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Featured Articles

Carotid plaque as a predictor of dementia in older adults: The Three-City Study

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Abstract

Background: The contribution of carotid atherosclerosis to incident dementia remains unclear. We examined the association between carotid plaques (CP) and common carotid intima media thickness (CCA-IMT) with incident dementia and its subtypes, and their added value for dementia risk prediction.
Methods: At baseline, 6025 dementia-free subjects aged 65–86 years underwent bilateral carotid ultrasonography measures of CP and plaque-free CCA-IMT. Subjects were followed-up over 7 years for the detection of dementia.
Results: After a mean 5.4 years of follow-up, 421 subjects developed dementia including 272 Alzheimer's disease and 83 vascular/mixed dementia (VaD). Only CP were independently related to VaD ($HR_{\geq 2 \text{ sites with plaques}} = 1.92$; 95% confidence interval or CI = 1.13–3.22) and improved VaD risk prediction (continuous Net Reclassification Index = 30.1%; 95%CI = 8.4–51.7) beyond known dementia risk factors. Accounting for stroke or competing risk by death marginally modified the results.
Conclusion: In older adults, CP are independent predictors of incident VaD and may improve VaD risk prediction.

Keywords: Epidemiology; Risk factors; Aging; Atherosclerosis; Dementia

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1. Introduction

Over the past decade there has been growing interest in exploring the role of atherosclerosis in the development of dementia [1]. Carotid atherosclerosis has been associated with prevalent dementia and cognitive decline [2–6], but there is limited prospective evidence linking dementia outcomes with carotid atherosclerosis [7–9]. These few available studies consistently reported significant associations between carotid intima media thickness (IMT) and incident dementia, however, observations related to carotid plaques remain inconclusive [8,9]. In most previous studies carotid IMT measurements included plaques, precluding the differentiation of their respective contribution to dementia incidence. Furthermore, most prior studies have focused on Alzheimer's disease (AD) whereas the association may differ according to the type of dementia. Interestingly, recent reports indicate that almost one-third of previously diagnosed AD cases may in fact be vascular/mixed dementia, suggesting that association between carotid atherosclerosis and dementia subtypes requires re-examination [10]. Methodologically, given that stroke is a major risk factor for dementia and that risk of death is very elevated in elderly, the effect of stroke, and competing risk by death should be taken into account. Finally, the ability to identify individuals at high risk of future dementia is a promising but challenging issue. Existing dementia risk prediction models are insufficiently sensitive and discriminative [11], so that easy, inexpensive and noninvasive markers such as carotid plaques or carotid IMT may improve the accuracy of dementia risk prediction.

In this study, we aimed to extend the results of prior studies on the prospective relationship between subclinical atherosclerosis and incident dementia by (1) dissociating the association of baseline focal carotid plaques from that of diffuse carotid IMT measured at a site free of any discrete plaques, (2) studying incident all-cause dementia and its major subtypes, (3) considering the effect of stroke and competing risk by death, (4) evaluating the added value of markers of carotid atherosclerosis for dementia risk prediction.

2. Methods

2.1. Population

The Three-City Study is a French multisite prospective study investigating the determinants of coronary heart disease, stroke and dementia in 9294 noninstitutionalized community dwellers, aged 65 years or older, who were selected from electoral rolls between March 1999 and March 2001 [12]. The study protocol has been approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and each participant signed an informed consent agreement.

2.2. Baseline collection

A detailed description of the data collection has been published elsewhere [12]. Briefly, at baseline trained interviewers conducted face-to-face interviews using a standardized questionnaire. Demographic characteristics, daily life habits, medical history and medications used in the past month were recorded. Brachial blood pressure was measured twice after at least 5 minutes of rest in a seated position, with an appropriately sized cuff placed on the right arm, using a validated digital electronic tensiometer (OMRON M4, OMRON Corp., Kyoto, Japan). Height and weight measurements were measured in light dress. Blood was collected following overnight fasting and centralized standard measurements of lipids and glucose levels were performed. Determination of the apolipoprotein E genotype (*APOE*) was carried out at the Lille Genopole (Lille, France, http://www.genopole.fr/).

2.3. Ultrasound examination

An ultrasound examination of the carotid arteries was offered to participants aged less than 86 years and who were able to come to the study center. Due to cost constraints, ultrasound examination was not performed in participants included during the last 4 months of recruitment. Subsequently 73.7% ($n = 6635$) of the eligible participants had carotid ultrasound measures. This subset of the population had a better baseline cardiovascular risk profile [13], lower prevalence of dementia (1.5% versus 3.6%, $P \leq .0001$) but a similar cumulated rate of dementia at 7 years follow-up (6.9% versus 8.2%, $P = .93$) than those aged less than 86 years who did not undergo ultrasound examination.

The protocol of carotid ultrasound is detailed in Supplementary File 1 and has been described previously [14]. Centralized readings were performed by a trained reader blinded to participant characteristics, at the Reference Reading Center (Broussais Hospital, Paris) according to a standardized protocol. The near and far walls of the following six sites including the common carotid arteries (CCAs), the bifurcations and the origin of the internal carotid arteries were scanned longitudinally and transversally to detect plaques. The presence of plaques was defined as localized echo structures encroaching into the vessel lumen for which the wall thickening was at least 50% greater than that of the surrounding vessel wall at any of the six sites.

The near and far wall of the right and left CCAs were scanned at least 1.5 cm proximal to the origin of the bulb. The IMT was measured only at a plaque-free site, along a 10-mm segment of the far wall of the left and right CCAs (at least 1.5 cm proximal to the origin of the bulb) and measured as the distance between the lumen–intima interface and the media–adventitia interface using an automated edge detection algorithm. The mean of 75 measurements was automatically performed on each image and on each side. Maximum IMT and IMT in other arterial segments were not measured during the study.

2.4. Follow up and ascertainment of events

Subjects were followed-up every two years over 7 years for the detection of vascular disease and dementia. In this analysis we excluded subjects with a prevalent dementia (n = 102), who died before the first follow-up visit (n = 122) or who were lost to follow-up (n = 386) (see Fig. 1). Subjects who died before the first visit were older ($P < .0001$), more often men ($P < .0001$), and had more cardiovascular risk factors ($P < .05$ for hypertension, hypercholesterolemia, diabetes, tobacco consumption, and personal history of cardiovascular disease) and had more often carotid plaques at baseline ($P < .0001$) than subjects with at least one follow-up visit. Subjects lost to follow-up were more often men ($P = .042$), had a lower level of education ($P = .036$), and had more often smoked ($P = .046$) than subjects with at least one follow-up visit.

2.4.1. *Diagnosis of dementia*

The protocol and criteria used to define dementia and its major subtypes have been previously defined [15]. The same procedure was used to diagnose prevalent and incident cases of dementia. In Bordeaux and Montpellier, all subjects underwent a comprehensive neuropsychological examination and were seen by a senior neurologist. In Dijon, because of a larger number of participants, only those suspected of having dementia based on their performance on the Mini Mental State Examination score [16] and the Isaacs's set test [17] according to educational level [18], underwent further examination. Finally, all potential cases of dementia were reviewed and ascertained by an independent committee of neurologists using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria [19], the Clinical Dementia Rating scale [20] and other information gathered at baseline including magnetic resonance imaging when available. We studied the three most frequent causes of dementia including AD, VaD, and mixed dementia. AD was defined according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Diagnosis of VaD or mixed dementia was based on history of neurovascular disease, neurological examination, Hachinski score, brain imaging reports (CT scan and/or MRI) when available, and National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria. VaD included cases in which a clinical history of cerebrovascular disease, ascertained if available, by CT scan or MRI reports recollected by hospital records, was considered the sole or primary cause of cognitive impairment on the basis of a time-dependent relationship. The mixed origin of dementia was suggested by the presence of CT scan or MRI findings (obtained in one third of the cases) of lacunae, leucoaraiosis, and/or a history of stroke or transient ischemic attacks associated with a typical progressive and insidious evolution of AD. In the present analysis, VaD and mixed dementia were combined together (VaD/mixed dementia).

Cognitive impairment was defined as a score in either global cognitive competence, language retrieval or visual memory (evaluated by Mini-Mental State Examination [16], Isaacs' Set Test [17], and Benton Visual Retention Test [21]) in the lowest 10th percentile of the age and education stratified test score distributions.

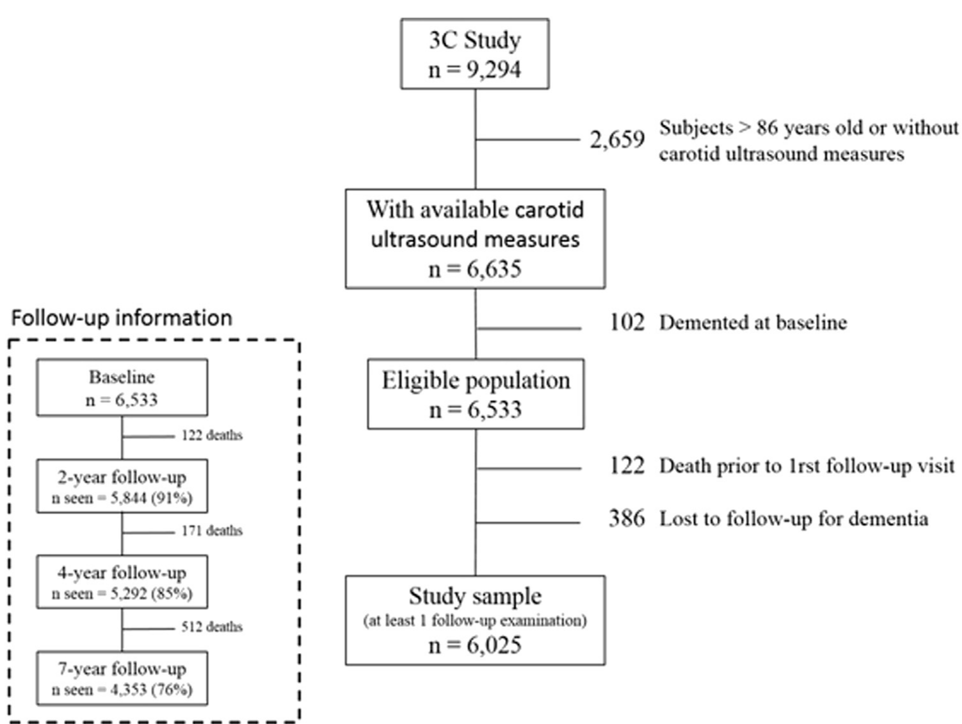

Fig. 1. Flow chart of the studied population.

Table 1
Subjects' baseline characteristics according to the number of sites with carotid plaques

	Number of sites with carotid plaques			
	0 (n = 3237)	1 (n = 1201)	≥2 (n = 1585)	Age-adjusted *P*-value
Age in years, m (SD)	72.4 (4.5)	73.8 (4.9)	75.0 (5.0)	<.0001
BMI in kg/m^2, m (SD)	25.4 (3.9)	25.7 (4.0)	26.0 (4.0)	<.0001
Sex, male	1094 (33.8)	482 (40.1)	757 (47.8)	<.0001
Low education	923 (28.5)	383 (31.9)	560 (35.4)	.004
APOE ε4	632 (19.8)	245 (20.8)	336 (21.7)	.007
Hypertension	2226 (68.8)	947 (78.9)	1356 (85.6)	<.0001
Hypercholesterolemia	1058 (32.9)	486 (40.8)	687 (43.9)	<.0001
Diabetes	221 (6.9)	139 (11.7)	191 (12.3)	<.0001
Ever smoker	1075 (33.2)	506 (42.1)	729 (46.0)	<.0001
History of CHD	232 (7.2)	157 (13.1)	256 (16.2)	<.0001
History of stroke	89 (2.8)	39 (3.3)	101 (6.5)	<.0001
Deceased	256 (7.9)	115 (9.6)	251 (15.8)	<.0001

Abbreviations: SD, standard deviation; CHD, coronary heart disease; BMI, body mass index; *APOE*, apolipoprotein E.

NOTE. Except age and BMI, data are reported as n (%); 210 subjects with missing values: n = 2 for carotid plaques; n = 8 for BMI; n = 2 for education level; n = 106 for *APOE* ε4; n = 60 for hypercholesterolemia; n = 94 for diabetes; n = 1 for smoking status; n = 67 for history of stroke.

2.4.2. Stroke ascertainment

Stroke was defined according to the diagnostic criterion of the World Health Organization [22] and validated by an adjudicated committee following standardized procedures defined previously [23].

2.4.3. Mortality ascertainment

Vital status and exact date of death were obtained through the French national mortality register (CépiDc-Inserm).

2.5. Statistical analysis

Baseline characteristics were compared according to the number of sites with carotid plaques (0, 1 or ≥2) and across quartiles of CCA-IMT using age-adjusted linear regression models. Cumulative incidence function was used to estimate the cumulative incidence of all-cause dementia, VaD/mixed dementia, and AD by number of sites with carotid plaques (0, 1 or ≥2) and across quartiles of CCA-IMT, using age as the time scale. Age at onset of dementia was the age at the middle of the interval between the last visit without dementia and the visit with dementia. Hazard ratios (HR) and 95% confidence interval (95% CI) by number of sites with carotid plaques, respectively used as continuous, and as categorical (for 1, ≥2 sites, using subjects without carotid plaques as the reference category) and by CCA-IMT, respectively, for 1 standard deviation (SD) increase (SD = 0.12) and by quartiles of CCA-IMT (using the first quartile as the reference category) were estimated on separate Cox proportional hazard models using age as the time scale and taking late entry into account [24]. When evaluating one particular subtype of dementia, cause-specific analyses were performed, censoring subjects developing other type of dementia at their age of dementia. The proportional hazards assumption was tested and met for each variable of interest using graphical methods by visual inspection of the Kaplan Meir plots (log versus log minus log plot) and using formal statistical methods testing for interaction between time (follow-up) and the variables of interest. HR and their 95% CIs were adjusted for sex and study center, educational level (less than graduate school, completed graduate school or high school, high school diploma or university), *APOE* ε4, obesity (body mass index [BMI] ≥ 30 kg/m^2), hypertension (blood pressure ≥140/90 mmHg or use of antihypertensive drug), hypercholesterolemia (total cholesterol ≥6.20 mmol/L or under lipid lowering treatment), diabetes mellitus (history of diabetes, fasting blood glucose ≥7 mmol/L or antidiabetes medication), smoking status (past/never/current), and personal history of cardiovascular disease (myocardial infarction and stroke) at baseline. Cross product interaction terms between carotid atherosclerosis markers and these confounders were tested one at a time using the Wald test. Missing covariates (n = 210 patients) were substituted using multiple-imputation in the multivariate Cox proportional hazards [25] using Rubin's rules [26]. The effect of stroke was evaluated by censoring follow up at the age of stroke, by excluding subjects with prevalent and stroke during follow-up and by adjusting for stroke as a time-dependent variable. Competing risk by death was further evaluated using the Fine and Gray method [27]. The added value of carotid plaques for dementia risk prediction was estimated by quantifying improvement in discrimination and reclassification. For discrimination, the c-statistic of a first model including independent predictors of dementia identified in our cohort ("basic model") was compared with that of the same model plus carotid plaques using the DeLong test [28]. For reclassification, we computed the continuous net reclassification index (NRI) associated with the addition of carotid plaques (modeled as continuous) to our "basic model" [29]. Statistical significance was set at two-sided $P \leq .05$. All analyses were performed using SAS statistical software version 9.2 (Cary, NC).

Table 2
Hazard ratios (95% CI) of all cause and dementia subtypes for carotid plaques and common carotid artery IMT

	All-cause dementia (n = 421)				Alzheimer's disease (n = 272)			Vascular or mixed dementia (n = 83)		
	nb of person-year*	Incidence (%)	HR (95% CI)		Incidence (%)	HR (95% CI)		Incidence (%)	HR (95% CI)	
			Age-adjusted	Adjusted†		Age-adjusted	Adjusted†		Age-adjusted	Adjusted†
Total	35,530	1.2			0.8			0.2		
Nb of sites with plaque										
1 unit increase			1.14 (1.04–1.24)	1.07 (0.98–1.17)		1.08 (0.97–1.21)	1.02 (0.91–1.14)		1.39 (1.16–1.66)	1.28 (1.06–1.55)
0	19,739	0.9	1 (reference)	1 (reference)	0.7	1 (reference)	1 (reference)	0.1	1 (reference)	1 (reference)
1	7063	1.2	1.02 (0.79–1.32)	0.91 (0.69–1.18)	0.8	0.97 (0.70–1.33)	0.84 (0.61–1.17)	0.2	1.35 (0.73–2.49)	1.31 (0.70–2.46)
≥ 2	8714	1.7	1.31 (1.05–1.62)	1.13 (0.90–1.43)	1.0	1.11 (0.84–1.46)	0.95 (0.71–1.27)	0.5	2.30 (1.40–3.76)	1.92 (1.13–3.22)
P for trend			0.020	0.300		0.494	0.689		0.0009	0.014
CCA-IMT (mm)										
1 SD increase			1.03 (0.94–1.14)	0.99 (0.90–1.10)		1.01 (0.90–1.14)	0.99 (0.87–1.12)		1.15 (0.93–1.42)	1.06 (0.85–1.32)
Q1: [0.39–0.62]	8615	1.0	1 (reference)	1 (reference)	0.7	1 (reference)	1 (reference)	0.1	1 (reference)	1 (reference)
Q2: [0.62–0.69]	8677	0.9	0.86 (0.64–1.16)	0.83 (0.61–1.13)	0.6	0.79 (0.54–1.14)	0.76 (0.51–1.09)	0.2	1.35 (0.65–2.81)	1.26 (0.61–2.64)
Q3: [0.69–0.79]	9660	1.2	0.92 (0.70–1.22)	0.86 (0.65–1.16)	0.8	0.84 (0.60–1.19)	0.80 (0.56–1.13)	0.3	1.44 (0.72–2.87)	1.21 (0.60–2.46)
Q4: [0.79–1.38]	7695	1.6	1.04 (0.79–1.38)	0.94 (0.71–1.40)	1.1	0.96 (0.68–1.35)	0.90 (0.63–1.27)	0.4	1.63 (0.82–3.26)	1.34 (0.66–2.73)
P for trend			0.610	0.883		0.990	0.744		0.175	0.484

Abbreviations: HR, hazard's ratio; CI, confidence interval; SD, standard deviation; CCA-IMT, common carotid intima media intima-media thickness.

*The total number of person-year by number of sites with carotid plaques or by quartiles of CCA-IMT differ slightly as two individuals had missing values for the number of sites with carotid plaques and 155 other individuals for CCA-IMT (see Methods section).

†Adjusted for age, center, sex, *APOE* ε4, education, obesity, diabetes, hypertension, hypercholesterolemia, tobacco status, personal history of coronary heart disease and stroke. In the 210 subjects with missing values, multiple imputation techniques were used (see statistical section).

3. Results

3.1. Baseline characteristics

The study flow chart is reported in Fig. 1. The studied sample includes 6025 participants aged (SD) 73.4 years (4.8) and comprised 60.5% of women. Two subjects had missing information regarding carotid plaques, and 155 regarding CCA-IMT measures. The mean (SD) CCA-IMT was 0.71 (0.12) mm and 46.5% (n = 3038) had carotid plaques at least at one site. Cardiovascular and dementia risk factors and mortality rate were all associated with the number of sites with carotid plaques (Table 1). Associations with CCA-IMT quartiles are shown in Supplementary File 2.

3.2. Incidence rates of dementia

After a mean (SD) study follow-up of 5.4 (2.0) years representing 35,530 person-years (PY), 421 subjects had dementia, among which 272 (64.6%) were AD and 83 (19.7%) VaD/mixed dementia, yielding incidence rates of 12 per 1000 PY, 8 per 1000 PY and 2 per 1000 PY respectively (Table 2). The cumulative incidence of all-cause dementia (Fig. 2A) and VaD/mixed dementia (Fig. 2B), but not AD (Fig. 2C), increased with the number of sites with carotid plaques; no trends were observed with baseline CCA-IMT (Supplementary File 3).

3.3. Associations with incident dementia

In age-adjusted analysis, the risk of all-cause dementia and VaD/mixed dementia increased 1.31-fold and 2.30-fold in subjects with carotid plaques on two sites or more as compared with those with no carotid plaques (Table 2). After adjusting for potential confounders the association remained significant only for VaD/mixed dementia with a 1.92 fold increased risk (P for trend = .014). Age, *APOE* ε4, education, diabetes mellitus, and prevalent stroke were the other predictors of VaD/mixed dementia. Conversely, no association was observed between mean CCA-IMT and incident dementia of any type.

As shown in Fig. 3, the age-adjusted association of carotid plaques with VaD/mixed dementia was consistent across sex, education, *APOE* ε4 genotype, diabetes mellitus, hypertension, and prevalent coronary heart disease and stroke, with no significant interaction.

3.4. Added value of carotid plaques for VaD risk prediction

Adding the number of sites with carotid plaques to our a model with independent predictors of VaD/mixed dementia identified in our study and including age, education, *APOE* ε4, diabetes, prevalent stroke, resulted in a nonsignificant increase of the c-statistic (from 0.705 to 0.804; P = .18) but a significant continuous NRI of 30.1% (95%CI = 8.42–51.7; P < .001). The reclassification improvement was confined

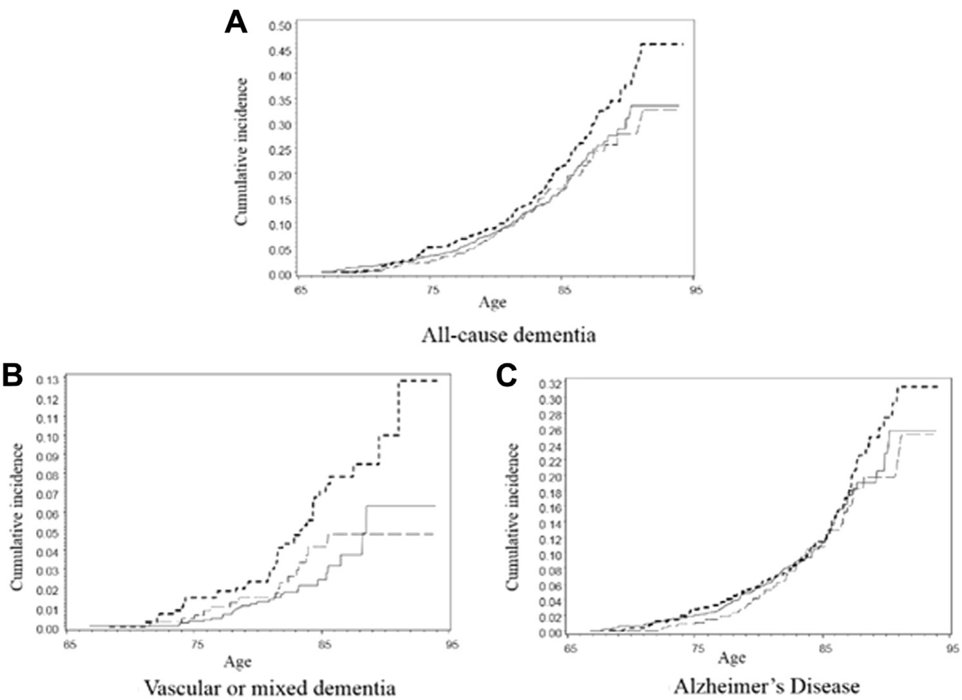

Fig. 2. Cumulative incidence function of all-cause dementia (A), vascular or mixed dementia (B), and Alzheimer's disease (C), according to the number of sites with carotid plaque (0 = solid line; 1 = dashed line; ≥2 = bold dashed line).

to "nonevent" participants ($NRI_{non\text{-}event}$ = 26.5%; 95% CI = 23.9–29.0; $P < .001$).

3.5. Sensitivity analysis

A series of sensitivity analyses confirms the robustness of our findings. Association of carotid plaques with VaD/mixed dementia persisted: (1) after censoring time at the age of stroke during follow-up (n = 184 strokes; $HR_{>=2\_sites\_with\_carotid\_plaque}$ = 2.72 (95% CI = 1.36–5.47), P for trend = .005) or after excluding the 391 subjects with stroke at baseline and during follow-up ($HR_{>=2\_sites\_with\_carotid\_plaque}$ = 3.22 (1.41–7.31) P for trend = .002) or when considering stroke as a time-dependent variable ($HR_{>=2\_sites\_with\_carotid\_plaque}$ = 1.67 (95% CI = 0.98–2.83), P for trend = .057); (2) when considering competing risk by death (Fine and Gray $HR_{>=2\_sites\_with\_carotid\_plaque}$ = 1.83 (95%CI = 1.06–3.17), P for trend = .032); (3) after excluding the 907 subjects with prevalent cognitive impairment ($HR_{>=2\_sites\_with\_carotid\_plaque}$ = 2.25 (95%CI = 1.15–4.35), P for trend = .016) or the 93 subjects who developed dementia within the first two years of follow-up ($HR_{\geq 2\_sites\_with\_carotid\_plaque}$ = 1.95 (95%CI = 1.08–3.56), P for trend = .024).

4. Discussion

In this large prospective population-based cohort of elderly individuals aged 65 to 86 years we found an association between baseline carotid plaques and incident vascular or mixed dementia over 7 years of follow-up. This association was independent of major cardiovascular and dementia risk factors at baseline, and was moderately explained by stroke. Competing risk by death did not seem to be involved in these associations. Furthermore, exploratory analyses suggest that carotid plaques may improve the prediction of vascular or mixed dementia beyond common vascular and nonvascular risk factors. Conversely, there was no association between CCA-IMT measured in sites free of carotid plaque and incident dementia of any type.

Three prospective studies, namely the Cardiovascular Health Study [7], the Rotterdam Study [8] and very recently the Baltimore Longitudinal Study of Aging [9] have previously examined the association between carotid atherosclerosis and the risk of dementia. Our findings differed in two aspects compared with these prior studies. Firstly, all have reported a significant and independent association with carotid IMT (HR ≈ 1.5) whereas in our study an association existed only for carotid plaques. Heterogeneity in the assessment of carotid IMT regarding the segments explored (CCA, bifurcation or ICA) and the metrics used (mean, maximum) is well established [30]. This is of importance because when IMT is measured in the bifurcation and/or the ICA, its value also reflects the presence of plaques. Accordingly, in two of these studies, IMT was measured in all carotid segments including the carotid bifurcation and internal carotid arteries where carotid plaques are present, whereas we assessed IMT specifically in a zone of the CCA-IMT devoid of carotid plaques [7,8].

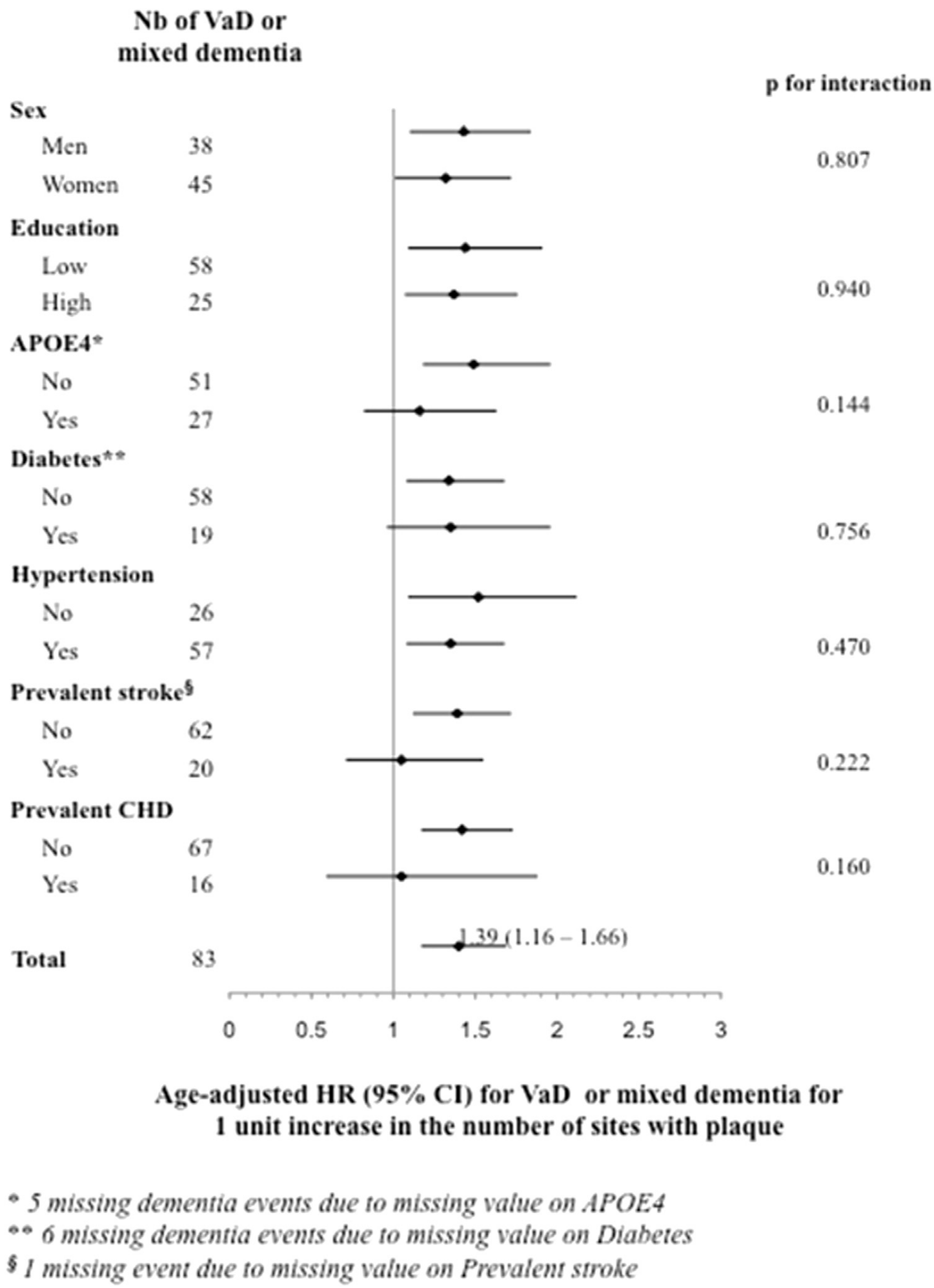

Fig. 3. Age-adjusted hazard ratios for vascular/mixed dementia (VaD) or mixed dementia for 1 unit increase in the number of sites with carotid plaques, stratified on dementia risk factors.

Furthermore, in these three studies, the association was significant only for the highest quintile of IMT (threshold effect), again probably reflecting the presence of carotid plaques. Therefore, it is likely that previously reported associations between IMT and dementia reflect an association with carotid plaques per se, which is in fact consistent with the results of our study. From an etiological perspective, it might be useful to study the respective predictive value of IMT per se and carotid plaques with dementia because although correlated IMT and plaques represent different stage and aspects of atherosclerosis [31–33]. These pathophysiological differences may translate into differences in prognostic power. In support of that, we have recently shown in the same cohort that carotid plaques but not CCA-IMT were predictive of incident coronary heart disease events [14]. Secondly, in most prior studies, the association was significant with AD while we found the relationship to be significant only for vascular or mixed dementia. We acknowledge that the distinction between pure AD and

VaD is a challenging issue. This is particularly true in late onset dementia, in which clinical and neuropathological patterns of AD and VaD generally coexist [34–36]. Current evidence supports the hypothesis of a continuous spectrum from pure AD to pure VaD rather than a clear distinction between the two phenotypes [35–37]. Interestingly, however, recent analyses from the Cardiovascular Health Study indicate that up to 30% of diagnosed AD using conventional clinical criteria were in fact (probable and possible) VaD when MRI criteria were taken into consideration [10]. As noted by the authors of this report, this has major implications not only for therapeutic but also for etiological research. Indeed, it suggests that prior evidence for an association between atherosclerosis and AD may in fact also be applicable to mixed dementia. It is likely that in our study, the absence of neuroimaging data for all dementia cases led to underestimate the incidence of VaD/mixed dementia, and thus the level of association between carotid plaques and VaD/mixed dementia, which however remained strong, robust and statistically significant. With this is mind it is therefore possible to reconcile our results with those of previously published studies regarding carotid atherosclerosis and dementia subtypes.

Several mechanisms may contribute to the association between carotid plaques and vascular or mixed dementia. Firstly, carotid atherosclerosis and dementia share common environmental and genetic risk factors, including age, diabetes, hypertension, and *APOE* ε4. However, in the present and other studies, association of carotid atherosclerosis with dementia was independent of these factors [38]. Secondly, the effect of stroke cannot be excluded as in the present study a 13% relative decrease (from 1.92 to 1.67) in the multivariate-adjusted association was seen after adjusting for stroke as a time-dependent variable. Adjusting for incident stroke may however be questionable as stroke is one key component of the diagnosis of VaD/mixed dementia, raising the possibility of over adjustment. Thirdly, residual confounding by prevalent cognitive impairment or by preexisting subclinical dementia is unlikely as our results were consistent after excluding prevalent cognitive impairment or early cases of dementia. MRI-defined brain infarcts and white matter hyperintensities may also be involved, given their known association with cognitive decline and incident dementia [39], and their recently reported relationship with carotid plaques [40]. Furthermore, regional cerebral hemodynamic alteration might confound the association between carotid plaques and vascular/mixed dementia [41,42], but such measures were not available at the time of enrolment in our cohort study. Also, the presence and degree of carotid stenosis have been related to cognitive impairment [43] and cognitive decline [3] and might therefore contribute to the association between carotid plaques and VaD/mixed dementia, but this measure was not present in our study. However, to date, there is no clear evidence for a longitudinal association between carotid stenosis and incident dementia [7].

Our results further suggest that carotid plaques may improve vascular/mixed dementia risk prediction. These are exploratory results because our model was not confronted to already existing dementia algorithms [44,45] and external validation was not performed.

This study suffers from limitations. Qualitative (echolucency or calcification) and quantitative (total plaque area) data on carotid plaques were not available, although their respective association with dementia remains to be investigated. Data on functional aspects of arteriosclerosis such as arterial stiffness were not available in our population. So far, however, arterial stiffness has been associated with cognitive decline [46,47] but not with incident dementia [48].

In summary, our results suggest that carotid plaques but not mean CCA-IMT measured in plaques free sites are independent predictors and may improve the prediction of incident VaD/mixed dementia in the elderly population.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2014.07.160.

RESEARCH IN CONTEXT

1. Systematic review: The few available studies on carotid atherosclerosis and incident dementia consistently reported associations with carotid intima-media thickness (cIMT), while observations related to carotid plaques (CP) remain inconclusive. In these previous studies cIMT measurements included plaques, precluding the differentiation of their respective contribution to dementia incidence. Furthermore, most prior studies have focused on Alzheimer disease whereas the association may differ according to the type of dementia.

2. Interpretation: We found a specific association between CP and vascular/mixed dementia (VaD), independent of major confounders, stroke, and competing risk by death. Furthermore, carotid plaques improved VaD risk prediction. Conversely, there was no association between plaque-free common carotid artery IMT (CCA-IMT) and dementia of any type.

3. Future directions: More studies are needed to elucidate the respective contribution of CP and plaque-free CCA-IMT to dementia and its subtypes. CP may be a new biomarker of interest in the emerging field of VaD risk prediction.

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