Relevant data will become available in the coming years. The vaccination effect appeared more pronounced in APOE4 non-carriers than in carriers. This may indicate that the harmful effects of APOE4 are harder to counteract. Acknowledgements This research was supported by the National Institutes of Health’s National Institute on Aging (NIA/NIH) grant R01AG076019. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA/NIH. This study was conducted using de-identified data provided by the UK Biobank under application number 82705.  ALZHEIMER’S ASSOCIATION AAIC 26
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