Journal of Alzheimer's Disease 96 (2023) 499–505
DOI 10.3233/JAD-230088
IOS Press

Short Communication

Vaccination Against Pneumonia May Provide Genotype-Specific Protection Against Alzheimer's Disease

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Accepted 29 August 2023
Pre-press 3 October 2023

Abstract. Vaccine repurposing that considers individual genotype may aid personalized prevention of Alzheimer's disease (AD). In this retrospective cohort study, we used Cardiovascular Health Study data to estimate associations of pneumococcal polysaccharide vaccine and flu shots received between ages 65–75 with AD onset at age 75 or older, taking into account rs6859 polymorphism in *NECTIN2* gene (AD risk factor). Pneumococcal vaccine, and total count of vaccinations against pneumonia and flu, were associated with lower odds of AD in carriers of rs6859 A allele, but not in non-carriers. We conclude that pneumococcal polysaccharide vaccine is a promising candidate for genotype-tailored AD prevention.

Keywords: Alzheimer's disease, Cardiovascular Health Study, immunity, pneumococcal polysaccharide vaccine, seasonal flu shots, vaccine repurposing

INTRODUCTION

Accumulating evidence suggests that infections could play a major role in Alzheimer's disease (AD); however, mechanism is poorly understood. Diverse studies linked different microorganisms (viruses, bacteria, fungi) to AD and related traits [1–4]. This indicates a possibility that the culprit may not (or not only) be a specific microbe, but compromised immunity that may increase vulnerability of the brain to various infections promoting neurodegeneration. Examples of factors that may compromise immunity include aging of the immune system, certain exposures (e.g., to air pollution), and genetic variation, among others [5–9]. For instance, aging is characterized by immunosenescence, which is accompanied by depletion of reserves of naive immune cells, slower and impaired responses to antigens, declining immune surveillance, increased permeability of the blood-brain-barrier (BBB), and chronic inflammation [5, 10, 11], all of which may increase vulnerability of the brain to a variety of microbes and their damaging byproducts. If compromised immunity (due to aging or other factors) does underly

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the connection between infections and AD, then approaches to strengthening immunity might confer protection against AD.

Vaccination is one such approach that may improve immunity broadly, in addition to making individuals more resistant/resilient to specific infections. Recent studies suggested that some vaccines may have beneficial heterologous (a.k.a. off-target, non-specific) effects on immunity that span beyond protection against the target disease [12, 13]. Mechanisms of such effects may involve heterologous lymphocyte responses, trained innate immunity, stabilization of the BBB, and other yet unknown factors [9, 12]. Several studies reported the beneficial off-target effects of pneumococcal and influenza vaccines on various health traits, including AD-related [14–17].

Here we conducted a retrospective cohort study among a subset of individuals who survived without AD as of age 75 in the Cardiovascular Health Study (CHS), to estimate associations of vaccinations against pneumonia and influenza (flu) received between ages 65 and 75 with AD onset at age $\geq$75 years, taking into account individual genotype, to explore the potential of these vaccines as candidates for personalized, genotype-tailored, prevention of AD. We focused on the rs6859 polymorphism of *NECTIN2* (nectin cell adhesion molecule 2, a.k.a. herpes virus entry mediator B) gene on chromosome 19 involved in adherens junctions that are important for controlling BBB permeability and protecting the brain from infections. We selected *NECTIN2* because it plays role in both AD and vulnerability to infections, and its rs6859 polymorphism is an established genetic risk factor for AD, which may also act independently of *APOE4*, as shown by our and others' previous genome-wide association studies and linkage disequilibrium analysis [7, 18]. We propose that this polymorphism may modulate the effects of vaccines on AD risk.

MATERIALS AND METHODS

Data

Version 7 of CHS data was provided by the NIH database of Genotypes and Phenotypes (dbGaP) resource of the National Center for Biotechnology Information (NCBI). The CHS Cohort has dbGaP study accession number phs000287. Genetic data were provided by the CHS Candidate Gene Association Resource (CARe), a sub-study of CHS Cohort. All study participants are 65 years or older (Table 1). Details of CHS data sample are provided in the Supplementary Material.

Variables

Exposure: vaccinations against pneumonia and/or influenza (flu), self-reported. Pneumonia vaccine in this study referred to a pneumococcal polysaccharide vaccine (Pneumovax 23, PPSV23), and influenza vaccine referred to a seasonal flu shot, received between ages 65 and 75, so that all vaccination events occurred before AD onset, to avoid reverse causation. Vaccination variables were as follows: 1) receipt of any pneumonia vaccine (binary variable: 0 – no, 1 – yes); 2) receipt of any influenza vaccine (binary variable: 0 – no, 1 – yes); 3) number of seasonal flu shots received (continuous variable); and 4) number of pneumonia and influenza vaccines received (continuous variable), between ages 65 and 75. When vaccine history information was available from multiple sources in the same year, the combined information was used to determine vaccination status. For example, Pneumovax 23 information was available in two sets of CHS data collected at baseline (*base1* and *baseboth)*. If an individual was shown as vaccinated in both these sets, we considered such individual as vaccinated once.

Outcome: AD onset was categorized as 0 = "no AD", and 1 = "AD onset at age $\geq$75 years", with condition of survival to age 75 and above in both groups. The AD diagnosis was based on the ICD-9-CM code 331.0 in hospitalization records of CHS participants. The occurrence of this code at discharge was used to define AD. Patients who did not have the code 331.0 at discharge were considered AD-free. Individuals diagnosed with AD before age 75 were excluded from the analysis. Additional details are provided in the Supplementary Material.

Genetic polymorphism: For the analyses stratified by genotype, the study sample was divided into two groups, according to carrier and non-carrier status of rs6859 A allele (AD risk factor). Alternative, non-risk, allele is G. The group of carriers of the A allele included individuals with genotypes AA and AG, and the group of non-carriers of the A allele included only individuals with GG genotype.

Covariates: self-reported sex (1 – male, 2 – female), race (1 – White, 2 – Black, 3 – other), birth cohort (year of birth), education level (0 – below high school, 1 – high school, 2 – above high school), and smoking status (0 – never smoked, 1 – ever smoked). These covariates were included because they are the most

common and best studied non-genetic factors that may influence AD risk and have been found to be correlated with vaccination status.

Analysis

The analytic sample included complete records with no missing values for respective covariates. Logistic regression models with all covariates were used to estimate odds of AD onset at age ≥75 years, following vaccinations against pneumonia (yes versus no) and influenza (yes versus no) received between ages 65 and 75. We also estimated associations of the total number of flu shots, and pneumonia and flu shots combined, received between ages 65 and 75, with AD onset at age ≥75 years, adjusting for the same covariates. We performed both unstratified and stratified analyses. In the stratified analysis, we evaluated associations between vaccinations and AD separately for carriers and non-carriers of the rs6859 A allele. Statistical significance was based on p-value <0.05 and 95% confidence intervals. Analyses were conducted with statistical software SAS 9.4 and R (version 4.2). Our study followed the STROBE reporting guidelines (checklist is provided in the Supplementary Material). We also created Kaplan-Meier survival trajectories of the probability of staying free of AD at ages 75 and older, following vaccination against pneumonia received between ages 65–75, in carriers and non-carriers of the rs6859 A allele, to additionally graphically illustrate genotype-specific effect of the vaccination on AD onset.

RESULTS

Characteristics of CHS participants are summarized in Table 1. Results of associations of vaccinations against pneumonia and flu with AD onset, unstratified, as well as stratified by carrier status of the rs6859 A allele, are shown in Table 2. Pneumonia vaccine received between ages 65–75 was associated with 33% lower odds of AD onset

Table 1
Characteristics of the CHS participants and subsamples used in the analysis

	Lifespan	Male	Female	White	Black	Total
CHS (total)	All	2,373	3,151	4,648	840	5,599
	≥75	2,162	2,984	4,350	763	5,146
	65–75	211	167	298	77	453
CHS (analytic sample)	≥75	1,359	2,028	2,891	477	3,387
Dichotomous Variables: Number (Percentage)						
AD onset at age ≥75[a]	≥75	115 (5.32)	182 (6.10)	255 (5.86)	39 (5.11)	297 (5.77)
Pneumonia vaccine between ages 65–75[b]	All	802 (33.80)	1,182 (37.51)	1,718 (36.96)	254 (30.24)	1,984 (35.43)
	≥75	718 (33.21)	1,098 (36.80)	1,582 (36.37)	222 (29.10)	1,816 (35.29)
	65–75	84 (39.81)	84 (50.30)	136 (45.64)	32 (41.56)	168 (37.09)
Flu shot between ages 65–75[c]	All	1,147 (48.34)	1,582 (50.21)	2,353 (50.62)	360 (42.86)	2,729 (48.74)
	≥75	1,011 (46.76)	1,467 (49.16)	2,149 (49.40)	314 (41.15)	2,478 (48.15)
	65–75	136 (64.45)	115 (68.86)	204 (68.46)	46 (59.74)	251 (55.41)
Education (high school and above)[d]	All	1,978 (83.35)	2,672 (84.80)	3,995 (85.95)	627 (74.64)	4,650 (83.05)
	≥75	1,811 (83.77)	2,530 (84.79)	3,750 (86.21)	566 (74.18)	4,341 (84.36)
	65–75	167 (79.15)	142 (85.03)	245 (82.21)	61 (79.22)	309 (68.21)
Ever smoked[e]	All	1,617 (68.14)	1,358 (43.10)	2,527 (54.37)	436 (51.90)	2,975 (53.13)
	≥75	1,447 (66.93)	1,257 (42.12)	2,309 (53.08)	384 (50.33)	2,704 (52.55)
	65–75	170 (80.57)	101 (60.48)	218 (73.15)	52 (67.53)	271 (59.82)
Continuous Variables: Mean (Standard Deviation)						
Age at enrollment[f]	All	73.35 (5.78)	72.52 (5.53)	72.85 (5.62)	73.00 (5.79)	72.88 (5.65)
	≥75	73.84 (5.79)	72.76 (5.57)	73.16 (5.65)	73.48 (5.81)	73.22 (5.68)
	65–75	68.32 (2.07)	68.19 (2.05)	68.28 (2.00)	68.27 (2.33)	68.25 (2.06)
Age at the last follow-up[g]	All	82.82 (5.77)	83.30 (5.34)	83.33 (5.43)	81.81 (5.86)	83.09 (5.53)
	≥75	83.87 (4.87)	83.91 (4.79)	84.09 (4.71)	82.77 (5.23)	83.89 (4.82)
	65–75	72.07 (2.15)	72.48 (1.98)	72.23 (2.07)	72.31 (2.15)	72.25 (2.08)
Follow-up time[h]	All	9.47 (4.19)	10.78 (3.58)	10.47 (3.95)	8.81 (3.34)	10.21 (3.91)
	≥75	10.03 (3.91)	11.14 (3.27)	10.93 (3.63)	9.29 (3.04)	10.68 (3.59)
	65–75	3.74 (2.31)	4.29 (2.31)	3.95 (2.29)	4.14 (2.44)	3.99 (2.33)
Birth cohort (birth year)[i]	All	1,913.92 (6.10)	1,914.84 (5.75)	1,914.09 (5.78)	1,916.47 (6.23)	1,914.45 (5.92)
	≥75	1,913.40 (6.09)	1,914.59 (5.77)	1,913.77 (5.81)	1,915.96 (6.24)	1,914.09 (5.93)
	65–75	1,919.22 (2.88)	1,919.34 (2.66)	1,918.67 (2.36)	1,921.56 (3.06)	1,919.27 (2.79)

Numbers of participants with missing data for variables in Table 1: [a]453; [b]1,842; [c]1,822; [d]91; [e]93; [f]75; [g]75; [h]75; [i]75.

at age 75 and older in carriers of A allele (OR = 0.67; $p = 0.0496$), but not in non-carriers, or in the total sample. The influenza vaccine alone did not show a statistically significant association with AD in any group, and the number of flu shots was only marginally statistically significantly (i.e., p-value slightly exceeding 0.05) associated with a lower AD risk in unstratified sample, and in carriers of A allele. The total count of vaccinations against pneumonia and flu was associated with lower odds of AD in the overall sample (OR = 0.94; $p = 0.049$), and in carriers of the A allele (OR = 0.93; $p = 0.048$), but not in non-carriers. Notably, all associations in the *non-carrier* group were not statistically significant, and most ORs were close to 1 (Table 2C). Kaplan-Meier survival trajectories of the probability of staying AD-free at ages 75 and older, following the vaccination against pneumonia between ages 65–75, additionally illustrated the protective effect of pneumonia vaccine on AD in carriers of the rs6859 A allele, but not in non-carriers (Supplementary Figure 1).

DISCUSSION

This retrospective cohort study among a subset of CHS participants found that pneumococcal polysaccharide vaccine, as well as total count of vaccinations against pneumonia and flu, received between ages 65–75, have genotype-specific associations with odds of AD onset at age $\geq$75 years, such that vaccinations were AD-protective only in carriers of the rs6859 A allele, but not in non-carriers. Results of this study are broadly consistent with the idea that strengthening immunity by the off-target effects of vaccines may provide protection against AD, and also suggest that variation in genes involved in AD and vulnerability to infections may influence such effects of vaccines and should be taken into account in personalized prevention of AD.

Other genes and polymorphisms beyond the rs6859 in *NECTIN2* might also influence the effects of vaccines on AD, e.g., our unpublished data (a conference abstract) suggested that rs2075650 in *TOMM40* is another candidate polymorphism that may modulate the effect of pneumococcal vaccine on AD. The rs2075650, however, is in linkage disequilibrium with multiple SNPs in *APOE* and *NECTIN2*, and is also the eQTL SNP that influences expression of these genes, so its biological effects, including possible role in vulnerability to infections, may potentially be related to functions of *APOE* and/or *NECTIN2* [7], which deserves separate investigation.

In addition to the possibility of a beneficial heterologous effect of pneumococcal vaccine on immunity, there is also a possibility that this vaccine may contribute to a reduction in AD risk by simply preventing cases of the originally targeted disease. For example, it was shown that bacterial pneumonia is associated with increased risk of AD [19]. If so, then preventing the pneumonia cases might reduce AD risk. Such mechanism seems plausible. Some studies, however, suggested that the off-target effects of vaccines cannot be fully explained by pathogen-specific immune protection, and that non-specific immune system modulation by vaccines may be a common phenomenon [20]. It is also possible that both mechanisms (i.e., boosting immunity broadly, along with preventing cases of target disease that may otherwise promote dementia) could be responsible for lowering the risk of AD by the pneumonia vaccine.

One potential reason for the lack of a significant effect of the flu vaccine on AD could be that this vaccine has a relatively short-term (seasonal) effect, so multiple flu shots might be needed to produce a noticeable long-term beneficial effect on immunity [21]. Another reason could be differences between off-target effects of pneumonia and flu vaccines, among other factors [9, 12].

We acknowledge that this study has limitations. Some are inherent to the CHS design, which includes potential response and participation biases [22], and unavailability of clinically verified AD diagnoses. A common limitation of studies that use hospital discharge records is that identifying disease cases based on such records may potentially lead to disease misclassification. For example, exclusion of participants with AD onset before age 75 might be incomplete because some participants with no prior hospitalizations would not be identified as having AD based on hospital records, and so could be misclassified as free of AD at the start of the follow-up (i.e., age 75). In such cases, there may be a possibility of reverse causality. Unavailability of sampling weights that would allow generalizability of findings to the general US population of respective ages is another limitation that is inherent to the CHS design. In addition, our analysis did not consider competing risks (e.g., due to mortality). One should also note that even though we adjusted all analyses for relevant covariates, such as sex, race, birth cohort, education, and smoking, we cannot fully exclude the possibility that people who obtain vaccinations, as compared to those who do not, may have a higher socioeconomic status, or

Table 2
Effects of vaccinations against pneumonia and influenza received between ages 65–75 on AD onset at age ≥75 years in CHS data. Unstratified and stratified by *carrier* versus *non-carrier* status of rs6859 A allele. Significance is based on *p*-value <0.05 and 95% confidence intervals

Predictor	Outcome	Beta	*p*	OR (95% CI)	*N*
A) Total sample, without stratification by genotype.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.256	0.126	0.774 (0.558, 1.075)	3,370
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.099	0.581	0.906 (0.637, 1.287)	3,385
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.068	0.068	0.934 (0.868, 1.005)	3,385
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.058	**0.049**	**0.944*** (0.891, 0.999)	3,385
B) Carriers of rs6859 A allele.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.400	**0.0496**	**0.671*** (0.450, 0.999)	2,064
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.106	0.629	0.900 (0.586, 1.381)	2,072
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.073	0.101	0.930 (0.852, 1.015)	2,072
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.070	**0.048**	**0.932*** (0.870, 0.999)	2,072
C) Non-carriers of rs6859 A allele.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.065	0.845	0.937 (0.489, 1.796)	1,143
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.236	0.501	0.790 (0.398, 1.568)	1,149
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.060	0.411	0.942 (0.817, 1.086)	1,149
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.042	0.472	0.959 (0.856, 1.075)	1,149

*Statistically significant results (*p*-value <0.05).

seek vaccinations due to other, yet unknown, factors. We also did not adjust for comorbidities, which may, potentially, impact likelihood of vaccination and/or risk of AD. Indeed, there may be many unknown factors that could impact propensity to vaccination and chances of AD.

We conclude that pneumococcal polysaccharide vaccine is a promising candidate for repurposing for genotype-tailored personalized prevention of AD. Multiple seasonal flu shots may potentially strengthen its effect, due to, e.g., additional stimulation of the immune system. This possibility, however, needs further investigation and confirmation. It is important to note that our study suggested the protective effect of the pneumococcal vaccine on AD onset among CHS participants specifically, so its results should not be generalized to other groups. Prospective, randomized, or pseudo-randomized (using propensity score matching) studies with adjudicated AD cases could help further support these findings.

ACKNOWLEDGMENTS

The authors thank the CHS study supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through R01 AG-15928, R01 AG-20098, and AG-027058 from the National Institute on Aging, R01 HL-075366 from the National Heart, Lung and Blood Institute, and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30-AG-024827. The CHS CARe genetic data were provided by dbGaP (accession number phs000377, a sub-study of phs000287 CHS Cohort). The list of principal CHS investigators and institutions can be found at: http://www.chs-nhlbi.org/pi.htm.

FUNDING

This research was supported by the National Institutes of Health's National Institute on Aging, grants R01AG076019, R01AG070487, and P30AG072958. This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health's National Institute on Aging.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The authors cannot make CHS data and study materials freely available to other investigators due to dbGaP Data Use Certification Agreement restrictions; however, interested parties can contact NIH dbGaP (https://www.ncbi.nlm.nih.gov/gap/) to request access to these data through the applicable data access request process.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230088.

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