Absolute 10-year risk of dementia by age, sex and *APOE* genotype: a population-based cohort study

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ABSTRACT

BACKGROUND: Dementia is a major cause of disability, and risk-factor reduction may have the potential to delay or prevent the disease. Our aim was to determine the absolute 10-year risk of dementia, by age, sex and apolipoprotein E (*APOE*) genotype.

METHODS: We obtained data from the Copenhagen General Population Study (from 2003 to 2014) and the Copenhagen City Heart Study (from 1991 to 1994 and 2001 to 2003). Participants underwent a questionnaire, physical examination and blood sampling at baseline. Diagnoses of dementia and cerebrovas-

cular disease were obtained from the Danish National Patient Registry up to Nov. 10, 2014.

RESULTS: Among 104 537 individuals, the absolute 10-year risk of Alzheimer disease in 3017 women and men who were carriers of the *APOE* ε44 genotype was, respectively, 7% and 6% at age 60–69 years, 16% and 12% at age 70–79 years, and 24% and 19% at age 80 years and older. Corresponding values for all dementia were 10% and 8%, 22% and 19%, and 38% and 33%, respectively. Adjusted hazard ratios (HRs) for all dementia increased by genotype, from

genotype ε22 to ε32 to ε33 to ε42 to ε43 to ε44 (*p* for trend < 0.001). Compared with ε33 carriers, ε44 carriers were more likely to develop Alzheimer disease (adjusted HR 8.74, 95% confidence interval [CI] 7.08–10.79), vascular dementia (adjusted HR 2.87, 95% CI 1.54–5.33), unspecified dementia (adjusted HR 4.68, 95% CI 3.74–5.85) and all dementia (adjusted HR 5.77, 95% CI 4.89–6.81).

INTERPRETATION: Age, sex and *APOE* genotype robustly identify high-risk groups for Alzheimer disease and all dementia. These groups can potentially be targeted for preventive interventions.

Dementia is a major cause of disability in later life, and the global prevalence is increasing, especially in low- and middle-income countries.[1,2] Reduction of risk factors for dementia may have the potential to delay or prevent one-third of dementia cases.[3] The estimation of absolute risk specific to age, sex and apolipoprotein E (*APOE*) genotype to identify high-risk individuals for targeted prevention is needed. Cerebrovascular disease is similarly a major cause of both morbidity and mortality,[1,4] and is closely associated with development of dementia.

The apolipoprotein E (apoE) protein is pivotal for peripheral and cerebral cholesterol metabolism as well as for cerebral clearance of amyloid-β in Alzheimer disease.[5–7] The ε4 allele of the *APOE* polymorphism is by far the strongest genetic risk factor implicated in common late-onset Alzheimer disease,[8] an association first recognized in 1993,[9] and since validated globally.[10]

Three human apoE isoforms, apoE2, apoE3 and apoE4, corresponding to 3 common alleles, ε2, ε3 and ε4, defined by 2 single nucleotide polymorphisms in *APOE* (rs429358/ε4, rs7412/ε2), give rise to 6 common *APOE* genotypes, ε22, ε32, ε33, ε42, ε43 and ε44. Whereas compelling evidence suggests that the *APOE* polymorphism is involved in risk of Alzheimer disease, the role for subtypes of dementia as well as for cerebrovascular disease — a major risk factor for dementia — is less clear despite repeated previous studies.[5,9,11–19] In particular, the estimation of 10-year absolute risk for dementia specific to age, sex and *APOE* genotype are lacking, information that is essential for providing targeted prevention against dementia in high-risk individuals.

We sought to determine the 10-year absolute risk of Alzheimer disease, vascular dementia and all dementia, stratified by age, sex and *APOE* genotype, as well as associations between *APOE* genotype and cerebrovascular disease.

Methods

Participants

We included individuals from 2 similar prospective studies of the Danish general population: the Copenhagen General Population Study and the Copenhagen City Heart Study.[20–23] The Copenhagen General Population Study was initiated in 2003 with the first enrolment period from 2003 to 2015, and with follow-up examinations ongoing. The Copenhagen City Heart Study was initiated in 1976–1978 with follow-up examinations in 1981–1983, 1991–1994 and 2001–2003. Data collection included a questionnaire, a physical examination, and blood sampling for biochemical and DNA analyses. Individuals were randomly selected from the national Danish Civil Registration System to reflect the adult population aged 20 years and older. There was no overlap of individuals between studies. All participants were white and of Danish descent. The studies combined included a total of 104 537 individuals, of whom 2160 developed dementia and 7520 developed cerebrovascular disease. Descriptions of the cohorts and definitions of clinical variables are detailed in Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180066/-/DC1.

Dementia and cerebrovascular endpoints

Information on diagnoses was collected from the Danish National Patient Registry, with data on all patient contacts from all clinical hospital departments in Denmark since 1977, and from the National Danish Registry of Causes of Death, with data on causes of all deaths in Denmark, as reported by hospitals and general practitioners since 1977.

We defined Alzheimer disease as the International Classification of Diseases (ICD) 8th and 10th revision codes ICD-8 290.10 and ICD-10 F00 and G30, vascular dementia as ICD-10 F01, and unspecified dementia as ICD-8 290.18 and ICD-10 F03. All dementia included Alzheimer disease, vascular dementia and unspecified dementia. Information on cerebrovascular disease (ICD-8 431–438 and ICD-10 I60-I69, G45) is described in Appendix 1.

For Cox regression models for *APOE* genotypes, follow-up began at birth or at the start of the registries (Jan. 1, 1977), whichever came last. For all other analyses, follow-up began at the time of blood sampling (2003 and onwards for the Copenhagen General Population Study, and 1991–1994 or 2001–2003 for the Copenhagen City Heart Study). Follow-up ended at occurrence of event, death, emigration or on Nov. 10, 2014 (last update of the registries), whichever came first. Median follow-up from start of the registries was 38 (range 0–38) years for both all dementia and cerebrovascular disease, with no individuals lost to follow-up.

Biochemical and genetic analyses

Biochemical and genetic analyses are described in Appendix 1. Based on prior studies and understanding of biological mechanisms, we hypothesized that associations between *APOE* genotype and risks of Alzheimer disease and all dementia would increase from ε22 to ε32 to ε33 to ε42 to ε43 to ε44. Because the ε42 genotype represents 2 hyperlipidemic alleles,[7] we hypothesized that risk for vascular endpoints — vascular dementia and cerebrovascular disease — would increase from ε22 to ε32 to ε33 to ε43 to ε42 to ε44. Finally, because the apoE2 isoform is defective in binding to the low-density lipoprotein (LDL) receptor, genotypes harbouring the ε2 allele have the highest plasma apoE levels. Hence, trends in lipoprotein and apolipoproteins are hypothesized to be associated with a decreasing trend in plasma apoE levels from ε22 to ε32 to ε42 to ε33 to ε43 to ε44. Consequently, the results are organized according to the hypothesized hierarchies of associations.

Statistical analysis

Absolute 10-year risk of Alzheimer disease and all dementia as a function of *APOE* genotype and stratified by age (in 3 age groups) and by sex was estimated by competing risk models.[24] Data were presented as estimated incidence rates (number of events per 10 years) in percent. Cumulative incidence curves and respective trends across genotypes were generated from competing risk regression models, according to the method of Fine and Gray.[24] Cumulative incidence was further evaluated by Kaplan–Meier curves and log-rank trend tests. To test whether *APOE* genotypes were associated with increased risk of dementia and cerebrovascular disease, we used Cox regression models adjusted for known biologically relevant risk factors and markers of lifestyle regardless of the sizes of their contributions. Additional details regarding the statistical analysis are described in Appendix 1.

Ethics approval

The Copenhagen General Population Study and the Copenhagen City Heart Study were approved by the Committee of Biomedical Research Ethics for Copenhagen, Denmark and relevant institutional review boards, and were conducted according to the Declaration of Helsinki, with written informed consent from participants. Separate ethics approval was not required for use of these data in this study.

Results

Baseline characteristics of the 104 537 individuals by *APOE* genotype are shown in Table 1. Levels of covariates were similar across *APOE* genotypes, except for lipid-lowering treatment, which varied significantly from 7% to 15% (*p* < 0.001). This finding was expected, as *APOE* genotype affects lipid levels.

10-year absolute risk for dementia

For Alzheimer disease, 10-year absolute risk increased by genotype, from ε32 to ε33 to ε42 to ε43 to ε44, whereas ε22 had a slightly higher 10-year absolute risk than ε32 and ε33 in both sexes across all age groups (Figure 1). Ten-year absolute risk of all dementia increased from ε22 to ε32 to ε33 to ε42 to ε43 to ε44 in both sexes across all age groups. The absolute 10-year risks for ε44 genotype for Alzheimer disease for age groups 60–69 years, 70–79 years, and 80 years or older were 7%, 16% and 24% for women, and 6%, 12% and 19% for men, respectively. Corresponding percentages for all dementia were 10%, 22% and 38% for women, and 8%, 19% and 33% for men. Percentages for vascular dementia were substantially lower, all below 3% (Figure 1).

Table 1: Characteristics of 104 537 study participants by *APOE* genotype*

Characteristic	% of participants†					
	ε22	ε32	ε33	ε42	ε43	ε44
Individuals, no. (%)	715 (0.7)	12 994 (12.4)	58 172 (55.6)	3013 (2.9)	26 626 (25.5)	3017 (2.9)
Age, yr, mean ± SEM	57.3 ± 0.5	58.0 ± 0.1	57.9 ± 0.1	57.4 ± 0.2	57.5 ± 0.1	56.6 ± 0.2
Female sex	55	55	55	55	55	57
Body mass index, mean ± SEM	26.2 ± 0.2	26.2 ± 0.0	26.1 ± 0.0	26.1 ± 0.1	26.0 ± 0.0	25.9 ± 0.1
Hypertension‡	58	59	60	59	59	58
Diabetes mellitus§	3	4	4	4	4	4
Smoking¶**	19	21	21	20	21	19
Alcohol consumption**††	17	18	17	16	17	16
Physical inactivity**‡‡	50	51	51	49	50	49
Postmenopausal**§§	62	67	68	65	67	65
Hormone replacement therapy**§§	11	11	11	11	11	11
Lipid-lowering therapy**¶¶	7	7	11	9	13	15
Education < 8 yr	11	13	13	12	12	11
Atrial fibrillation***	7	7	7	7	7	7

Note: SEM = standard error of the mean.
*Values are from the day of enrolment (2003–2014 for the Copenhagen General Population Study and 1991–1994 or 2001–2003 for the Copenhagen City Heart Study). Missing data on categorical and continuous covariates (< 0.4%) were imputed from age, sex and population using multiple imputations.
†Unless stated otherwise.
‡Hypertension was defined by the use of antihypertensive medication, systolic blood pressure of ≥ 140 mm Hg, and/or diastolic blood pressure of ≥ 90 mm Hg.
§Diabetes mellitus was defined by self-reported disease, use of insulin or oral hypoglycemic agents, and/or nonfasting plasma glucose level of > 11 mmol/L (> 198 mg/dL).
¶Smoking was defined by current smoking.
**Smoking, alcohol consumption, physical inactivity, menopausal status, hormonal replacement therapy, lipid-lowering therapy, and education were self-reported and reviewed together with an investigator on the day of attendance to clarify any uncertainties.
††Alcohol consumption was defined by > 14/21 units per week for women/men (1 unit = 12 g alcohol, equivalent to 1 glass of wine or spirit or 1 beer [33 cL = 330 mL]).
‡‡Physical inactivity was defined by ≤ 4 hours per week of light physical activity in leisure time.
§§In women only (n = 57 543). Women reported menopausal status and use of hormonal replacement therapy.
¶¶Lipid-lowering therapy primarily consisted of statins (yes/no).
***Atrial fibrillation was defined by any diagnosis of atrial fibrillation ever.

APOE genotype and risk of dementia

Cumulative incidence of Alzheimer disease, unspecified dementia and all dementia increased with increasing number of ε4 alleles from ε42 to ε43 to ε44 (*p* for trend < 0.001 for all). In contrast, cumulative incidence of vascular dementia was highest in ε44 and ε42 genotypes, and lowest for ε22 genotype and hardly increased with age (*p* for trend = 0.04) (Figure 2). Multivariable-adjusted hazard ratios (HRs) increased from ε32 to ε33 to ε42 to ε43 to ε44 for Alzheimer disease, from ε33/ε32 to ε43 to ε42 to ε44 for vascular dementia, and from ε22 to ε32 to ε33 to ε42 to ε43 to ε44 for unspecified dementia and all dementia (*p* for trends < 0.001 for all) (Figure 3). Estimates were similar for age- and sex-adjusted analyses (Appendix 1, Supplemental Table 1) after additional adjustments for lipids and lipoproteins, when entry at time of blood sampling was used, and when competing risk models were used (data not shown). Interaction terms between *APOE* genotype and sex reached significance for Alzheimer disease (*p* = 0.03) and all dementia (*p* = 0.05) (Appendix 1, Supplemental Table 2). Estimates for vascular dementia remained similar after exclusion of 45 individuals with both Alzheimer disease and vascular dementia (Appendix 1, Supplemental Figure 1).

Other covariates independently associated with an increased risk of all dementia included smoking (adjusted HR 1.68, 95% confidence interval [CI] 1.52–1.85), less than 8 years of education (adjusted HR 1.34, 95% CI 1.23–1.47), diabetes mellitus (adjusted HR 1.30, 95% CI 1.09–1.55) and physical inactivity (adjusted HR 1.16, 95% CI 1.06–1.27). In contrast, male sex (adjusted HR 0.62, 95% CI 0.40–0.96), lipid-lowering therapy (adjusted HR 0.81, 95% CI 0.71–0.93) and hypertension (adjusted HR 0.82, 95% CI 0.74–0.91) were associated with a decreased risk of all dementia (Table 2).

APOE genotype, cerebrovascular disease, and lipids, lipoproteins and apolipoproteins

Multivariable-adjusted HRs were 1.22 (95% CI 1.01–1.48) and 1.31 (95% CI 1.08–1.58) for ε42 and ε44 versus ε33 for ischemic stroke (Appendix 1, Supplemental Figure 2). Similarly, HRs were 1.19 (95% CI 1.03–1.37) and 1.29 (95% CI 1.12–1.48) for ischemic cerebrovascular disease, 1.15 (95% CI 0.78–1.71) and 1.81 (95% CI 1.29–2.53) for hemorrhagic stroke, and 1.17 (95% CI 1.03–1.34) and 1.30 (95% CI 1.15–1.48) for all cerebrovascular disease for ε42 and ε44 versus ε33 (Appendix 1, Supplemental Figure 2). Estimates were similar after adjustment for lipids and lipoproteins, when entry at time of blood sampling was used, and when competing risk models were used (data not shown).
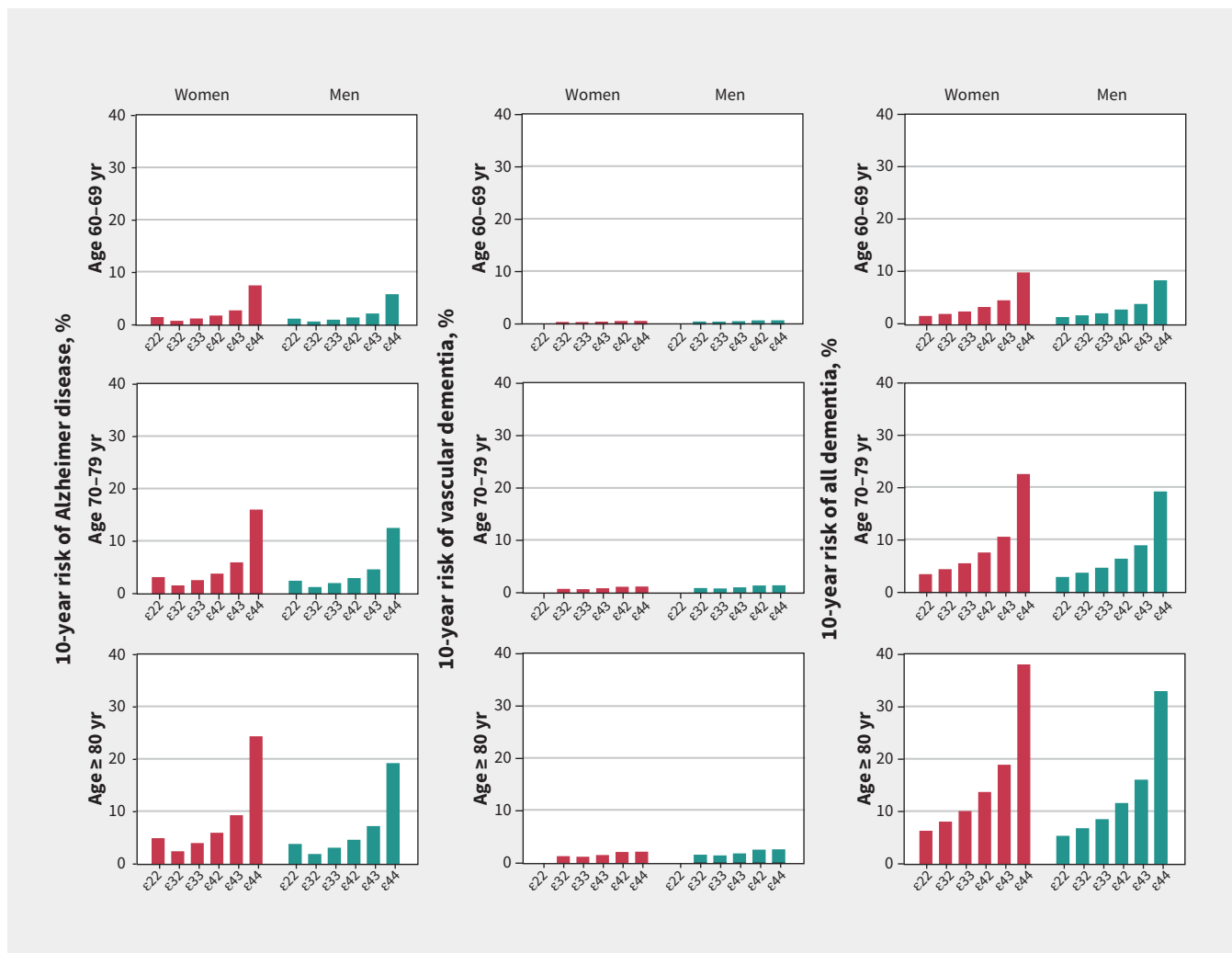
Figure 1: Absolute 10-year risk of Alzheimer disease, vascular dementia and all dementia for *APOE* genotypes stratified by sex and age groups. Competing risk was accounted for by the method of Fine and Gray.[24]

Risk of all dementia after a diagnosis of cerebrovascular disease increased from ε32 to ε33 to ε43 to ε42 to ε44 (*p* for trend = 0.002) (Appendix 1, Supplemental Figure 3). A similar pattern was observed for a multivariable-adjusted competing risk model (Appendix 1, Supplemental Figure 3).

For the 6 common *APOE* genotypes, total cholesterol, LDL cholesterol and apolipoprotein B increased from ε22 to ε32 to ε42 to ε33 to ε43 to ε44 (*p* for trend < 0.001 for all), whereas high-density lipoprotein cholesterol and apolipoprotein AI levels decreased from ε22 to ε32 to ε42 to ε33 to ε43 to ε44 (*p* for trend < 0.001 for all) (Appendix 1, Supplemental Figure 4). For triglycerides and remnant cholesterol, U-shaped curves were observed with the highest levels in ε22 and ε44 carriers (*p* < 0.001 for both). Appendix 1, Supplemental Figure 5, shows all 9 possible genotype combinations. Owing to rarity, ε442, ε422 and ε4422 were excluded from further analyses.

Other covariates independently associated with an increased risk of all cerebrovascular disease included lipid-lowering therapy (adjusted HR 2.25, 95% CI 2.13–2.38), atrial fibrillation (adjusted HR 1.52, 95% CI 1.44–1.61), smoking (adjusted HR

1.49, 95% CI 1.41–1.57), hypertension (adjusted HR 1.17, 95% CI 1.11–1.24) and physical inactivity (adjusted HR 1.13, 95% CI 1.08–1.18). In contrast, male sex (adjusted HR 0.64, 95% CI 0.57–0.73) was associated with a decreased risk of all cerebrovascular disease (Table 2).

Interpretation

We found that the absolute 10-year risk of dementia for ε44 carriers is modified by age and sex. Absolute 10-year risk increased from 6%–7% at age 60–69 years up to 19%–24% at age 80 years and older for Alzheimer disease, and from 8%–10% up to 33%–38% for all dementia, respectively. Such estimates have the potential to facilitate the identification of high-risk individuals for targeted preventive interventions.

Our study provides age- and sex-specific absolute 10-year risk as a function of each of the 6 common *APOE* genotypes based on a large general population sample with more than 3000 ε44 carriers. Absolute risk was recently estimated in 4 different studies with a total of 392 ε44 carriers, but with no sex stratification
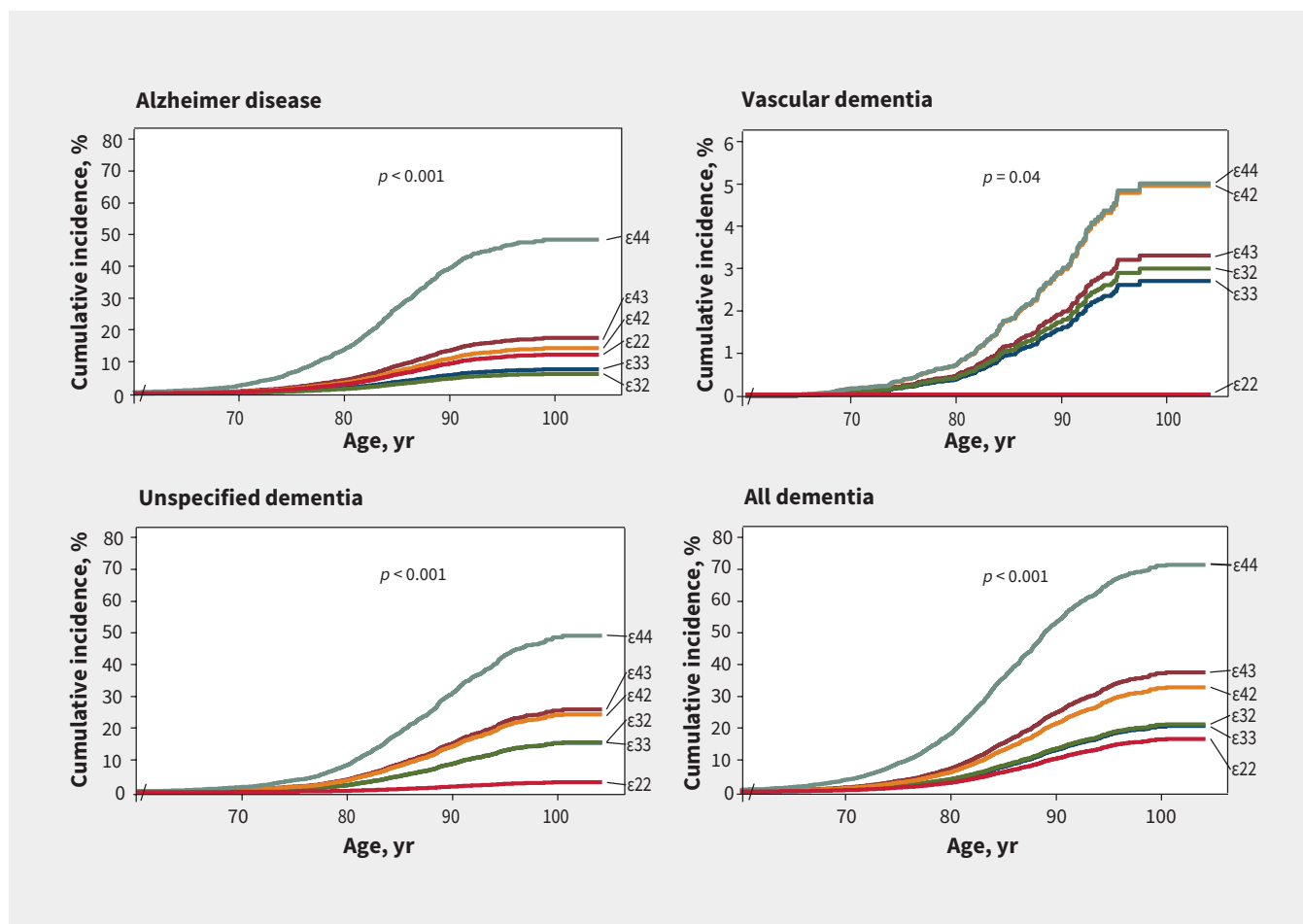
Figure 2: Cumulative incidence of dementia, by the method of Fine and Gray,[24] as a function of age and *APOE* genotype. The *p* values are trends across genotypes from ε22 to ε32 to ε33 to ε42 to ε43 to ε44 for the unadjusted competing risk regression (age as time scale).

owing to a lack of power.[25] Sex-specific estimates for absolute risk are important because of differences in life span between the sexes and because the effect of *APOE* genotype may be modified by sex,[25] where age-dependent sex hormone changes in apoE-mediated lipid metabolism could have an influence.[26] Because dementia at present remains effectively untreatable, reducing the risk is of major importance. A third of all cases of dementia has recently been calculated to be preventable with early intervention for hypertension, smoking, diabetes, obesity, depression and hearing loss.[3] Further, declines in incidences in some high-income countries have been suggested to be caused by improved prevention and treatment of vascular risk factors.[27,28] Therefore, robust absolute risk estimates will be pivotal instruments for identification of high-risk individuals who will benefit the most from targeted preventive intervention.

The present data also illustrate how the ε4 allele of the *APOE* polymorphism affects risk of both dementia and cerebrovascular disease in a dose-dependent manner, consistent with the existing literature.[5,9,16–19,22,25] The data on subtypes of dementia and cerebrovascular disease show that the ε42 genotype is more important than the ε43 genotype for vascular components of dementia, as well as for cerebrovascular disease, than previously reported.[11–19] This is biologically plausible, given that the

ε42 genotype is a combination of 2 hyperlipidemic alleles: ε2 has low receptor affinity for the LDL receptor, resulting in susceptibility to type III hyperlipoproteinemia with increased levels of triglycerides and remnant particles,[7,29] whereas ε4 is associated with increased plasma levels of LDL cholesterol and triglycerides.[30] The decreased receptor affinity for apoE2 leads to a decreased apoE-mediated uptake and an upregulation of the LDL receptor, probably explaining the associated low LDL cholesterol and high triglyceride levels.[31] The preference of apoE4 for very low-density lipoprotein in plasma increases hepatic clearance and results in lower apoE levels, subsequently causing downregulation of LDL receptors and corresponding increases in plasma levels of LDL cholesterol.[7,32] The biological mechanism behind increased triglyceride levels in ε4 carriers is not well understood. Further, given that stroke and cerebrovascular disease likely make the brain more prone to dementia,[33,34] we assessed the genotype-specific risk pattern for all dementia after a diagnosis of cerebrovascular disease. We found that ε44 and ε42 were robustly associated with the highest risk, consistent with the vascular effects of ε42, and in accordance with earlier reports in smaller studies.[33,34]

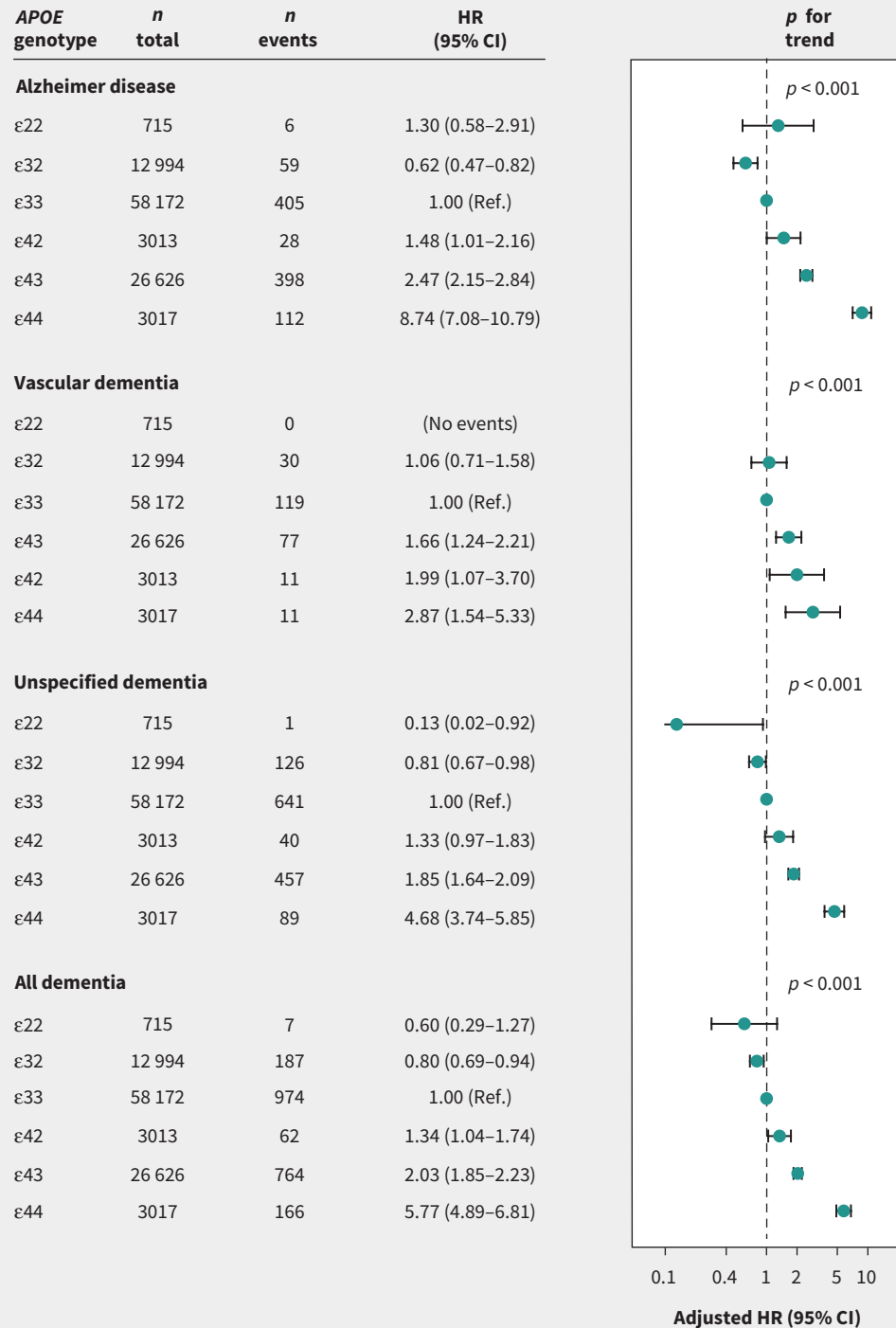The underlying mechanisms for our findings are only partly understood. Likely biological explanations involve direct

APOE genotype	*n* total	*n* events	HR (95% CI)	*p* for trend
Alzheimer disease				*p* < 0.001
ε22	715	6	1.30 (0.58–2.91)	
ε32	12 994	59	0.62 (0.47–0.82)	
ε33	58 172	405	1.00 (Ref.)	
ε42	3013	28	1.48 (1.01–2.16)	
ε43	26 626	398	2.47 (2.15–2.84)	
ε44	3017	112	8.74 (7.08–10.79)	
Vascular dementia				*p* < 0.001
ε22	715	0	(No events)	
ε32	12 994	30	1.06 (0.71–1.58)	
ε33	58 172	119	1.00 (Ref.)	
ε43	26 626	77	1.66 (1.24–2.21)	
ε42	3013	11	1.99 (1.07–3.70)	
ε44	3017	11	2.87 (1.54–5.33)	
Unspecified dementia				*p* < 0.001
ε22	715	1	0.13 (0.02–0.92)	
ε32	12 994	126	0.81 (0.67–0.98)	
ε33	58 172	641	1.00 (Ref.)	
ε42	3013	40	1.33 (0.97–1.83)	
ε43	26 626	457	1.85 (1.64–2.09)	
ε44	3017	89	4.68 (3.74–5.85)	
All dementia				*p* < 0.001
ε22	715	7	0.60 (0.29–1.27)	
ε32	12 994	187	0.80 (0.69–0.94)	
ε33	58 172	974	1.00 (Ref.)	
ε42	3013	62	1.34 (1.04–1.74)	
ε43	26 626	764	2.03 (1.85–2.23)	
ε44	3017	166	5.77 (4.89–6.81)	

Adjusted HR (95% CI)

Figure 3: Risk of dementia as a function of *APOE* genotype. Hazard ratios (HRs) were adjusted for age (time scale), sex, body mass index, hypertension, diabetes mellitus, smoking, alcohol consumption, physical inactivity, menopausal status and hormonal replacement therapy (only women), lipid-lowering therapy and education. The *p* values are trends across genotypes from ε22 to ε32 to ε33 to ε42 to ε43 to ε44, except for vascular dementia, where trend was calculated from ε22 to ε32 to ε33 to ε43 to ε42 to ε44. CI = confidence interval, Ref. = reference.

Table 2: Hazard ratios for covariates in multivariable-adjusted Cox regression models for all dementia and all cerebrovascular disease

Covariate	HR (95% CI) All dementia	HR (95% CI) All cerebrovascular disease
APOE genotype	ε22: 0.60 (0.29–1.27) ε32: 0.80 (0.69–0.94) ε33: 1.00 (Ref.) ε42: 1.34 (1.04–1.74) ε43: 2.03 (1.85–2.23) ε44: 5.77 (4.89–6.81)	ε22: 0.89 (0.66–1.21) ε32: 1.00 (0.93–1.08) ε33: 1.00 (Ref.) ε43: 1.01 (0.95–1.06) ε42: 1.17 (1.03–1.34) ε44: 1.30 (1.15–1.48)
Male sex	0.62 (0.40–0.96)	0.64 (0.57–0.73)
Body mass index		
Lowest tertile (CCHS: < 23.3; CGPS: < 24.0)	1.00 (Ref.)	1.00 (Ref.)
Middle tertile (CCHS: 23.3–26.8; CGPS: 24.0–27.4)	0.97 (0.88–1.08)	0.98 (0.93–1.04)
Highest tertile (CCHS: > 26.8; CGPS: > 27.4)	0.96 (0.86–1.07)	1.04 (0.98–1.10)
Hypertension*	0.82 (0.74–0.91)	1.17 (1.11–1.24)
Diabetes mellitus†	1.30 (1.09–1.55)	1.02 (0.93–1.11)
Smoking‡	1.68 (1.52–1.85)	1.49 (1.41–1.57)
Alcohol consumption§	1.00 (0.89–1.12)	0.97 (0.92–1.03)
Physical inactivity¶	1.16 (1.06–1.27)	1.13 (1.08–1.18)
Postmenopausal status and hormonal replacement therapy**		
Premenopausal	1.00 (Ref.)	1.00 (Ref.)
Postmenopausal without hormonal replacement therapy	0.65 (0.42–1.00)	0.47 (0.42–0.54)
Postmenopausal with hormonal replacement therapy	0.72 (0.46–1.13)	0.53 (0.46–0.62)
Lipid-lowering therapy††	0.81 (0.71–0.93)	2.25 (2.13–2.38)
Education < 8 yr	1.34 (1.23–1.47)	1.02 (0.97–1.07)
Atrial fibrillation‡‡	–	1.52 (1.44–1.61)

Note: CCHS = Copenhagen City Heart Study, CGPS = Copenhagen General Population Study, CI = confidence interval, Ref. = reference.
*Hypertension was defined by use of antihypertensive medication, systolic blood pressure of ≥ 140 mm Hg, and/or diastolic blood pressure of ≥ 90 mm Hg.
†Diabetes mellitus was defined by self-reported disease, use of insulin or oral hypoglycemic agents, and/or nonfasting plasma glucose level of > 11 mmol/L (> 198 mg/dL).
‡Smoking was defined by current smoking.
§Alcohol consumption was defined by > 14/21 units per week for women/men (1 unit = 12 g alcohol, equivalent to 1 glass of wine or spirit or 1 beer [33 cL = 330 mL]).
¶Physical inactivity was defined by ≤ 4 hours per week of light physical activity in leisure time.
**Women reported menopausal status and use of hormonal replacement therapy. The individual hazard ratios for postmenopausal status and hormonal replacement therapy should be interpreted with caution, because the covariate in itself reflects age, and these estimates are from the full model with adjustment for age as the time scale. Adjusting for postmenopausal status and hormonal replacement therapy as a covariate is still appropriate, and the inclusion of this does not change the genetic estimates (Appendix 1, Supplemental Table 1).
††Lipid-lowering therapy primarily consisted of statins (yes/no).
‡‡Atrial fibrillation was defined by any diagnosis of atrial fibrillation ever.

effects in brain tissue, and blood–brain barrier and vascular effects subsequently affecting brain functions. Brain apoE mediates clearance of amyloid-β, which exerts its toxic function by accumulating in brain tissue. Clearance of amyloid-β is decreased in Alzheimer disease,[6,35] and the ε4 allele is associated with increased brain amyloid burden in a dose-dependent manner in healthy older individuals and in patients with mild cognitive impairment.[36,37] These human findings are supported by apoE isoform–specific effects on both amyloid-β oligomer formation and plaque deposition in animal models.[38–40] Accumulation of amyloid-β in the cerebral vasculature causes cerebral amyloid angiopathy,[5] and both ε4 and ε2 are associated with increased risk of lobar intracerebral hemorrhage related to cerebral amyloid angiopathy.[41–43] Among the subtypes of cerebrovascular disease in the present study, the highest risk

for ε44 carriers is observed for hemorrhagic stroke, supporting the hypothesis that the ε4 allele increases cerebral vasculature fragility. It is likely that deposition of amyloid-β in arterioles in the central nervous system combined with degradation of the blood–brain barrier altogether leaves a rather frail intracerebral vasculature prone to cerebrovascular disease.[5,44,45] This concept is supported by previous studies and the present large-scale general population study on major subtypes of cerebrovascular disease. Finally, an atherogenic lipid profile is a well-known risk factor for cerebrovascular disease,[46] and both ε22 homozygosity and the ε4 allele are associated with hyperlipidemia. This is in line with the present observations that the ε42 genotype confers higher risk in cerebrovascular disease and vascular dementia (i.e., diseases with vascular components) than previously assumed.

Limitations

The generalizability of our study is limited by the inclusion of only white individuals. *APOE* allele frequencies vary between ancestries, and *APOE* genotypes may not be associated with adverse outcomes in all populations.[7] Another potential limitation is information on dementia diagnoses, where misclassification in the outcome may be present. This might explain the similar directions of the effects of *APOE* genotype on Alzheimer disease and all dementia. A previous thorough examination of 200 dementia diagnoses from the national registries showed after a full clinical workup that 33% of cases of Alzheimer disease were misclassified as dementia without specification (which is a subgroup of our all-dementia diagnosis). However, once the Alzheimer disease diagnosis was entered in the registries, it was correct in 81% of the cases.[47] Consequently, the misclassified fraction of Alzheimer disease is most likely included in our all-dementia diagnosis, and will only bias our results for Alzheimer disease toward the null hypothesis, making these estimates conservative. These issues with potential misclassification emphasize the rationale for presenting results on both Alzheimer disease and all dementia, as we have done. Further, we ensured that about 80% of observations from 1996 were obtained at specialized units by scoring all individual Alzheimer-disease and all-dementia events in our cohorts.[23]

Conclusion

We found that the absolute 10-year risk of dementia for ε44 carriers is modified by age and sex. Absolute 10-year risk increased from 6%–7% at age 60–69 years up to 19%–24% at age 80 years and older for Alzheimer disease, and from 8%–10% up to 33%–38% for all dementia, respectively. The present absolute 10-year risk estimates of dementia by age, sex and *APOE* genotype have the potential to identify high-risk individuals for early targeted preventive interventions. Taken together, the present findings emphasize *APOE* genotype as an important component in the individual risk assessment of dementia and cerebrovascular disease.

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