Hypertension and Hypercholesterolemia Modify Dementia Risk in Relation to *APOE* ε4 Status

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Abstract

Background: There is significant interest in understanding the role of modifiable vascular risk factors contributing to dementia risk across age groups.

Objective: Risk of dementia onset was assessed in relation to vascular risk factors of hypertension and hypercholesterolemia among cognitively normal *APOE* ε4 carriers and non-carriers.

Methods: In a sample of prospectively characterized longitudinal cohort from the National Alzheimer's Coordinating Center database, 9,349 participants met criteria for normal cognition at baseline, had a CDR-Global (CDR-G) score of zero, and had concomitant data on *APOE* ε4 status and medical co-morbidities including histories of hypertension and hypercholesterolemia. Multivariable Cox proportional hazards models adjusted for well-known potential confounders were used to compare dementia onset among *APOE* ε4 carriers and non-carriers by young (65 years) and old (> 65 year) age groups.

Results: 519 participants converted to dementia within an average follow up of 5.97 years. Among older *APOE* ε4 carriers, hypercholesterolemia was related to lower risk of dementia (HR (95% CI), 0.68 (0.49–0.94), *p* = 0.02). Among older *APOE* ε4 non-carriers, hypertension was related to higher risk of dementia (HR (95% CI), 1.44 (1.13–1.82), *p* = 0.003). These results were corroborated among a subset with autopsy data characterizing underlying neuropathology. Among younger participants, vascular risk factors did not impact dementia risk, likely from a lower frequency of vascular and Alzheimer's as etiologies of dementia among this cohort.

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Conclusion: A history of hypercholesterolemia related to a lower risk of dementia among older *APOE ε*4 carriers, while hypertension related to a higher risk of dementia among older *APOE ε*4 non-carriers.

Keywords

*APOE ε*4; dementia; dementia risk; depression; hypercholesterolemia; hypertension; longitudinal cohort study; mixed dementia; neuropathology; normal cognition cohort

INTRODUCTION

Given the lack of therapies to cure dementing illnesses, it is crucial to identify and treat modifiable risk factors when present to prevent or decrease the odds of dementia onset. Many studies have evaluated environmental, lifestyle, and clinical factors on dementia risk [1–3]. With prevention of dementia being a major focus, clinical trials targeting cognitively unimpaired individuals at risk for Alzheimer's disease (AD) using Apolipoprotein *ε*4 (*APOE ε*4) as a surrogate are ongoing [4, 5].

*APOE ε*4 carrier status is associated outright with worse cognitive abilities [6] in addition to its reported impact on cardiovascular disease, stroke, and late life depression [7–10]. Among *APOE ε*4 carriers, physical inactivity, smoking and alcohol use, depression, and sleep disturbances increase dementia risk by age group [11, 12]. There is also significant interest in understanding the role of vascular disease risk factors contributing to dementia risk given the prevalence of mixed dementia among the older population [13].

Hypertension in midlife and the development of a cognitive decline years later in life is well supported, while late life randomized clinical trials targeting it have shown inconsistent results [14]. The combination of hypertension and hypercholesterolemia has also been reported to increase risk of AD [15] and vascular dementia in later life [16], but other studies report no association between plasma cholesterol and AD dementia [17, 18]. Hypercholesterolemia has been reported as a high-risk factor in midlife measurements [15, 19–23] and strikingly as low risk in late life measurements impacting dementia onset [23–25], but the contribution from *APOE ε*4 genotype in these findings is still debated. Hypertension and type 2 diabetes taken together are associated with an increased risk of AD and cognitive decline among *APOE ε*4 carriers [26–29].

In evaluating this slew of results, it is often difficult to parse which of these reported effects of vascular risk factors with regards to *APOE ε*4 carrier status are specific to a) all-cause dementia versus specific dementia etiologies like AD or mixed pathology; and b) how these results are impacted by variation in the frequency of dementia etiologies among young versus older age individuals [30].

We therefore undertook the current study in the National Alzheimer's Coordinating Center (NACC) dataset that includes a highly ascertained cohort across multiple sites across the United States with consistent cognitive characterization, including those with normal cognition at baseline, some of whom developed dementia during their longitudinal follow. We had two initial hypotheses: 1) Among older (> 65 years), who often have mixed

dementia pathologies, a history of hypertension or hypercholesterolemia would be associated with an increased risk of all-cause dementia among *APOE* ε4 carriers compared to *APOE* ε4 non-carriers; 2) The key results of these risk factors on all-cause dementia onset would be corroborated among the subset of participants with a clinical diagnosis of AD dementia and underlying mixed dementia pathology.

MATERIALS AND METHODS

Participants and study design

This is a retrospective cohort study using the NACC dataset. The complete dataset includes participant information collected from 39 past and present Alzheimer's Disease Centers (ADC) funded by the National Institute on Aging. Data from the uniform data set (UDS) maintained by NACC between September 2005 and September 2018 was used for the present analysis. All contributing ADCs are required to obtain informed consent from their participants and maintain their own separate IRB review and approval from their institution prior to submitting data to NACC. Details on approximately annual data collection and data curating are well documented [31]. In brief, NACC data are collected by trained clinicians and clinic personnel from participants and their co-participants (usually a close friend or family member). The UDS is collected using a standardized evaluation of participants. All of the ADC personnel use the same standard forms and coding guidebooks that provide guidance on filling out the forms. The UDS is longitudinal, and its protocol requires approximately annual follow-up for as long as the participant is able to be involved. Late-stage participants forced to drop out due to health may continue to be followed strictly for autopsy purposes. Determinations of cognitive status in NACC are based on a clinical consensus after review of all available information at each center. In addition, there is evidence supporting good agreement on measures from the NACC neuropathology form across centers used in this study [32].

Clinical and pathological assessment

All participants included had completed CDR® Dementia Staging Instrument score and had a Clinical Dementia Rating-Global (CDR-G) scale of zero at initial visit. The CDR-G scale assesses the participant's current cognitive and functional status. The CDR-G ratings are calculated using a complex algorithm and range from 0 (no dementia) to 3 (severe dementia) [33]. To enable consistent evaluations for the purpose of this analysis, normal functional status was defined as CDR-G = 0 and dementia was defined as CDR-G ≥ 1.

Rationale for participant inclusion/exclusion criteria was to determine the likelihood of onset of dementia (transition to CDR-G ≥ 1) across the groups of interest. All participants included in this analysis had known *APOE* ε4 status and complete data from their medical comorbidities profile of interest. Young and old participants groups were separated for analysis based on 65 years being the common cutoff used for young onset dementia [34].

Data on hypercholesterolemia, hypertension, thyroid disease, and vitamin B12 deficiency were collated from the medical history of the participants at initial visit in the NACC database. There was no secondary validation of the medical diagnosis with a supporting

biomarker, including data on LDL or total cholesterol levels and a limited number of subjects in NACC had data on statin use and therefore these data were not used for further analysis given likely biases in the data.

For secondary analyses, primary etiological diagnosis as determined by clinician at last visit was collated for each participant that underwent transition to dementia (CDR-G). Clinicians are asked to mark only one condition as primary to the observed cognitive impairment which is documented in UDS Form D1. A subset of participants included in the analysis had neuropathology of AD (Braak stages III-VI and moderate or frequent neuritic plaques), Lewy body pathology (Brainstem-predominant, Limbic or amygdala-predominant, Neocortical, or have Lewy bodies present but region unspecified), vascular pathology (ischemic, hemorrhagic, or other vascular pathology), had any two of the above three pathologies documented concomitantly (mixed dementia), or frontotemporal lobar degeneration pathologies.

Statistical analysis

9,349 participants were included in the analysis and of them 519 (5.55%) converted to dementia. Flow chart for participant selection, limiting participants to those without missing data of interest is noted in Fig. 1. Sex (male, female), active depression in the past two years, hypertension, hypercholesterolemia, thyroid disease, and vitamin B12 deficiency (present versus absent) were included in the models as dichotomous variables. Age, education, and smoker years (one point per year) were included in the models as continuous variables. Shapiro-Wilks test was conducted for continuous variables to assess normality. A t-test was applied to compare normally distributed continuous variables, Wilcoxon rank sum test was applied to compare non-normally distributed continuous variables, and Pearson's Chi-square test was applied to compare categorical variables. Normally distributed measures were summarized as means (standard deviations), non-normally distributed continuous measures were described using median and inter quartile range, and categorical factors were presented as frequencies (percentages).

Our primary goal was to evaluate how vascular risk factors predicted risk of dementia onset within older *APOE* ε4 carrier groups compared to older non-carriers as *APOE* ε4 peak dementia risk is in the over 65 years age group [4]. As we expected to identify different risk factors across these subgroups, a stratified approach was chosen. Compared to the alternative higher order interaction approach, a stratified approach was expected to deliver more parsimonious models for clearer interpretation. Multivariable Cox proportional hazard regression was employed as our study's goal was to identify risk factors instead of making predictions on clinical outcomes [35]. To assess association between time to develop dementia (with event of interest being onset of dementia defined as Clinical Dementia Rating Global scale CDR-G ≥ 1) and potential risk factors, among *APOE* ε4 carriers and non-carriers separately for age ≤ 65 and age > 65 separately. There were 310 patients (3.3%) who died the same year or one year after their last follow up. This low death rate suggested death was not a competing risk in the analysis arms. Multicollinearity was assessed for all variables for their impact on final results.

There were over 2500 participants per *APOE ε*4 carrier group or the age categories defined. Secondary comparisons stratifying by both these factors yielded sample sizes of at least 900. With this smaller sample size and the dementia conversion rate of 5% at 5 years seen in this cohort, there was 80% power to detect hazard ratios of at least 1.6 for risk factors for stratification by age or *APOE ε*4 carrier status, and hazard ratios of more than 2.0 for risk factors with stratification for both factors. Calculations assume a prevalence of at least 40% among the risk factors, as was observed for both hypertension and hypercholesterolemia.

In a follow up analysis to confirm the main group results and to evaluate whether their significance is consistent among those with specific clinical diagnosis of AD dementia and neuropathological corroboration of mixed dementia (AD, vascular, and/or Lewy body pathology), Kaplan-Meier survival curves were compared for each of these diagnoses on hypertension and hypercholesterolemia by using the log-rank test and a Schoenfeld residual method was used to assess proportionality of hazards and *p* values were larger than 0.05. Given the reduced sample sizes within these subgroups, multivariable models were not fit. All tests were two-tailed and performed at a significance level of 0.05. Given the *a priori* hypotheses on hypertension and hypercholesterolemia alone, we considered these results without false discovery rate (FDR) correction [36]. FDR corrections across models for each of the other variables are provided for interpretation. R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Data availability

The data used in the study are publicly accessible after a formal request to NACC.

RESULTS

The demographics of participants in the cohort are described in Table 1 and Supplementary Table 1. The average age at initial visit who converted to dementia on follow up was 77.6 years (Std dev 10.1), with a time to dementia conversion from initial evaluation at 71.6 months (Std dev 32.1). In the overall cohort, *APOE ε*4 carriers had a significant increase in risk (1.56 (95% CI: 1.28–1.89, $p < 0.001$) for dementia as expected.

> 65 years, older age group

Among all older participants, the median age at initial visit was 75.0 [IQR 70.0; 80.0], 34.5% of participants were *APOE ε*4 carriers. *APOE ε*4 allele significantly increased the risk of dementia onset (HR 1.5 (95% CI (1.2–1.8), $p < 0.001$), along with recent depression history, thyroid disease, and hypertension, while higher education and hypercholesterolemia were related to lower risk of all-cause dementia onset (Table 2A).

Among older *APOE ε*4 carriers, hypercholesterolemia decreased risk of dementia onset during follow up (HR 0.68 (95% CI (0.49–0.94), $p = 0.02$) (Fig. 2A), while active depression in the last two years increased dementia risk (HR 1.56 (95% CI (1.05–2.31), $p = 0.028$). Among older *APOE ε*4 non-carriers, higher education years mitigated dementia onset risk (HR 0.92 (95% CI (0.889–0.96), $p < 0.001$), while hypertension increased all-cause dementia risk (HR 1.435 (95% CI (1.134, 1.816), $p = 0.0026$) (Fig. 2b, Table 3).

65 years, younger age group

Within the younger age group, the median age at initial visit at 61.0 years [IQR 56.0; 64.0], 32.7% of participants were *APOE ε*4 carriers among them. *APOE ε*4 did not significantly increase risk of dementia onset (HR 0.8 (95% CI (0.4–1.5), $p = 0.452$). Additionally, none of the clinical factors evaluated impacted all-cause dementia onset except higher educational attainment decreasing its risk (Table 2B).

Within both young *APOE ε*4 carriers and non-carrier subgroups, vascular risk factors did not differentially impact the risk in progressing from normal cognition to all-cause dementia. There was a significant effect of higher education years in mitigating dementia risk among young *APOE ε*4 carriers (HR 0.84 (95% CI (0.72–0.97), $p = 0.015$) and male sex in increasing all-cause dementia risk among young *APOE ε*4 non-carriers (HR 2.28 (95% CI (1.13–4.6), $p = 0.022$) (Table 4).

Analysis of specific underlying etiologies of dementia

Clinical etiology for the participants who converted to dementia during follow up is provided by age group in Supplementary Table 2. The younger age group compared to the older age group had a lower frequency of a primary clinical diagnosis of AD dementia (27.3% versus 70.6%) and vascular dementia (3% versus 13.1%) and a higher frequency of frontotemporal dementia (54.5% versus 5.6%) ($\chi^2 = 41.3$, $p < 0.00001$). Among the subgroup in whom neuropathology data was available, the results are presented in Supplementary Table 3 noting the high prevalence of vascular and AD pathology among the older age group.

In the supplementary analyses, when participants were categorized according to subgroups with clinical and neuropathology data of specific dementia etiologies, similar patterns for the effect of hypercholesterolemia and hypertension were noted between the 'all-cause dementia' analysis and in the supplementary analyses for the older age group. Dementia-free survival time was higher in older *APOE ε*4 carrier participants with hypercholesterolemia with a clinical AD diagnosis (log-rank test: $p = 0.02$) and lower among those with hypertension with a clinical AD diagnosis (log-rank test: $p = 0.02$) (Supplementary Figure 1A, B).

In the neuropathology defined sub analyses, dementia-free survival time was higher in older *APOE ε*4 carrier participants with hypercholesterolemia and mixed dementia (log-rank test: $p = 0.03$) and lower among those with hypertension and mixed dementia (log-rank test: $p = 0.02$) (Supplementary Figure 2A, B).

DISCUSSION

Our results from this large well characterized longitudinal cohort clearly shows among older *APOE ε*4 carriers, a medical history of hypercholesterolemia was related to a lower risk of all-cause dementia. Among older *APOE ε*4 non-carriers, a medical history of hypertension increased risk of converting to dementia when compared to *APOE ε*4 carriers. The results were statistically significant even after adjustment for common clinical comorbidities. These results were also consistent within the older age mixed dementia subgroup defined by

neuropathology burden of AD, vascular, and Lewy body pathologies. Among younger *APOE ε*4 carriers compared to non-carriers, hypertension and hypercholesterolemia did not significantly impact the risk of progressing from normal cognition to all-cause dementia.

This study noted that *APOE ε*4 increases risk of dementia in the older age group but not in the younger age group. A closer age stratification by each decade in the NACC data previously noted that *APOE ε*4 carrier status and *APOE ε*4 dose, both significantly predicted risk of progression to AD in all age groups of cognitively normal individuals greater than 60 years but not in those less than or equal to 60 years group [37]. Given the interquartile age range of the young onset dementias in the current study (56–64 years), the findings likely reflect the non-linear effects of *APOE ε*4 carrier status on dementia risk at younger ages.

Even as the role of hypercholesterolemia on atherogenesis is well appreciated, recent evidence suggests that rather than high-density lipoproteins (HDL) alone, sub fractions of HDL are differentially associated with coronary heart disease [38] and dementia [39]. The role for hypercholesterolemia is therefore not surprisingly more nuanced as a dementia risk with the presence of *APOE ε*4 genotype. Similar results to ours on the risk lowering effect of hypercholesterolemia on risk of all-cause dementia has been previously reported [23–25] and in relation to *APOE ε*4 status in population studies [40, 41]. In a clinical trial over 30 weeks, high-cholesterol-*APOE ε*4 group was found to have slower decline than a high cholesterol non-*APOE ε*4 allele group [42]. The biological reasons for these findings are still a subject of active investigation.

Hypertension during midlife has been reported to be a risk factor for cognitive decline and dementia in many reports, while optimal blood pressure ranges for older adults may depend on earlier life hypertension history [4, 43–45]. There have been limited number of studies that have evaluated the direct effect of hypertension between *APOE ε*4 carriers and non-carriers when controlling for other confounders [46]. In the current study, with a larger number of subjects in a longitudinal aging cohort, the risk of dementia onset from hypertension beyond other co-morbidities on dementia onset appears to be significant among *APOE ε*4 non-carriers.

The differential effects of midlife and late life effects of cardiovascular risk factors on all-cause dementia risk though well-known [10–25], the current results evaluate more closely the role for these factors taking into account age, *APOE ε*4 carrier status, and common clinical comorbidities likely explaining variations in its relative effect of these comorbidities. In addition, all participants in this analysis started from a normal functional baseline that was formally evaluated unlike some population reports. Our findings on the impact of vascular risk in relation to *APOE ε*4 status among older subjects has important implications. Identifying individuals at greatest genetic risk for AD and understanding the differential impact of modifiable risk factors may help with providing appropriate individual clinical decision making and risk stratifying patients in a clinical trial of *APOE ε*4 carriers. In addition, these results prompt us to determine the underlying biology behind the role of hypercholesterolemia among older *APOE ε*4 carriers in decreasing their dementia risk.

In prior studies, *APOE ε*4 status has been reported to modify the association between depressive symptoms and dementia [47, 48]. The current report also notes older *APOE ε*4 carriers with depression have heighted risk of dementia onset. Education has been reported to be a protective influence on the risk of developing dementia even when adjusting for the number of *APOE ε*4 alleles [49]. In this study, the mitigating effect of education on dementia onset was seen among younger *APOE ε*4 non-carriers and older *APOE ε*4 carriers, suggesting its effect is likely modulated by the relative strength of other comorbidities and factors including age and *APOE ε*4 status.

A recent meta-analysis did not report a difference between sexes on dementia risk between 55 and 85 years and noted women have an increased risk at younger ages [50]. It is likely that multiple environmental and clinical factors contribute to these differences noted across studies [51]. Female *APOE ε*4 carriers have shown more pronounced AD-like changes in neuroimaging and neuropathological measures when compared to their *APOE ε*3 homozygous peers [52–54]. The higher proportion of non-AD dementias in the young age group in this study could potentially account for male sex to be associated with higher all-cause dementia risk among young *APOE ε*4 non-carriers. In addition, the current analysis takes into account other confounders that also have sex differences with age (cardiovascular risk, coronary artery disease, type II diabetes, depression) [55–57] that were often not considered in some of the biomarker focused studies.

The impact of vascular risk factors (hypertension, hypercholesterolemia, diabetes) to moderate *APOE*-related differences in cognitive performance with age has been noted to differ based on the nature of characterization of the risk factors (self-report versus biomarkers) and between longitudinal versus cross-sectional studies [58–61]. These differences make generalizations across studies challenging but likely provide complementary information on the relative strength of the associations. Moreover, the actual differences in risk even though significant for hypertension and hypercholesterolemia between *APOE ε*4 carriers and non-carriers is relatively small; these could therefore have been easily missed in earlier studies with smaller subject numbers.

Vascular risk factors hypertension and diabetes have been related to lower performance in visuospatial skills/speed and verbal fluency domains [62]. Vascular co-morbidities, including hypertension and hypercholesterolemia, have been associated with greater impairments in immediate verbal memory and delayed visual memory, verbal reasoning, set shifting, and visuospatial skills [63]. There have been limited studies examining the effect of hypercholesterolemia alone on specific cognitive domains with age and *APOE ε*4 status.

Furthermore, the term 'obesity paradox' has been used to describe the effect of excess weight improving predicted survival in elderly [64] and risk of dementia [65], with increasing weight loss per decade from midlife to late life a marker for mild cognitive impairment [66]. In this light, it is possible that the presence of hypercholesterolemia among elderly is a proxy for lack of significant weight loss. It is also possible that there are biological explanations for this phenomenon; since brain ApoE4 is less lipidated and stable than are ApoE3 and ApoE2 [67, 68], increasing brain ApoE levels and lipidation has therefore been proposed as a therapeutic approach [69]. Hypercholesterolemia among *APOE*

ɛ4 carriers could then be a natural counterweight on the poorly lipidated state of ApoE4 decreasing the risk of dementia onset as noted. These intriguing possibilities need biomarker confirmation.

Limitations and strengths

Some key variables including hypertension, hypercholesterolemia, diabetes, thyroid disease, and vitamin B12 deficiency were defined by clinical diagnoses and not based on biomarkers as they were not available to corroborate the diagnoses. Use of CDR-G score of zero to define the functionally unimpaired at baseline also has its limitations as subtle cognitive changes related to early disease progression could be misattributed as normal. Despite the large size of the initial NACC cohort, sub-stratification by age can make the analysis of some subgroups small. Given the smaller number of subjects, possible recruitment biases and lower frequency of vascular and AD etiology as the primary cause of dementia among the younger age group in this cohort, the results should be interpreted with caution.

Small numbers of subjects in some subgroups also limits our analysis on follow up questions of interest to this study, especially when trying to understand the role of concomitant medication use (statins, hypertension medications) on the results given the low frequency of dementia onset within each of the subgroups. The potential limitations from missing data were addressed by limiting analyses to participants with completed data fields in the variables of interest, as no clear rationale for a rigorous imputation methods (e.g., multiple imputation) could be met. Study results would have to be therefore interpreted with caution regarding unforeseen biases from this analysis method. Participant dropout could result in survivorship bias, although it is less likely for three reasons: 1) number of participants followed remain fairly consistent over time across comparison groups (with and without hypercholesterolemia/hypertension), 2) low death rate in the analysis arms as noted earlier, and 3) additionally, survivorship bias alone is not likely to account for protective benefit seen only with hypercholesterolemia and not with hypertension or diabetes which also have a higher risk of early mortality. The study also evaluated the underlying dementia etiology to corroborate the results of all-cause dementia risks to clarify if it applies to AD and mixed dementia pathologies as well. Given the strengths and biases of the NACC cohort, it is likely the current results are generalizable to other prospective research cohorts tracking normal cognition *APOE* ɛ4 carriers and non-carriers including clinical trials.

CONCLUSIONS

APOE ɛ4 status differently impacts the relevance of clinical factors including hypercholesterolemia, hypertension, and depression on the risk of dementia onset. These results are worthy of further pursuit to clarify the nature of the protective effect of hypercholesterolemia among older *APOE* ɛ4 carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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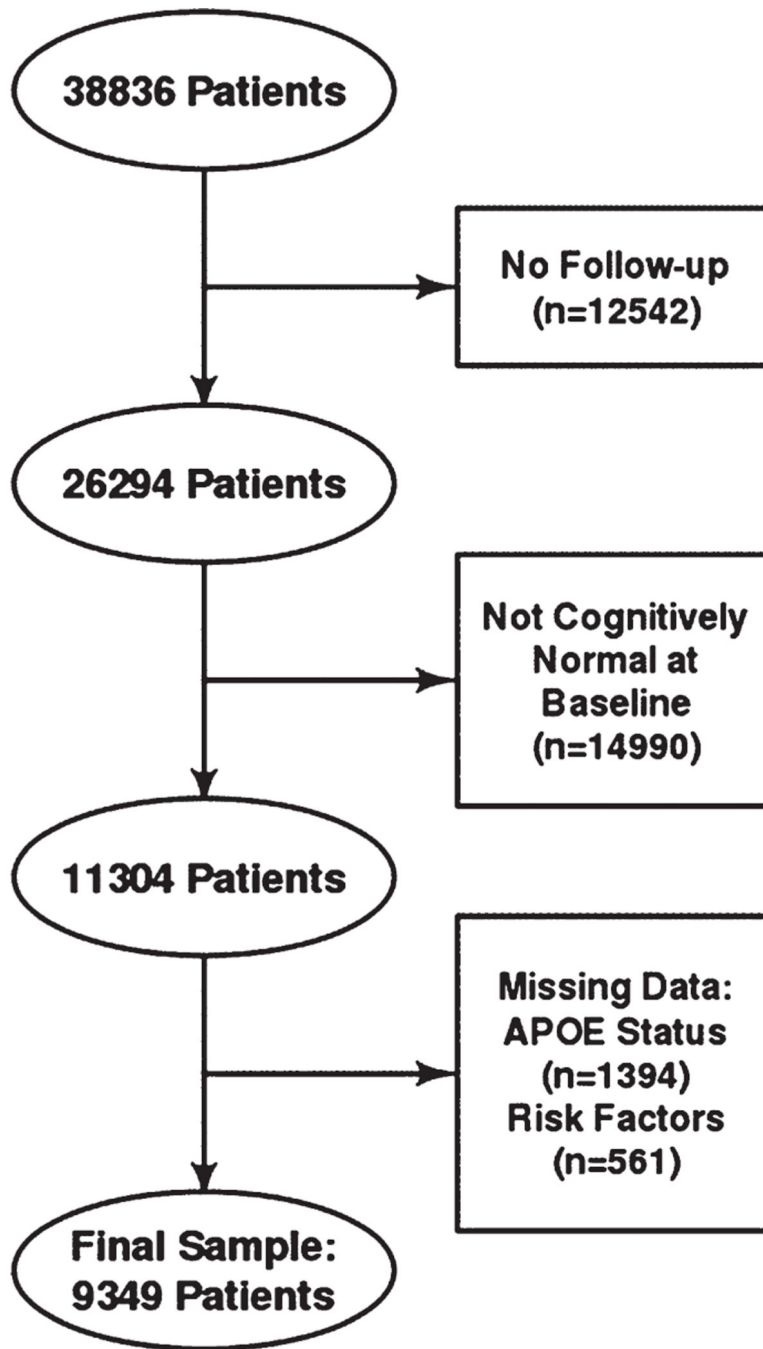
Fig. 1.
Participant selection flow chart.
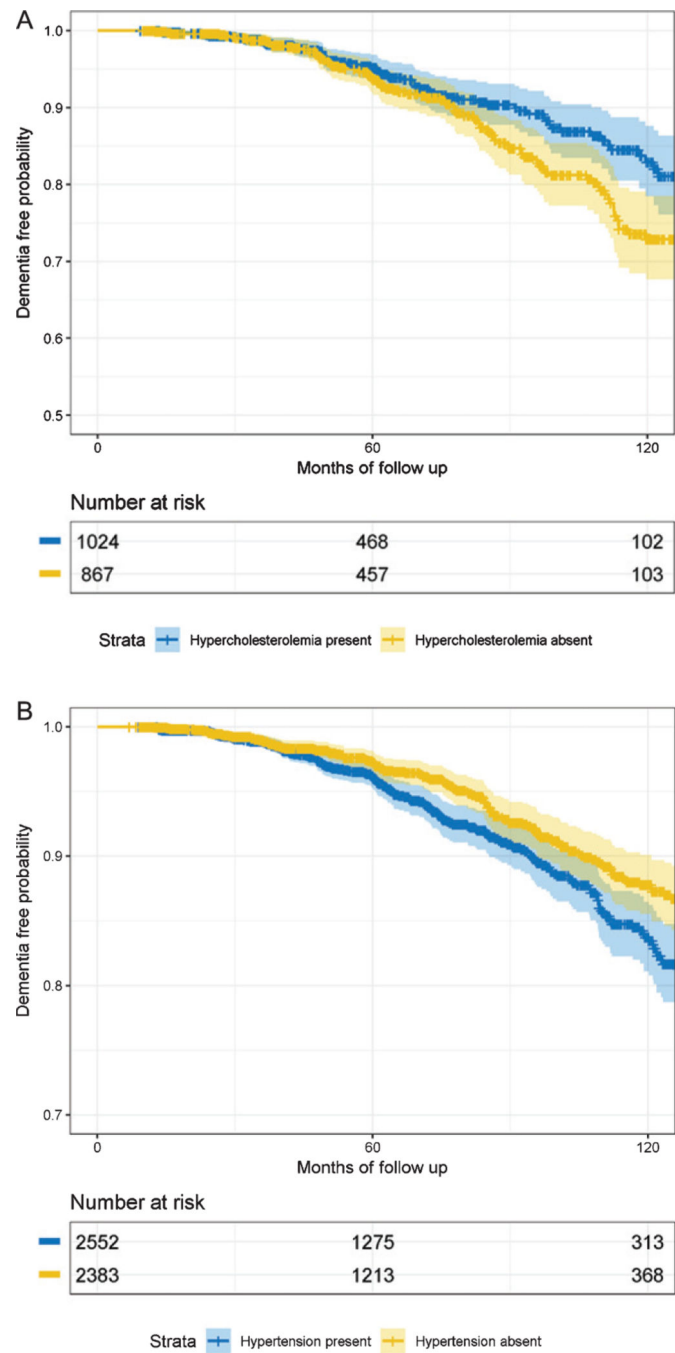
Fig. 2.
A) Kaplan Meier curves for older *APOE ε*4 carriers with hypercholesterolemia as a significant predictor for all-cause dementia. B) Kaplan Meier curves for older *APOE ε*4 non-carriers with hypertension as a significant predictor for all-cause dementia.

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Table 1

Participant demographics. Median, IQR (inter quartile range)

	APOE ε4 carriers (n = 2,806)	APOE ε4 non-carriers (n = 6,543)	p
Age at initial visit [y] Median [IQR]	69.00 [64.00;76.00]	72.00 [66.00;79.00]	< 0.001
65 y	32.61%	24.58%	
> 65 y	67.39%	75.42%	
Follow up time [y] Median [IQR]	4.81 [2.70;7.45]	4.88 [2.40;7.88]	0.86
Dementia at follow up	6.34%	5.21%	0.032
Education [y] Median [IQR]	16.00 [14.00;18.00]	16.00 [14.00;18.00]	0.49
Smoker y Median [IQR]	0 [0–15]	0 [0–18]	0.071
Female sex	65.65%	65.29%	0.76
Diabetes	9.62%	10.13%	0.473
Hypertension	43.66%	46.39%	0.016
Hypercholesterolemia	50.68%	43.31%	< 0.001
Vitamin B12 deficiency	2.28%	2.43%	0.72
Thyroid disease	15.22%	16.60%	0.10
Active depression in past 2 y	16.71%	15.97%	0.39
APOE ε4/ε4 homozygotes	9.1%	-	-

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Table 2

Multivariable Cox proportional hazard regression for young and old age groups

a: > 65 y (Old) Variables	Hazard ratio (95% CI)	p	FDR
Education, y	0.94 (0.91, 0.97)	<0.001	0.001
Smoker, y	0.99 (0.99, 1.003)	0.265	0.53
Sex - Male versus Female	1.12 (0.92, 1.37)	0.261	0.261
Diabetes - present versus absent	0.91 (0.66, 1.27)	0.586	0.846
Hypertension - present versus absent	1.35 (1.11, 1.63)	0.002	NA
Hypercholesterolemia - present versus absent	0.77 (0.63, 0.93)	0.007	NA
Vit B12 deficiency - present versus absent	1.03 (0.56, 1.87)	0.933	0.933
Thyroid disease - present versus absent	1.29 (1.03, 1.63)	0.029	0.058
Depression - present versus absent	1.40 (1.1, 1.79)	0.007	0.014
APOE e4 + ve status	1.50 (1.24, 1.82)	<0.001	0.001

b. 65 y (Young) Variables	Hazard ratio (95% CI)	p	FDR
Education, y	0.89 (0.81, 0.98)	0.015	0.015
Smoker, y	0.996 (0.972, 1.021)	0.74	0.74
Sex - Male versus Female	1.76(0.98, 3.15)	0.059	0.118
Diabetes - present versus absent	1.11 (0.37, 3.31)	0.846	0.846
Hypertension - present versus absent	0.79 (0.4, 1.59)	0.511	NA
Hypercholesterolemia - present versus absent	0.92 (0.48, 1.75)	0.8	NA
Vit B12 deficiency - present versus absent	1.35 (0.18, 10.05)	0.767	0.933
Thyroid disease - present versus absent	0.53 (0.16, 1.73)	0.292	0.292
Depression - present versus absent	1.76 (0.95, 3.26)	0.07	0.07
APOE e4 + ve status	0.79 (0.43, 1.45)	0.452	0.452

FDR, False discovery rate.

Table 3

Multivariable Cox proportional hazard regression for older (>65 y) *APOE* ε4 carriers and non-carriers

Variables	Hazard ratio (95% CI)	*p*	FDR
APOE **ε4 non-carriers**			
Education, y	0.92 (0.9, 0.96)	<0.001	0.002
Smoker, y	0.99 (0.99, 1.006)	0.77	0.828
Sex - Male versus Female	1.21 (0.95, 1.54)	0.13	0.262
Diabetes - present versus absent	1.02 (0.70, 1.50)	0.91	0.909
Hypertension - present versus absent	1.44 (1.13, 1.82)	0.003	NA
Hypercholesterolemia - present versus absent	0.82 (0.65, 1.04)	0.11	NA
Vit B12 deficiency - present versus absent	0.91 (0.426, 1.93)	0.80	0.799
Thyroid disease- present versus absent	1.31 (0.98, 1.74)	0.06	0.256
Depression- present versus absent	1.30 (0.96, 1.78)	0.09	0.125
APOE **ε4 carriers**			
Education, y	0.98 (0.93, 1.04)	0.50	0.495
Smoker, y	0.99 (0.98, 1.002)	0.10	0.404
Sex - Male versus Female	1.001 (0.71, 1.42)	0.99	0.994
Diabetes - present versus absent	0.72 (0.38, 1.36)	0.31	0.718
Hypertension - present versus absent	1.22 (0.89, 1.69)	0.22	NA
Hypercholesterolemia - present versus absent	0.68 (0.49, 0.94)	0.02	NA
Vit B12 deficiency - present versus absent	1.45 (0.53, 3.97)	0.47	0.699
Thyroid disease - present versus absent	1.32 (0.89, 1.95)	0.16	0.322
Depression - present versus absent	1.56 (1.05, 2.31)	0.03	0.112

FDR, False discovery rate.

Table 4

Multivariable Cox proportional hazard regression for younger (65 y) *APOE ε4* carriers and non-carriers

	APOE ε4 non-carriers		
Variables	**Hazard ratio (95% CI)**	***p***	**FDR**
Education, y	0.91 (0.81, 1.03)	0.14	0.191
Smoker, y	1.003 (0.98, 1.03)	0.83	0.828
Sex - Male versus Female	2.28 (1.13, 4.59)	0.02	0.088
Diabetes - present versus absent	0.74 (0.17, 3.32)	0.70	0.909
Hypertension - present versus absent	0.45 (0.18, 1.17)	0.10	NA
Hypercholesterolemia - present versus absent	1.24 (0.57, 2.69)	0.59	NA
Vit B12 deficiency - present versus absent	2.19 (0.29, 16.37)	0.45	0.699
Thyroid disease - present versus absent	0.57 (0.13, 2.49)	0.46	0.458
Depression - present versus absent	1.90 (0.91, 3.95)	0.09	0.125
	APOE ε4 carriers		
Education, y	0.84 (0.72, 0.97)	0.02	0.03
Smoker, y	0.98 (0.93, 1.04)	0.51	0.828
Sex - Male versus Female	0.99 (0.33, 2.95)	0.99	0.994
Diabetes - present versus absent	2.11 (0.43, 10.40)	0.36	0.718
Hypertension - present versus absent	2.22 (0.73, 6.71)	0.16	NA
Hypercholesterolemia - present versus absent	0.48 (0.16, 1.48)	0.20	NA
Thyroid disease - present versus absent	0.31 (0.04, 2.44)	0.26	0.351
Depression - present versus absent	1.63 (0.50, 5.27)	0.41	0.414

Vitamin B12 deficiency not included in the model as no subject was recorded to be deficient. FDR, False discovery rate.