

Short Report

Risk of Alzheimer's disease incidence attributable to vascular disease in the population

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Abstract

Background: Although Alzheimer's disease (AD) is a neurodegenerative disorder, there is growing interest in the influence of vascular factors on its incidence.

Methods: In a population-based longitudinal epidemiological study, we fit Cox proportional hazard models to examine the risk of incident dementia and AD associated with self-reported vascular disease. The population-attributable risk percent (percent of the incidence of dementia and AD in the population that would be eliminated if vascular disease was eliminated) was calculated using the adjusted hazard ratios (HR).

Results: Of 822 eligible participants, 94 individuals developed incident dementia, with 79 having AD (probable/possible AD) during the follow-up period of on average 8 years. Stroke/transient ischemic attack history was associated with incident dementia (HR = 2.6) as well as AD (HR = 2.4) among non-apolipoprotein E ε4 carriers.

Conclusions: At the community level, the risk of dementia could be potentially reduced by 10.8% by eliminating overt cerebrovascular disease, and the risk of AD by 9.1% for non-apolipoprotein E ε4 carriers.

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Keywords:

Population-Attributable Risk % (PAR%); Epidemiology; Vascular disease; AD; APOEε4

1. Introduction

Although Alzheimer's disease (AD) is a neurodegenerative disorder, vascular factors may influence its incidence and clinical manifestations [1–5]. Public health practice can benefit from knowing how much of the risk of AD can be attributed to vascular factors, at the population level. The population-attributable risk % (PAR%) [6] was examined, the percent of the incidence of dementia and AD in the population that would be eliminated if overt vascular disease was eliminated, using data from a longitudinal population-based epidemiological study.

2. Methods

The Monongahela Valley Independent Elders Survey (MoVIES) project was conducted between 1987 and 2002 in southwestern Pennsylvania. The original MoVIES cohort of 1681 participants aged ≥65 years comprised an age-stratified random sample of 1422 older adults drawn from voter registration lists and 259 volunteers, who responded to the present study advertisement and met the same inclusion criteria [7,8]. The study was approved by the University of Pittsburgh IRB. Assessments were repeated in approximately 18-month data-collection waves for >12 years. Average attrition not due to mortality was 2.8% between consecutive waves. When data regarding specific health conditions were first collected, wave 3 (1991–1992) is the study baseline for these analyses. Of 1056 participants assessed at wave 3, 110 prevalent cases of dementia with

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onset before their wave 3 assessment were excluded. The current analysis is further restricted to 822 subjects (78% of 1056) with apolipoprotein (*APOE*) genotyping data [9]. These 822 participants were significantly younger (mean [standard deviation]: 71.6 [4.7] vs 75.1 [6.4], $P < .001$, Wilcoxon rank sum test), more likely to be female (64.4% vs 51.5%, $P < .001$, χ^2 test), and had a higher proportion with high school or higher educational attainment at the study enrollment (63.4% vs 50.2%, $P < .001$, χ^2 test), than those not included in this analysis.

2.1. Diagnosis of dementia

At each wave, participants with operationally defined cognitive impairment or decline, and a randomly selected comparison group of individuals with normal cognitive scores, were selected to undergo a clinical assessment for dementia [8,10]. An expert consensus diagnosis was made of (1) dementia [10,11], (2) approximate date of onset based on all available information, (3) stage of dementia based on Clinical Dementia Rating [12], and (4) clinical diagnosis of probable and possible AD [13], both included in the AD definition in this study.

2.2. Defining vascular disease

Following standard epidemiological practice, the presence of various medical conditions was ascertained by self-report, asking participants whether a doctor or nurse had ever told them that they had a given condition. For the present analyses, we included reports of overt cerebrovascular disease (CVD) as manifested by stroke or TIA, heart disease (myocardial infarction, angina pectoris, other heart disease including heart failure and rheumatic heart disease), hypertension, diabetes mellitus, hypercholesterolemia, or taking cholesterol-lowering medications.

2.3. Statistical analysis

Three subgroups of the cohort were characterized: (1) incident AD (probable and possible), (2) incident non-AD dementia, and (3) those who remained free from dementia diagnosis over follow-up, including the deceased. Those developing dementia and those remaining dementia-free were compared on demographic characteristics and vascular factors using χ^2 statistics or Wilcoxon rank sum test.

The hazard ratios (HR) of vascular factors on the incidence dementia and AD were examined using Cox proportional hazard models with time to onset as the outcome, and death being treated as a competing risk in the former model (event = dementia), and death and incidence of non-AD dementia being treated as competing risks in the latter model (event = AD). Age at wave 3, gender, education, and recruitment status (volunteer vs random) were controlled. PAR% was then calculated on the basis of the relative risk (RR, using the adjusted HR from the Cox model) and prevalence of vascular factors in this cohort (P_{exp}) using

the formula $([P_{\text{exp}} \{RR-1\}]/[P_{\text{exp}} \{RR-1\} + 1]) \times 100$ [6]. Proportionality assumptions were examined through visual inspection of log-log survival curves, and analytical assessments [14] by using the Schoenfeld residuals and Kolmogorov-type supremum test. If the assumption was deemed violated using any of the approaches, we included interaction terms of time \times covariate in the model. Data analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC) and STATA version 11 (Stata Corp., College Station, TX).

3. Results

Of 822 subjects, 94 individuals developed dementia (79 probable or possible AD, 15 non-AD dementia) with Clinical Dementia Rating ≥ 1 . Mean (standard deviation) duration of follow-up was 8.0 (2.1) years from wave 3 assessment to the event, death, drop-out, or being censored at December 31, 2001, whichever came first. Comparing baseline (wave 3) characteristics, those who developed dementia were more likely to be older, less likely to have high school or higher educational attainment, and more likely to be *APOE* $\epsilon 4$ carriers and report CVD history, than those who remained dementia-free (Table 1). Results of the Cox proportional hazard models (Table 2) are shown for the sample as a whole and by *APOE* $\epsilon 4$ status. As the proportionality assumptions for gender and history of high cholesterol were deemed violated by statistical assessments when the outcome event was overall dementia, their interactions with time were included in the model. As the main results did not change, we report the results without these interactions in the table.

3.1. Overall dementia

Among vascular disease factors, only CVD was a significant predictor of dementia among the whole sample (HR = 2.11, 95% confidence interval [CI]: 1.18–3.77, $P = .01$) and *APOE* $\epsilon 4$ non-carriers (HR = 2.64, 95% CI: 1.27–5.51, $P = .01$) but not *APOE* $\epsilon 4$ carriers. On the basis of these HRs and $P_{\text{exp}} = 0.083$ and $P_{\text{exp}} = 0.074$, the prevalence of lifetime CVD among the whole sample and *APOE* $\epsilon 4$ non-carriers, the PAR% for CVD was 8.4% among the whole sample and 10.8% among *APOE* $\epsilon 4$ non-carriers. That is, at least 8.4% of dementia incidence could potentially be removed by eliminating overt stroke and transient ischemic attack (TIA).

3.2. Probable and possible AD

CVD was also a predictor of incident AD among *APOE* $\epsilon 4$ non-carriers (HR = 2.35, 95% CI: 1.03–5.34, $P = .04$). On the basis of the HR, 9.1% of AD incidence could potentially be removed by eliminating overt stroke and TIA among *APOE* $\epsilon 4$ non-carriers.

Among *APOE* $\epsilon 4$ carriers, vascular factors were associated with neither subsequent incident dementia nor AD.

Table 1
Cohort characteristics at baseline

Baseline (wave 3) characteristics	Those who developed possible or probable AD during follow-up (1) n = 79	Those who developed non-AD dementia during follow-up (2) n = 15	Those who remained free from dementia during follow-up (3) n = 728 [†]	Differences between those who developed dementia and who remained dementia-free (1 + 2) vs (3) P value [‡]
Age (mean) (SD) at wave 3	79.1 (5.4)	77.5 (4.1)	75.4 (4.5)	<.001 ^{§**}
Women (%)	70.9	66.7	63.6	.21
High school or higher education (%)	53.2	53.3	64.7	.02*
Recruitment status (volunteer %)	16.5	6.7	23.5	.06
<i>APOE</i> ϵ 4 carrier (%)	27.9	40.0	19.8	.02*
Mean duration (years) of follow-up (from wave 3 to an event or being censored)	4.6 (2.4)	6.2 (1.9)	8.4 (1.7)	<.001 ^{§**}
History of vascular factors				
Heart disease (%)	30.4	40.0	30.6	.79
Stroke/TIA (%)	12.7	26.7	7.4	.01*
Diabetes mellitus (%)	12.7	6.7	8.8	.36
Hypertension (%)	50.6	33.3	45.3	.64
High cholesterol (%)	27.9	33.3	31.7	.55

*Significant at $P < .05$.

[†]Including those censored by death (n = 195).

[‡]Chi-square test unless noted otherwise.

[§]Wilcoxon Rank Sum nonparametric test.

**Significant at $P < .01$.

However, the number of *APOE* ϵ 4 carriers in our sample is relatively small. Assuming the true HR of 2.0 and the sample size of 172 with the similar censoring schedule and follow-up duration observed in this study, we had only 25% power to detect this HR ($\alpha = 0.05$, two-tailed) for the dementia outcome.

4. Discussion

Recent community-based autopsy studies indicate that pure AD neuropathology is relatively rare, and a mixed vascular-degenerative picture is common, among individuals with dementia [15,16]. CVD can not only lead to vascular dementia but also contribute to dementia of AD; previous studies and potential mechanisms have been discussed at length elsewhere [1–5]. It was found that CVD, as evidenced solely by the self report of stroke or TIA of nondemented participants, was a significant predictor of subsequent incident overall dementia as well as AD. Although some studies did not find this association (e.g., [17]), the results of present study are consistent with those of the Kame Project [18] in which self-reported TIA was associated with incidence AD among *APOE* ϵ 4 non-carriers. Similarly, the Washington Heights-Inwood Columbia Ageing Project (WHICAP) [19] found increased risk of incident AD among those with a clinical history of stroke. In the present study, the corresponding PAR% suggests that about 8.4% of dementia incidence could be eliminated in the population as

a whole by preventing stroke and TIA. Among *APOE* ϵ 4 non-carriers, the effect is even larger: 10.8% of dementia incidence and 9.1% of AD incidence could be eliminated. Although a potential limitation of the present study is that cerebrovascular history was obtained by self-report, previous work [20] suggests such reports are accurate. It is noteworthy that the self-reported presence or absence of history of CVD was established before the onset of dementia. Self-report of stroke and TIA likely underestimates the presence of CVD; if this under-reporting occurs to a similar extent among all those without dementia at the time of reporting (whether or not they subsequently develop dementia), our PAR% figures might also be underestimates.

We lack neuroimaging data to examine whether the PAR would be higher if unreported CVD was included. An obvious question is whether the diagnosis of AD itself was valid in the presence of CVD and specifically whether distinctions between AD and vascular dementia can be made without neuroimaging. In a largely rural population cohort study, in which assessments were carried out in participants' homes, it was not practical to require brain scans for diagnosis. Rather, the diagnosis was made on the basis of history and examination, paying attention to the course, temporal sequence, and clinical manifestations of the dementia. The absence of statistically significant effects of vascular factors among *APOE* ϵ 4 carriers may have been because of low power. Thus, caution should be exercised in inferring that preventing vascular diseases will not

Table 2
Risk of incident dementia and AD associated with history of vascular disease: results of Cox proportional hazard model

	Overall (n = 822) HR (95% CI)	Among those without <i>APOE</i> ε4 (n = 650) HR (95% CI)	Among those with <i>APOE</i> ε4 (n = 172) HR (95% CI)
Outcome is dementia (any subtypes) with death being treated as a competing risk			
History of vascular disorders [†]			
Heart disease	0.99 (0.63–1.54)	0.84 (0.48–1.45)	1.28 (0.56–2.93)
Cerebrovascular disease (stroke/TIA)	2.11* (1.18–3.77)	2.64** (1.27–5.51)	1.43 (0.54–3.84)
Diabetes mellitus	1.47 (0.78–2.78)	1.83 (0.89–3.76)	1.23 (0.27–5.56)
Hypertension	1.03 (0.68–1.56)	1.17 (0.71–1.91)	0.75 (0.34–1.65)
High cholesterol	1.09 (0.68–1.74)	1.31 (0.75–2.30)	0.75 (0.30–1.88)
Outcome is AD (probable or possible AD) with death/other type of dementia being treated as competing risks			
History of vascular disorders [†]			
Heart disease	0.92 (0.57–1.50)	0.76 (0.41–1.38)	1.21 (0.47–3.08)
Cerebrovascular disease (stroke/TIA)	1.73 (0.88–3.39)	2.35* (1.03–5.34)	1.00 (0.29– 3.45)
Diabetes mellitus	1.58 (0.81–3.10)	1.84 (0.85–3.96)	1.65 (0.35–7.68)
Hypertension	1.17 (0.75–1.84)	1.30 (0.77–2.12)	0.83 (0.34–2.02)
High cholesterol	1.04 (0.62–1.75)	1.26 (0.67–2.31)	0.67 (0.23–1.95)

**P* < .05.

[†]Controlling for age, gender, education, recruitment status (random/volunteer).

***P* < .01.

reduce incidence of AD among *APOE* ε4 carriers; rather, the analysis should be replicated in samples with larger numbers of *APOE*ε4 carriers, and including neuroimaging for detection of CVD.

Unlike neurodegenerative disease, CVD is potentially preventable with current knowledge. Reducing stroke risk in the population have the added benefit of reducing dementia and AD.

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