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ORIGINAL RESEARCH ARTICLE

Higher risk for incident heart failure and cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination

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Abstract

Aims Octogenarians have the highest incidence of heart failure (HF) that is not fully explained by traditional risk factors. We explored whether lack of pneumococcal vaccination is associated with higher risk of incident HF among octogenarians.

Methods and results In the Cardiovascular Health Study (CHS), 5290 community-dwelling adults, ≥65 years of age, were free of baseline HF and had data on pneumococcal vaccination. Of these, 851 were octogenarians, of whom, 593 did not receive pneumococcal vaccination. Multivariable-adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for associations of lack of pneumococcal vaccination with incident HF and other outcomes during 13 years of follow-up were estimated using Cox regression models, adjusting for demographics and other HF risk factors including influenza vaccination. Octogenarians had a mean (±SD) age of 83 (±3) years; 52% were women and 17% African American. Overall, 258 participants developed HF and 662 died. Lack of pneumococcal vaccination was associated with higher relative risk of incident HF (aHR, 1.37; 95% CI, 1.01–1.85; $P = 0.044$). There was also higher risk for all-cause mortality (aHR, 1.23; 95% CI, 1.02–1.49; $P = 0.028$), which was mostly driven by cardiovascular mortality (aHR, 1.45; 95% CI, 1.06–1.98; $P = 0.019$). Octogenarians without pneumococcal vaccination had a trend toward higher risk of hospitalization due to pneumonia (aHR, 1.34; 95% CI, 0.99–1.81; $P = 0.059$). These associations were not observed among those 65–79 years of age.

Conclusions Among community-dwelling octogenarians, lack of pneumococcal vaccination was associated with a significantly higher independent risk of incident HF and mortality, and trend for higher pneumonia hospitalization.

Keywords Octogenarians; Pneumococcal vaccination; Heart failure; Mortality

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Introduction

Octogenarians are among the fastest growing segments of the US population, and they also have the highest incidence of heart failure (HF).[1–3] However, traditional risk factors for incident HF do not appear to explain this incidence as their impact appears to attenuate with ageing.[4–7] For example, in the Cardiovascular Health Study (CHS), among those <78 years of age, 18% and 13% of those with and without isolated systolic hypertension (ISH) developed new HF, respectively, which corresponded with a 44% higher relative risk for those with ISH.[4] In contrast, among those ≥78 years of age, 24% and 25% of those with and without ISH developed new HF. Similarly, isolated diastolic hypertension was associated with a 33% significantly higher independent risk of incident HF, which was only observed among those <75 years of age.[5]

Thus, there is a need to identify non-traditional risk factors for incident HF among the oldest old who have the highest incidence of HF that is not well explained by traditional risk factors. In this context, we conducted an exploratory analysis to determine if lack of pneumococcal vaccination is associated with higher risk of incident HF. Although pneumococcal infection is a major cause of cardiovascular morbidity,[8] it has been suggested that pneumococcal vaccination may reduce the risk of cardiovascular events.[9,10] Therefore, in the current study, we examined whether lack of pneumococcal vaccination is associated with higher risk of incident HF in community-dwelling octogenarians.

Methods

Data source and study participants

We used de-identified copies of the CHS data obtained from the National Heart, Lung and Blood Institute (NHLBI), which also sponsored the study. The rationale and design of the CHS have been previously reported.[11] The CHS is an ongoing, prospective, community-based epidemiologic study based on 5888 Medicare-eligible community-dwelling older adults, aged 65 year and older, from Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. An initial cohort of 5201 participants was recruited between 1989 and 1990, and a second cohort of 687 African Americans was recruited between 1992 and 1993. Of the 5888 CHS participants, 5795 consent to be included in the public-use copy of the data. Of these, 240 without data on baseline pneumococcal vaccination and 265 with baseline prevalent HF were excluded. Of the remaining 5290, 851 were 80 years and older and 4439 were 65 to 79 years of age at baseline. Data on pneumococcal vaccination were collected at baseline by asking the questions: 'Have you ever had a shot to prevent pneumonia (pneumovax)?'[12] Additional data on socio-demographic characteristics, health behaviours, self-rated health and vaccination history, comorbid conditions, medications, vital signs, markers of inflammation, and other biochemical covariates were collected at baseline and have been previously described in details.[11] Missing values for variables were imputed based on values predicted by age, sex, and race.

Outcomes

Primary outcomes for the current analysis were incident HF and all-cause mortality during 13 years of follow-up. Incident HF was centrally adjudicated by the CHS Events Committee, which has been well described in literature.[13] The process began with self-reports of physician-diagnosed HF, which were then confirmed by review of medical records for symptoms, signs, medications, and other evidence of HF.[4–7] The CHS criteria for HF diagnosis have been shown to be more stringent than those used in the Framingham Heart Study.[14] Secondary outcomes of interest were cardiovascular and non-cardiovascular mortality, as well as all-cause hospitalization and hospitalization due to pneumonia.

Statistical analysis

For descriptive analyses, we used Pearson's χ^2 for categorical variables and analysis of variance for continuous variables. Kaplan Meier survival analysis was used to determine the association of pneumococcal vaccination with outcomes during 13 years of follow-up. Unadjusted and multivariable-adjusted Cox regression models were used to estimate the association of lack of pneumococcal vaccination with outcomes. All statistical tests were two-sided, and tests with P-value <0.05 were considered significant. SPSS for Windows (Version 18) was used for data analysis. We repeated our analysis in participants 65 to 79 years of age.

Results

Baseline characteristics

Octogenarians had a mean (±SD) age of 83 (±3) years; 52% were female, and 17% were African American. The distribution of baseline characteristics between participants receiving or not receiving pneumococcal vaccination was generally balanced (*Table 1*). A greater proportion of octogenarians receiving pneumococcal vaccination also received influenza vaccination and had higher prevalence of chronic obstructive pulmonary disease and pneumonia.

Incident heart failure

During 13 years of follow-up, among octogenarians, a non-receipt of pneumococcal vaccination at baseline was associated with significantly higher risk of incident HF [adjusted hazard ratio (aHR), 1.37; 95% confidence interval (CI), 1.01–1.85; *Figure 1* and *Table 2*). In contrast, among those 65–79 years, a non-use of pneumococcal vaccination was not associated with incident HF (aHR, 0.88; 95% CI, 0.74–1.04; *Table 2*).

Mortality

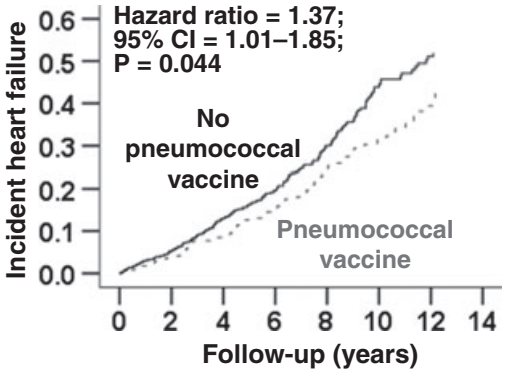
Compared with octogenarians who received pneumococcal vaccination, non-receipt of pneumococcal vaccination was associated with significantly higher risk of all-cause mortality

Table 1 Baseline characteristics by pneumococcal vaccination in CHS

	Age ≥80 years (n = 851)			Age 65–79 years (n = 4439)		
	Pneumococcal vaccination			Pneumococcal vaccination		
Variables mean (±SD) or n (%)	No (n = 593)	Yes (n = 258)	P-value	No (n = 3273)	Yes (n = 1166)	P-value
Age, years	83 (±3)	83 (±3)	0.447	71 (±4)	72 (±3)	<0.001
Female	298 (50%)	144 (56%)	0.136	1943 (59%)	688 (59%)	0.830
African American	111 (19%)	31 (12%)	0.016	521 (16%)	134 (12%)	<0.001
Married	300 (51%)	145 (56%)	0.132	2293 (70%)	805 (69%)	0.515
Education college or higher	252 (43%)	125 (48%)	0.108	1335 (41%)	566 (49%)	<0.001
Income ≥$25K	161 (27%)	90 (35%)	0.023	1201 (37%)	519 (45%)	<0.001
Smoke, pack years	11 (±24)	14 (±25)	0.152	18 (±27)	19 (±27)	0.351
Walk blocks last week	25 (±40)	25 (±36)	0.939	41 (±57)	44 (±57)	0.212
Body mass index, kg/m^2	25.5 (±3.9)	25.7 (±3.8)	0.596	26.8 (±4.0)	26.5 (±4.1)	0.046
Instrumental ADL	0.5 (±0.9)	0.7 (±1.0)	0.050	0.3 (±0.6)	0.31 (±0.6)	0.073
Centers for Epidemiologic Studies Depression (CES-D) scale score	5.0 (±4.5)	5.4 (±4.9)	0.253	4.5 (±4.5)	4.5 (±4.3)	0.918
Mini-Mental State Examination	25.7 (±3.9)	26.6 (±3.3)	0.001	27.8 (±2.4)	28.1 (±2.2)	0.001
Flu vaccination	225 (38%)	201 (78%)	<0.001	979 (30%)	905 (78%)	<0.001
Medical history						
Coronary heart diseases	124 (21%)	58 (23%)	0.608	506 (16%)	223 (19%)	0.004
Acute myocardial infarction	61 (10%)	18 (7%)	0.126	240 (7%)	98 (8%)	0.236
Hypertension	409 (69%)	176 (68%)	0.827	1816 (56%)	680 (58%)	0.094
Diabetes	92 (16%)	32 (12%)	0.237	515 (16%)	182 (16%)	0.916
Stroke	37 (6%)	14 (5%)	0.646	99 (3%)	54 (5%)	0.010
Atrial fibrillation	20 (3%)	11 (4%)	0.524	48 (2%)	31 (3%)	0.008
LVH by electrocardiogram	46 (8%)	19 (7%)	0.843	122 (4%)	40 (3%)	0.642
LV systolic dysfunction	66 (11%)	25 (10%)	0.532	214 (7%)	80 (7%)	0.704
Left bundle branch block	73 (12%)	29 (11%)	0.659	240 (7%)	101 (9%)	0.143
COPD	46 (8%)	49 (19%)	<0.001	329 (10%)	230 (20%)	0.094
Pneumonia	110 (19%)	97 (38%)	<0.001	765 (23%)	436 (37%)	<0.001
Laboratory data						
Serum creatinine, g/dL	1.09 (±0.4)	1.04 (±0.4)	0.093	0.9 (±0.4)	0.9 (±0.5)	0.902
Serum C-reactive protein, mg/L	5.1 (±9.1)	4.0 (±5.7)	0.072	4.6 (±7.8)	4.8 (±9.1)	0.473

CHS, Cardiovascular Health Study; ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; LVH, left ventricular hypertrophy.

Figure 1 Multivariable-adjusted risk for incident heart failure among Cardiovascular Health Study participants aged 80 years or older (Hazard ratio when non-use of pneumococcal vaccination is compared with their use).



(aHR, 1.23; 95% CI, 1.02–1.49), CV mortality (aHR, 1.45; 95% CI, 1.06–1.98), but not of non-CV mortality (aHR, 1.10; 95% CI, 0.87–1.40; *Table 2*). Pneumococcal vaccination had no association with mortality among those 65–79 years of age (*Table 3*).

Hospitalization

Among octogenarians, non-receipt of pneumococcal vaccination had no association with all-cause hospitalization (aHR, 1.04; 95% CI, 0.87–1.40), but there was a trend toward higher risk of hospitalization due to pneumonia (aHR, 1.35; 95% CI, 1.00–1.82; *Table 2*). None of these associations were significant among those 65–79 years of age(*Table 3*).

Discussion

Findings from the current study demonstrated that among community-dwelling octogenarians, the lack of a prior pneumococcal vaccination was associated with higher risk of incident HF and cardiovascular mortality. We also observed that there was a trend toward higher risk of hospitalization due to pneumonia. Lack of pneumococcal vaccination, however, had no association with these outcomes among older adults 65 to 79 years of age. These findings are hypothesis generating and suggest that pneumococcal infections may be a non-traditional risk factor for incident HF among octogenarians, and that pneumococcal vaccination may lower the risk of HF among octogenarians.

The association of lack of pneumococcal vaccination and higher incident HF is unlikely to be confounded by other major HF risk factors such as prior myocardial infraction, hypertension, diabetes, and left ventricular systolic dysfunction as they were similarly distributed at baseline between octogenarians with and without prior pneumococcal vaccination and we adjusted for those in our multivariable model. They are also unlikely to be explained by chronic obstructive pulmonary disease and pneumonia as fewer octogenarians not receiving pneumococcal vaccination had these conditions, likely explained by the fact that they were potential indications for pneumococcal vaccination.[12] Findings from animal studies suggest that human C-reactive protein (CRP) may protect mice from pneumococcal infection[15] and pneumococcal vaccination is often associated with higher CRP levels.[16] Octogenarians without a prior pneumococcal vaccination had higher CRP levels, and although adjusted for in our multivariable model, residual bias is possible. Influenza vaccination has been shown to be associated with lower cardiovascular events.[17–20] Octogenarians without pneumococcal vaccination were less likely to receive influenza vaccination. Although this was adjusted for, residual bias is possible. It is also possible that lack of vaccination was a marker of less healthy life style for octogenarians with no prior vaccination, which may have contributed to their poor cardiovascular outcomes. However, there was no difference in

Table 2 Association of lack of pneumococcal vaccination with outcomes in octogenarians in the CHS

	Events (%)			
	Pneumococcal vaccination		Hazard ratio* (95% confidence interval); *P*-value	
	No (n = 593)	Yes (n = 258)	Unadjusted	Multivariable-adjusted†
Incident heart failure	183 (31%)	75 (29%)	1.21 (0.92–1.58); P = 0.165	1.37 (1.01–1.85); P = 0.044
All-cause mortality	474 (80%)	188 (73%)	1.29 (1.09–1.53); P = 0.003	1.23 (1.02–1.49); P = 0.028
Cardiovascular	201 (34%)	68 (26%)	1.50 (1.14–1.98); P = 0.004	1.45 (1.06–1.98); P = 0.019
Non-cardiovascular	272 (46%)	120 (47%)	1.16 (0.94–1.44); P = 0.168	1.10 (0.87–1.40); P = 0.426
All-cause hospitalization	530 (89%)	236 (92%)	1.01 (0.87–1.18); P = 0.919	1.04 (0.87–1.24); P = 0.643
Pneumonia	184 (31%)	75 (29%)	1.20 (0.92–1.57); P = 0.183	1.35 (1.00–1.82); P = 0.051

CHS, Cardiovascular Health Study.
*Hazard ratio, when non-use of pneumococcal vaccination was compared with their use.
†Adjusted for age ≥85 years, sex, race, married, education college or higher, income ≥$25K, smoking ≥32 pack-years, walk blocks last week ≥10, body mass index ≥25 kg/m^2, instrumental activities of daily living ≥1, Centers for Epidemiologic Studies Depression (CES-D) scale score, Mini-mental state examination (30 item), influenza vaccination, coronary heart diseases, hypertension, diabetes, stroke, acute myocardial infarction, atrial fibrillation, left ventricular hypertrophy, left ventricular systolic dysfunction, left bundle branch block, chronic kidney disease, chronic obstructive pulmonary disease, pneumonia, serum C-reactive protein ≥2.4 mg/L.

Table 3 Association of lack of pneumococcal vaccination with outcomes in those 65–79 years of age in the CHS

	Events (%)		Hazard ratio* (95% confidence interval); *P*-value	
	Pneumococcal vaccination			
	No (n = 3273)	Yes (n = 1166)	Unadjusted	Multivariable-adjusted†
Incident heart failure	568 (17%)	247 (21%)	0.78 (0.67–0.91); $P = 0.001$	0.88 (0.74–1.04); $P = 0.126$
All-cause mortality	1182 (36%)	468 (40%)	0.87 (0.78–0.97); $P = 0.009$	0.96 (0.85–1.08); $P = 0.480$
Cardiovascular	485 (15%)	187 (16%)	0.89 (0.75–1.06); $P = 0.181$	0.96 (0.79–1.16); $P = 0.667$
Non- cardiovascular	692 (21%)	281 (24%)	0.85 (0.74–0.97); $P = 0.017$	0.95 (0.81–1.10); $P = 0.512$
All-cause hospitalization	2650 (81%)	994 (85%)	0.85 (0.79–0.92); $P < 0.001$	0.94 (0.86–1.02); $P = 0.111$
Pneumonia	577 (18%)	246 (21%)	0.80 (0.69–0.93); $P = 0.003$	0.89 (0.75–1.06); $P = 0.182$

CHS, Cardiovascular Health Study.
*Hazard ratio, when non-use of pneumococcal vaccination was compared with their use.
†Adjusted for age ≥70 years, sex, race, married, education college or higher, income ≥$25K, smoking ≥32 pack-years, walk blocks last week ≥10, body mass index ≥25 kg/m^2, instrumental activities of daily living ≥1, Centers for Epidemiologic Studies Depression (CES-D) scale score, Mini-mental state examination (30 item), influenza vaccination, coronary heart diseases, hypertension, diabetes, stroke, acute myocardial infarction, atrial fibrillation, left ventricular hypertrophy, left ventricular systolic dysfunction, bundle branch block, advance chronic kidney disease, chronic obstructive pulmonary disease, pneumonia, serum C-reactive protein ≥2.4 mg/L

other markers of healthy life style such body mass index between the two groups suggesting a healthy life style cannot fully explain our findings.

We used very similar risk-adjustment models for both octogenarians and those 65–79 years of age. Further, between-group prevalence of major HF, risk factors were also similar for both octogenarians and those 65–79 years of age. Yet, despite a larger sample size and higher number of events in those 65–79 years of age, pneumococcal vaccination had no association with incident HF or mortality. This may suggest that the associations observed among the octogenarians are due to chance. However, prior studies have reported that pneumococcal vaccination to be associated with better CV outcomes.[9,10] In one study, the use of pneumococcal vaccination was associated with higher risk of CV outcomes among those <65 years of age, while there was no such association among those ≥65 years of age.[21,22] Taken together with the findings from our study, these findings suggest that there might exist a potential age-related variation in the benefit of pneumococcal vaccination. Oxidized low-density lipoproteins play an important role in atherogenesis, and antibodies against them may cause regression of atherosclerosis.[23,24] In laboratory animals, pneumococcal vaccination has been shown to decrease atherosclerotic lesion.[25] Preliminary findings from human studies suggest that pneumococcal vaccination may induce antibodies against oxidized low-density lipoproteins.[26] Although oxidized low-density lipoproteins are not known HF risk factors, they have been shown to be associated with other cardiovascular events.[27]

Pneumococcal disease is common among older adults, specifically among octogenarians,[28,29] and pneumococcal vaccination is recommended for all adults ≥65 years of age.[30] Findings from the current study suggest that this vaccination might also lower the risk of HF and CV mortality among octogenarians. Prospective studies of pneumococcal vaccination in octogenarians would be unethical as it would require delaying vaccination until that age. However, if these findings can be replicated in other octogenarian populations, this might provide an inexpensive tool for improving the health and outcomes of the fastest growing segment of the US population. It will also provide additional rationale to increase the utilization of pneumococcal vaccination, which remains low, about 60% among adults ≥65 years of age in 2010.[8]

Our study has several limitations. As discussed earlier, an important limitation of any observational study is the potential for bias due to unmeasured confounders, and ours is no exception. We had no data on the time of pneumococcal vaccination. The 23-valent polysaccharide pneumococcal vaccine was licenced in 1977 and has been reimbursed by Medicare since 1981.[31,32] Although utilization of pneumococcal vaccination has improved over the years,[8] use was low in 1989 when participants were enrolled in the CHS. Octogenarians are survivors, and the survival bias is likely to be more

pronounced among those with prior pneumococcal vaccination. However, despite accumulation of higher proportion of susceptible patients, we observed a lower risk of incident HF and cardiovascular events among these patients. It is possible that some of the octogenarians in the unvaccinated group were vaccinated during follow-up or that recollection of vaccination was inaccurate resulting in incorrect classification. However, this would be expected to result in regression dilution and underestimation of the true association.[33] Finally, because findings of our study are hypothesis-generating and do not provide mechanistic insights, they need to be interpreted with caution.

Conclusions

Among community-dwelling octogenarians, lack of pneumococcal vaccination was associated with higher risk for incident HF and CV mortality, with a trend toward higher risk for hospitalization due to pneumonia. However, none of these associations were observed among those 65–79 years of age. If these hypothesis-generating findings can be replicated in other octogenarian populations, it may provide a tool to lower the risk of HF among octogenarians, the fastest growing segment of the population in developing nations who also has the highest risk of HF.

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Conflict of Interest

None declared.

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