Traffic-Related Air Pollution as a Risk Factor for Dementia: No Clear Modifying Effects of *APOE* ε4 in the Betula Cohort

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Abstract. It is widely known that the apolipoprotein E (*APOE*) ε4 allele imposes a higher risk for Alzheimer's disease (AD). Recent evidence suggests that exposure to air pollution is also a risk factor for AD, and results from a few studies indicate that the effect of air pollution on cognitive function and dementia is stronger in *APOE* ε4 carriers than in non-carriers. Air pollution and interaction with *APOE* ε4 on AD risk thus merits further attention. We studied dementia incidence over a 15-year period from the longitudinal Betula study in Northern Sweden. As a marker for long-term exposure to traffic-related air pollution, we used modelled annual mean nitrogen oxide levels at the residential address of the participants at start of follow-up. Nitrogen oxide correlate well with fine particulate air pollution levels in the study area. We had full data on air pollution, incidence of AD and vascular dementia (VaD), *APOE* ε4 carrier status, and relevant confounding factors for 1,567 participants. As expected, air pollution was rather clearly associated with dementia incidence. However, there was no evidence for a modifying effect by *APOE* ε4 on the association (p-value for interaction > 0.30 for both total dementia (AD+VaD) and AD). The results from this study do not imply that adverse effects of air pollution on dementia incidence is limited to, or stronger in, *APOE* ε4 carriers than in the total population.

Keywords: Air pollution, Alzheimer's disease, apolipoprotein E, dementia

INTRODUCTION

Dementia is a huge global health problem. With an aging population, and the fact that there are currently no disease modifying interventions available, the prevalence of dementia can be expected to triple between 2010 and 2050 [1]. The etiology is not fully understood but, on a population level, environmental factors may be a contributing factor to the disease [2].

Alzheimer's disease (AD)-like pathological findings linked to air pollution was first reported in a pilot study of children and dogs from Mexico City [3]. Air pollution is now considered a plausible risk factor for cognitive decline and other dementia-related outcomes, as stated in a literature review from 2016 [4].

Our group has previously reported a relationship between long-term exposure to nitrogen oxides (NO_x) and incident dementia in the Betula study from Northern Sweden [5], in a study area where air pollution levels are rather low in an international perspective. The adjusted hazard ratio for dementia was 1.66 (95% Confidence Interval (CI); 1.04–2.65),

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associated with the highest quartile of NO_x compared to the lowest quartile. The population attributable fraction was 16%, implying that air pollution may be a significant factor for overall risk for dementia in this low exposed population. In the same population, we subsequently showed that particles from domestic wood burning and vehicle exhaust were independently associated with dementia [6], and that traffic-related noise did not confound the association between air pollution and dementia [7].

Apolipoprotein E (*APOE*) *ε*4 is a known risk factor for AD. However, *APOE* *ε*4 and other common genetic loci, identified in genome-wide-association-studies, account for less than 50% of heritable AD risk. Gene-gene interactions, rare high penetrant variants, epigenetic factors, or exogenous factors such as lifestyle is suggested to play a role in explaining the remaining heritability [8].

Given that air pollution may be an important environmental risk factor for cognitive decline and dementia, the interactions with *APOE* *ε*4 and other genes merits attention. In a German study, the association between traffic exposure and cognitive impairment in the visuospatial domain was evident only in *APOE* *ε*4 carriers [9], and in a US study, the link between all-cause dementia and air pollution was stronger in *APOE* *ε*4/4 carriers than in non-carriers [10]. There is thus some scientific support for a modifying effect of the *APOE* *ε*4 allele but the number of studies on this topic are still few.

The severe impact of dementia on individuals and society makes it important from a public health perspective to investigate potential modifiable risk factors, and to identify susceptible groups in the population. The aim of the present study was to investigate if the *APOE* *ε*4 allele modifies the association between air pollution and dementia previously observed in the Betula study [5].

MATERIALS AND METHODS

Study sample

We used the same study sample and similar methods as in previous studies on air pollution and dementia in the Betula study [5–7], a population-based longitudinal study on memory, health, and aging [11], this time stratifying on *APOE* *ε*4 allele carrier status.

The Betula study invites randomly selected study subjects from the population of approximately 125,000 inhabitants in Umeå municipality (situ-

ated in Västerbotten County in northern Sweden). The Betula study started with a first test wave in 1988–1990 (T1) where a first sample (S1) of 1000 participants was tested. Subsequent test waves (T2-T6) have taken place every five years, where new samples have been added and participants from previous samples have been subjected to follow-ups. In each test wave, the participants were examined on two occasions, about one week apart, with a health examination, and a test of cognitive functioning. The baseline of the present study is the second test wave T2 (1993–1995), where sample 3 (S3) was introduced, and sample 1 (S1) was tested for the second time. The fifth test wave T5 (2008 – 2010) was the endpoint of our study period. Participants who were younger than 55 at baseline were excluded, along with participants for whom pollution data was not available. Moreover, participants with other subtypes of dementia that was not vascular dementia (VaD) or dementia of the Alzheimer's type (AD) were excluded along with 11 participants who received a dementia diagnosis after the study endpoint (2010). The final sample consisted of 1,567 participants from cohorts S1 and S3, aged 55 to 85 years (mean 69) at baseline (Fig. 1, Table 1). Participants were followed until the study endpoint or time of dementia onset/death/lost-to-follow-up depending on what event came first. In the analysis, we investigated AD both separately and clustered with VaD (total dementia).

Dementia diagnosis assessments

A detailed description of the diagnostic procedures for dementia in the Betula project have been described elsewhere [12, 13]. In short, diagnostic evaluations were conducted every five years adjacent to each test wave (T1-T6). Relevant medical assessments, obtained from medical records principally from the primary care, neurology, medicine, and geriatric clinics were considered in the assessment of determining possible dementia. That is, general medical and social status, clinical symptoms, medication, neurological diseases, and results from available neuroradiological examinations such as computer tomography, single photon emission computed tomography, and magnetic resonance tomography. For those participating in the health and cognitive test assessments, attention was also paid to low test results/performance on cognitive tests and the Mini-Mental-State Examination (MMSE), the test staff's observations as well as the study participants

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                    ┌─────────────────────────┐
                    │      At risk at T1       │
                    │  S1 baseline (n = 1000)  │
                    └─────────────────────────┘
                                 │
                                 │        ┌──────────────────────────────────────┐
                                 │        │  EXCLUDED (n=155)                    │
                                 │        │  ┌────────────────────────────────┐  │
                                 ├────────┤  │ Dementia disorder (n = 33)     │  │
                                 │        │  │ Deceased (n = 37; whereof n = 2│  │
                                 │        │  │ with a dementia disorder)      │  │
                                 │        │  │ Lost to follow-up (n = 11)     │  │
                                 │        │  │ Termination (n = 76)           │  │
                                 │        │  └────────────────────────────────┘  │
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CURRENT STUDY

At risk at T2
S1 returnees (n = 845)
S2 baseline (n = 995)
S3 baseline (n = 963)
(n = 2803)

< 55 years of age at T2
(n = 973)

At risk at T2 ≥ 55 y
(n=1830)

Data not available on exposure
or potential confounders
(n = 263)

Follow up through T5
(n = 1567); of which (n = 275)
were given a dementia diagnosis
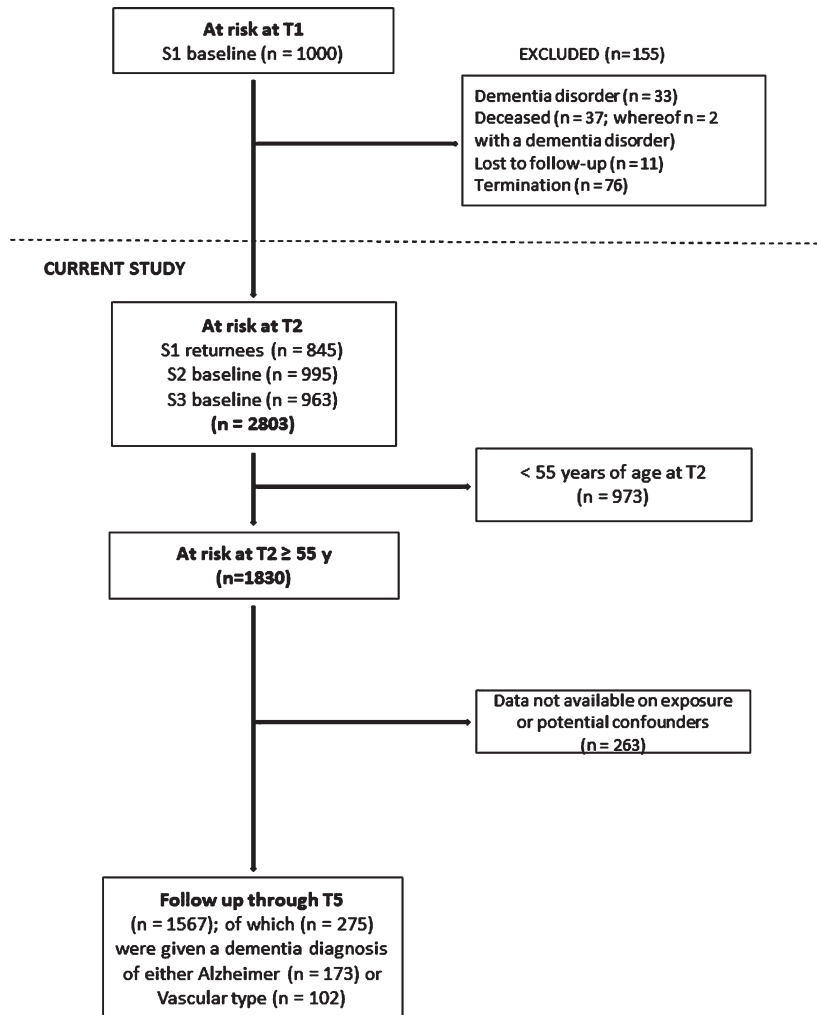of either Alzheimer (n = 173) or
Vascular type (n = 102)

Fig. 1. Flow-chart from study inclusion to end of follow-up.

subjective perception of memory failure and/or concern of dementia. The diagnostic evaluation was coordinated by the same senior research geropsychiatrist (co-author R.A.) throughout the study period. Diagnosis was set in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria [14].

APOE genotyping

Being a $\varepsilon 4$ carrier of *APOE* adds substantially to the risk of developing AD [15]. The participants of Betula were therefore genotyped with respect to *APOE*, and details on the methods for the genotyping is described by Nilsson and colleagues [16]. The binary variable for the analysis of the present study was defined as the presence of at least one $\varepsilon 4$ allele or not.

Potential confounders

Potential confounders were defined according to the participant's status at baseline (T2). In addition to age, there is moderate or strong evidence for associations between genetic, vascular, and psychosocial factors and the risk for dementia [17]. We considered several social and lifestyle variables as potential confounding variables. Education, an indicator of socioeconomic status, was categorized into elementary school, upper secondary school, and university level education depending on the highest achieved education. Alcohol consumption was classified into

Table 1
Distribution of dementia and population characteristics at baseline according to quartiles of NOx exposure in complete-case cohort (non-complete data is available in a previous publication) [5]

Characteristic	NO$_x$ Q1 4.8–9 µg/m^3 N (%)	NO$_x$ Q2 >9–17 µg/m^3 N (%)	NO$_x$ Q3 >17–26 µg/m^3 N (%)	NO$_x$ Q4 >26 µg/m^3 N (%)	All N (%)
All observations	379	410	397	281	1567
Vascular dementia *or* Dementia of the Alzheimer's type	50 (13)	59 (14)	82 (21)	84 (29)	275 (18)
Dementia of the Alzheimer's type	30 (60)	39 (66)	52 (63)	52 (62)	173 (63)
Sex					
Men	177 (47)	176 (43)	174 (44)	160 (42)	687 (44)
Women	292 (53)	234 (57)	223 (56)	221 (58)	880 (56)
Age					
55	75 (20)	77 (19)	59 (15)	49 (13)	260 (17)
60	54 (14)	83 (20)	63 (16)	46 (12)	246 (16)
65	60 (16)	82 (20)	67 (17)	46 (12)	255 (16)
70	59 (16)	63 (15)	63 (16)	62 (16)	247 (16)
75	63 (17)	56 (14)	65 (16)	57 (15)	241 (15)
80	46 (12)	37 (9)	54 (14)	78 (20)	215 (14)
85	22 (6)	12 (3)	26 (7)	43 (11)	103 (7)
Education					
Compulsory	318 (84)	311 (76)	301 (76)	304(80)	1234 (79)
High school	30 (8)	42 (10)	29 (7)	18(5)	119 (8)
University	31 (8)	57 (14)	67 (17)	59(15)	214 (14)
Physical activity					
Never	77 (20)	75 (18)	90 (23)	114 (30)	356 (23)
Occasionally	48 (13)	56 (14)	45 (11)	37 (10)	186 (12)
Few times per month	37 (10)	41 (10)	39 (10)	48 (13)	165 (11)
Weekly	134 (35)	146 (36)	141 (36)	109 (29)	530 (34)
Daily	83 (22)	92 (22)	82 (21)	73 (19)	330 (21)
Smoking					
Non-smoker	208 (55)	234 (57)	211 (53)	212 (56)	865 (55)
Smoker	53 (14)	44 (11)	54 (14)	58 (13)	199 (13)
Ex-smoker	118 (31)	132 (32)	132 (33)	121 (32)	503 (32)
Alcohol					
Yes	251 (66)	286 (70)	282 (71)	279 (73)	1098 (70)
No, never	110 (29)	104 (25)	90 (23)	88 (23)	392 (25)
No, have quit	18 (5)	20 (5)	25 (6)	14 (4)	77 (5)
BMI[a]					
Overweight	261 (69)	287(70)	257(65)	250(66)	1055(67)
WHR[b]					
>Recommended	149 (39)	168(41)	161(41)	173(45)	651 (42)
*APOE ε*4 carrier	100(27)	106(26)	116(29)	124(33)	446(29)

[a]BMI (body mass index). BMI cut-off between normal weight and overweight were 23.8 for women and 25.0 for men. [b]WHR (Waist-hip-ratio). Cut-off of 0.8 for women and 1.0 for men.

present consumers, previous consumers, and non-consumers at baseline. Smoking was categorized into present smokers, previous smokers, and non-smokers at baseline. Body mass index (BMI, kg/m^2) was in a previous study associated with inflammatory effects associated with traffic pollution [18], and BMI was in another study associated with cognitive decline in women in the Betula cohort [19]. We therefore chose to include BMI as a potential confounding variable in the statistical analysis. Following the National Health Institute standards from 1985 [20], the BMI cut-offs between normal weight and overweight were 23.8 for women and 25.0 for men. We also considered waist-hip-ratio (WHR) as a potential confounding variable

with a cutoff of > 0.8 for women and > 1.0 for men [21]. Physical activity was assessed from interview data based on the participants' answer to the following question: "Did you during the last three months do any sports, exercises or strolling". The following alternatives were given: "never", "occasionally", "a few times per month", "weekly", and "daily" and used as a five-category variable in the analyses. Diabetes [22], stroke [23], and hypertension [24] are all potential risk factors for dementia, and may be intermediate factors on the causal pathway between air pollution exposure and dementia. Based on our previous results we decided not to consider them as potential confounders in the present study [5].

Air pollution exposure

We used baseline annual mean levels of nitrogen oxides (NO_x), as a marker of long-term exposure to traffic-related air pollution, similar to what we have done before in the Betula study [5]. NO_x is created by combustion and is often used as a marker for traffic-related air pollution in our study area since NO_x is highly correlated to fine particulate matter from vehicle exhaust [6]. We used a Land Use Regression (LUR)-model to estimate the concentration at the residence of each study person. To create the LUR-model, NO_x (and NO_2) were measured at 36 sites throughout the city of Umeå. The measurements took place during four weeks between November 2009 and June 2010. The LUR model explained 76% (adjusted $r^2 = 0.76$) of the measured NO_x variation and the spatial resolution was $50\,m \times 50\,m$. The LUR model is well-validated and has for example been used in the Umeå part of the ESCAPE project [25–27]. The NO_x concentration estimates for 2009-2010, were divided into quartiles. Annual mean exposure of NO_x exposure was $<9\,\mu g/m^3$ for the lowest quartile, 19 to $<17\,\mu g/m^3$ for the second quartile, $17\,\mu g/m^3$ to $<26\,\mu g/m^3$ for the third quartile, and $\geq 26\,\mu g/m^3$ for the fourth (highest) quartile. Using data from the Swedish population register, the address of residency for each participant at baseline (1993–1995) was geocoded. This way every participant was assigned to a square in the grid. The NOx-concentration at the grid square of the participants' baseline residence was used as marker of exposure.

Statistical methods

We used Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for dementia incidence (AD+VaD or AD only). Participants were censored at the end of the study period (2010), or the time of death, dementia onset, or loss to follow-up (either due to moving outside the catchment area or did not consent for evaluation of the medical records). We used complete-case analysis, where all subjects included have non-missing values on outcome (dementia status), exposure (baseline NOx), confounder(s), and APOE ε4. The final models were adjusted only for baseline age, as a categorical variable since all other potential confounders did not have any substantial (<10%) influence on the estimated HRs. Data on exposure, incidence of AD and VaD, APOE ε4 status, as well as the relevant confounding factors were obtained for 1567

participants. Education, physical activity, smoking, sex, BMI (body mass index), WHR (waist-hip-ratio), and alcohol consumption were additionally adjusted for, simultaneously, in supplementary analysis. Data were further stratified on APOE ε4 (carrier of at least one allele or none). In the non-stratified analysis, we adjusted for APOE ε4 (as the influence on the estimates was > 10%). We also tested effect modification statistically by including interaction terms of NO_x (linear variable) and *APOE* ε4 into the models. We also ran all analyses separately for men and women.

The statistical analyses were carried out with SAS version 9.4. The research was done in accordance with the ethical standards of the Helsinki Declaration of 1975. The study was approved by the regional ethical review board in Umeå Dnr: 2012-12-31M.

RESULTS

Descriptive data of the variables in association with residential air pollution (NO_x) concentrations are shown in Table 1. The presence of AD and VaD were higher in the highest quartile of NO_x than in the lowest quartile. Table 1 also display differences with respect to age distributions and *APOE* ε4 frequency across exposure quartiles. The other covariates were quite evenly distributed across exposure quartiles.

Comparing the fourth quartile of annual exposure to NO_x to the first quartile, data indicate an association between total dementia (AD+VaD) and residential concentrations of annual NO_x (Table 2). We found no clear evidence for effect modification by *APOE* ε4 on this association. For example, the HR for total dementia in the fourth quartile of NOx compared to the first quartile was 1.40 (0.90–2.17) for *APOE* ε4 non-carriers and 1.44 (0.84–2.47) for *APOE* ε4 carriers. The *p*-value for effect modification by *APOE* ε4 and the linear NO_x-variable was > 0.3 for total dementia. The pattern was similar when analyzing only AD cases (excluding VaD). The HRs for AD stratified by *APOE* ε4 were 1.72 (0.94–3.15) for non-carriers and 1.41 (0.75–2.66) for carriers. The point estimates thus suggest a somewhat stronger association in *APOE* ε4 non-carriers than in *APOE* ε4 carriers. However, the *p*-value for interaction was > 0.30 also here.

In the analyses that were not stratified for *APOE* ε4, the HR for AD in association with the fourth compared to the first quartile was 1.53 (95% CI: 0.99–2.36), compared to the AD+VaD HR of 1.41 (1.01–1.98). Furthermore, sex did not modify the

Table 2
Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for total dementia (Vascular dementia *or* Dementia of the Alzheimer's type) and for Dementia of the Alzheimer's type in association with baseline annual NO_x concentration from Cox proportional hazards models. Number of cases (n) and total number of participants (N), stratified by *APOE ε*4

| | | Whole cohort | | | APOE ε4 | | | | | |
| | | | | | No | | | Yes | | |
	NO_x	n (N)	HR[1]	95% CI	n (N)	HR[2]	95% CI	n (N)	HR[2]	95% CI
Vascular dementia *or*	Quartile 1[3]	55 (416)	1		35 (304)	1		20 (112)	1	
Dementia of the	Quartile 2[3]	65 (443)	1.11	0.77–1.59	32 (332)	0.91	0.56–1.47	33 (111)	1.44	0.82–2.53
Alzheimer's type	Quartile 3[3]	90 (429)	1.52	1.08–2.12	54 (303)	1.48	0.97–2.27	36 (126)	1.49	0.86–2.59
	Quartile 4[3]	92 (421)	1.41	1.01–1.98	48 (287)	1.40	0.90–2.17	44 (134)	1.44	0.84–2.47
	Linear[4]	1.03 (0.97–1.10)				1.03	0.96–1.12		1.02	0.92–1.14
Dementia of the	Quartile 1[3]	32 (393)	1		17 (286)	1		15 (107)	1	
Alzheimer's type	Quartile 2[3]	43 (421)	1.25	0.79–1.98	17 (317)	1.04	0.53–2.05	26 (104)	1.51	0.80–2.87
	Quartile 3[3]	59 (398)	1.72	1.12–2.65	31 (280)	1.79	0.99–3.24	28 (118)	1.61	0.86–3.01
	Quartile 4[3]	57 (386)	1.53	0.99–2.36	28 (267)	1.72	0.94–3.15	29 (119)	1.41	0.75–2.66
	Linear[4]	1.04	0.96–1.13			1.06	0.96–1.17		1.01	0.89–1.14

[1]Models adjusted for baseline age (categorical variable) and *APOE ε*4. [2]Models adjusted for baseline age (categorical variable). Complete-case analysis, where subjects included all have non-missing values on outcome (dementia status), exposure (baseline NOx), age and *APOE ε*4. [3]Quartile 1 : 4.8-9 µg/m³, Quartile 2: >9–17 µg/m³, Quartile 3: >17–26 µg/m³, Quartile 4: >26 µg/m³. [4]Per 10 µg/m³ increase in NOx.

effect (data not shown). Additional analyses show that the results were only marginally affected by choice of confounding variables (Supplementary Table 1).

DISCUSSION

There was (an expected) association between air pollution and dementia incidence; however, there was no clear support for a modifying effect of the *APOE ε*4 allele. Our findings suggest that adverse effects of air pollution on dementia incidence is not limited to, or stronger in, *APOE ε*4 carriers than in the total population, at least not in our study population.

The results are somewhat in contrast with two previous studies where the association between long-term exposure and cognitive impairment/risk for all-cause dementia was stronger in *APOE ε*4 carriers than in non-carriers [9, 10]. In the first study, from Germany, different markers of air pollution were cross-sectionally associated with cognitive impairment in the visuospatial domain, and an association was observed only in participants carrying the *APOE ε*4 allele. The other study, from the US, showed that residing in places with high levels of $PM_{2.5}$ increased the risks for all-cause dementia and that the effects were stronger in *APOE ε*4/4 carriers [10]. However, our study differs from these two studies in several important respects. For example, our study was on both sexes whereas in the other two studies only women were included. We do not consider this a plausible explanation for the differences in findings,

however, since our results were similar for men and women in stratified analyses. Furthermore, the outcomes differed; especially with the German study where the outcome was cognitive impairment in the visuospatial domain. The outcome in the US study was all-cause dementia, whereas our data allowed for separate analysis of VaD and AD, and we excluded other subtypes of dementia from the analysis. In our data, VaD and AD were the dominating causes of dementia (around 90%), and the results for VaD and AD were similar, but we do not know the distribution of dementia types in the US study. Another major difference between the present study and the two other studies, which may be a possible explanation for the differences in findings, is that the levels of air pollution are substantially lower in our study than in the other two studies. In the study from the US, participants with a 3-year average exposure were classified as 'high' if exceeding $PM_{2.5}$ (>12 µgm⁻³). In the German study, the mean annual $PM_{2.5}$ levels were 33.3 µgm⁻³ at baseline (1995) and 17.4 µgm⁻³ in 2007. As a comparison, in Umeå municipality, the annual mean $PM_{2.5}$-levels have been below 8 µgm⁻³ even in the most polluted street, at least since 2007 when the measurements started. We cannot study effect modification of *APOE ε*4 at higher levels of air pollution in our study area. Thus, we cannot rule out that *APOE ε*4 would modify the association between air pollution and dementia at higher levels of air pollution in our study population.

There are both strengths and weaknesses of the present study. The present study has a major strength in its longitudinal design and the high-quality data

on a well-characterized study population represented by both sexes and a certain variation in age (55–85 years). For example, the high validity of diagnosis made it possible to stratify data on type of dementia and the rich dataset made it possible to account for a number of potential confounders. The exposure assessment model (of NO_x) had a high spatial resolution and validity, which also is a major strength. We have previously observed that the association between NO_x and dementia incidence in the Betula study can be generalized to that between dementia and $PM_{2.5}$ from vehicle exhaust [6].

Exposure misclassification must be discussed in all epidemiological studies on long-term exposure to air pollution. We used exposure data from 2009 and assumed that contrasts in exposure would be similar back in time over the follow-up period (the first recruitments took place in 1988–1990). Furthermore, exposure was modeled at the home address and other sources of exposure such as exposure at work or indoor exposure were not considered. Although these are obvious sources of exposure misclassification in many epidemiological studies of air pollution health effects, for example in the ESCAPE project [25, 26], furthermore we know from a previous study in the study area that residential mobility does not seem to cause major differential misclassification [28]. Also, exposure misclassification would have to differ between *APOE ε4* carriers and non-carriers to cause bias in the present study. Exposure misclassification may thus have reduced precision in our estimates, but the point estimates do not suggest that the association between air pollution and dementia would be stronger in *APOE ε4* carriers than in non-carriers. Therefore, we do not consider low precision to be a plausible explanation for the (lack of) findings in the present study.

It should also be mentioned that the results are to some extent inconsistent. For example, we only saw a statistically significant association in the higher quartiles 3 and 4 with AD and VaD combined, and only in the third quartile for AD only. Furthermore, the effect estimates were slightly lower in quartile 3 than in quartile 4 (Table 2), which could possibly depend on other sources of exposure, such as exposure to wood-smoke from small-scale residential heating.

We used annual levels of NO_x at the residential address as a marker for long-term exposure to air pollution. This is generally a good marker for traffic-related air pollution, but other sources of air pollution could have yielded different results. In the studied area, the median level of annual NOx was 17 μg/m^3,

which is considered rather low in an international perspective. It cannot be ruled out that higher levels of air pollution would have impact on the results. Our results may therefore not be generalizable across settings with different levels of air pollution. Similarly, the generalizability may depend on the *APOE ε4* allele distribution, which is known to vary across populations and be particularly high in Northern Scandinavian populations [29].

In conclusion, we observed no clear evidence for effect modification by *APOE ε4* on the association between exposure to air pollution and dementia incidence. Our results are in contrast with those of two pioneering studies, where the results suggest a stronger effect of air pollution on cognitive impairment/all-cause dementia in *APOE ε4* carriers than in non-carriers. The role of *APOE ε4* in the association between exposure to air pollution and cognitive impairment/dementia thus needs to be further investigated. Our study was undertaken in a low exposure area, and the possibility that *APOE ε4* may modify the association between air pollution and dementia only at higher levels of air pollution should be addressed in future studies.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-181037.

REFERENCES

[1] Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* **80**, 1778-1783.

[2] Killin LO, Starr JM, Shiue IJ, Russ TC (2016) Environmental risk factors for dementia: A systematic review. *BMC Geriatr* **16**, 175.

[3] Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, Chapman S, Valencia-Salazar G, Jewells V, Maronpot RR (2008) Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. *Brain Cogn* **68**, 117-127.

[4] Power MC, Adar SD, Yanosky JD, Weuve J (2016) Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology* **56**, 235-253.

[5] Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, Nordin S, Adolfsson R, Nilsson L-G (2015) Traffic-related air pollution and dementia incidence in Northern Sweden: A longitudinal study. *Environ Health Perspect* **124**, 306-312.

[6] Oudin A, Segersson D, Adolfsson R, Forsberg B (2018) Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PloS One* **13**, e0198283.

[7] Andersson J, Oudin A, Sundström A, Forsberg B, Adolfsson R, Nordin M (2018) Road traffic noise, air pollution, and risk of dementia–results from the Betula project. *Environ Res* **166**, 334-339.

[8] Farrer LA (2015) Expanding the genomic roadmap of Alzheimer's disease. *Lancet Neurol* **14**, 783-785.

[9] Schikowski T, Vossoughi M, Vierkötter A, Schulte T, Teichert T, Sugiri D, Fehsel K, Tzivian L, Bae I-s, Ranft U (2015) Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. *Environ Res* **142**, 10-16.

[10] Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, Serre ML, Vizuete W, Sioutas C, Morgan TE (2017) Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Transl Psychiatry* **7**, e1022.

[11] Nilsson L-G, BÄCkman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, Karlsson S, Widing M, Winblad B (1997) The Betula prospective cohort study: Memory, health, and aging. *Aging Neuropsychol Cogn* **4**, 1-32.

[12] Boraxbekk C-J, Lundquist A, Nordin A, Nyberg L, Nilsson L-G, Adolfsson R (2015) Free recall episodic memory performance predicts dementia ten years prior to clinical diagnosis: Findings from the Betula longitudinal study. *Dement Geriatr Cogn Disord Extra* **5**, 191-202.

[13] Rönnlund M, Sundström A, Adolfsson R, Nilsson L-G (2015) Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: Evidence from the Betula prospective cohort study. *Alzheimers Dement* **11**, 1385-1392.

[14] American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Publisher, Washington, DC.

[15] Anttila T, Helkala E-L, Kivipelto M, Hallikainen M, Alhainen K, Heinonen H, Mannermaa A, Tuomilehto J, Soininen H, Nissinen A (2002) Midlife income, occupation, APOE status, and dementia: A population-based study. *Neurology* **59**, 887-893.

[16] Nilsson L-G, Adolfsson R, Bäckman L, Cruts M, Nyberg L, Small BJ, Van Broeckoven C (2006) The influence of APOE status on episodic and semantic memory: Data from a population-based study. *Neuropsychology* **20**, 645.

[17] Fratiglioni L, Von Strauss E, Qiu C (2008) Epidemiology of the dementias of old age. In *The Oxford Textbook of Old Age Psychiatry*, Jacoby R, Oppenheimer C, Dening T, Thomas A, eds. *Oxford University Press*, pp. 391-406.

[18] Zeka A, Zanobetti A, Schwartz J (2006) Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol* **163**, 849-859.

[19] Thilers PP, MacDonald SW, Nilsson L-G, Herlitz A (2010) Accelerated postmenopausal cognitive decline is restricted to women with normal BMI: Longitudinal evidence from the Betula project. *Psychoneuroendocrinology* **35**, 516-524.

[20] Van Itallie TB (1985) Health implications of overweight and obesity in the United States. *Ann Intern Med* **103**, 983-988.

[21] Nilsson LG, Nilsson E (2009) Overweight and cognition. *Scand J Psychol* **50**, 660-667.

[22] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P (2006) Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurol* **5**, 64-74.

[23] Savva GM, Stephan BC, Alzheimer's Society Vascular Dementia Systematic Review Group (2010) Epidemiological studies of the effect of stroke on incident dementia: A systematic review. *Stroke* **41**, e41-e46.

[24] Sharp SI, Aarsland D, Day S, Sønnesyn H, Alzheimer's Society Vascular Dementia Systematic Review Group, Ballard C (2011) Hypertension is a potential risk factor for vascular dementia: Systematic review. *Int J Geriatr Psychiatry* **26**, 661-669.

[25] Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, Wolf K, Samoli E, Fischer P, Nieuwenhuijsen M (2014) Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* **383**, 785-795.

[26] Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Xun WW, Katsouyanni K, Dimakopoulou K, Brunekreef B, Weinmayr G, Hoffmann B (2014) Long-term exposure to air pollution and cardiovascular mortality: An analysis of 22 European cohorts. *Epidemiology* **25**, 368-378.

[27] Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, Hoffmann B, Fischer P, Nieuwenhuijsen MJ, Brunekreef B (2013) Air pollution and lung cancer incidence in 17 European cohorts: Prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* **14**, 813-822.

[28] Oudin A, Forsberg B, Strömgren M, Beelen R, Modig L (2012) Impact of residential mobility on exposure assessment in longitudinal air pollution studies: A sensitivity analysis within the ESCAPE project. *ScientificWorldJournal* **2012**, 125818.

[29] Kern S, Mehlig K, Kern J, Zetterberg H, Thelle D, Skoog I, Lissner L, Blennow K, Börjesson-Hanson A (2015) The distribution of apolipoprotein E genotype over the adult lifespan and in relation to country of birth. *Am J Epidemiol* **181**, 214-217.