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Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study

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Short running title: Air pollution and incident dementia

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Abstract

Background: Exposure to ambient air pollution is suspected to cause cognitive effects, but a prospective cohort is needed to study exposure to air pollution at the home address and the incidence of dementia.

Objectives: We aimed to assess the association between long-term exposure to traffic-related air pollution and dementia incidence in a major city in northern Sweden.

Methods: Data on dementia incidence over a 15-year period were obtained from the longitudinal Betula study. Traffic air pollution exposure was assessed with a Land Use Regression Model with a spatial resolution of 50 m x 50 m. Annual mean nitrogen oxide levels at the residential address of the participants at baseline (the start of follow-up) was used as a marker for long-term exposure to air pollution.

Results: Out of 1806 participants at baseline, 191 were diagnosed with Alzheimer's disease during follow-up, and 111 were diagnosed with vascular dementia. Participants in the highest exposure group were more likely to be diagnosed with dementia (Alzheimer's disease or vascular dementia), with a Hazard Ratio (HR) of 1.43 (95% Confidence Interval (CI): 0.998, 2.05 for the highest versus lowest quartile). The estimates were similar for Alzheimer's disease (HR 1.38) and vascular dementia (HR 1.47). The HR for dementia associated for the third quartile versus the lowest quartile was 1.48 (95% CI: 1.03, 2.11). A sub-analysis that excluded a younger sample that had been re-tested after only 5 years of follow-up suggested stronger associations with exposure than in the full cohort (HR = 1.71; 95% CI: 1.08, 2.73 for the highest versus lowest quartile).

Conclusions: If the associations we observed are causal, then air pollution from traffic might be an important risk factor for vascular dementia and Alzheimer's disease.

Introduction

Cardiopulmonary effects of air pollutants are well established (Rückerl et al. 2011), and there is a growing body of evidence that air pollution causes neuropathological effects and central nervous system disease (Block and Calderón-Garcidueñas 2009; Guxens and Sunyer 2012; Rückerl et al. 2011; Genc et al. 2012). Dementia is a neuropathological disease that is relevant in this context (Weuve 2014). Dementia takes a heavy toll on the patient, the patient's close relatives, and society as a whole. Within the next 40 years, the prevalence of Alzheimer's disease is expected to triple unless preventive measures are developed (Hebert et al. 2013).

The number of studies suggesting traffic pollution to be associated with cognitive function in adults is increasing. In a cross-sectional study of 399 elderly women in Germany, the exposure to traffic-related particles was estimated by the distance to the closest busy road, and consistent associations between traffic-related particle exposure and mild cognitive impairment were found (Ranft et al. 2009). In another cross-sectional study of 1,764 adults in the US, ozone levels in the home county were associated with inferior performance on neurobehavioral tests (Chen and Schwartz 2009). In a third cross-sectional study of 680 elderly men in the US, long-term exposure to traffic-related air pollution was associated with lower Mini Mental State Examination (MMSE) scores as well as with lower global cognitive function (Power et al. 2011). A similar study of 765 community-dwelling seniors showed residential proximity to a major roadway to be associated with poorer performance on cognitive tests, but weaker associations with modeled outdoor levels of black carbon (Wellenius et al. 2012). In the Nurses' Health Study Cognitive Cohort, which included 19,409 elderly women in the US, long-term exposure to particles preceding baseline cognitive testing was assessed (Weuve et al. 2012a). The main

outcome measure was cognition via validated telephone assessments at approximately 2-year intervals. Long-term exposure was found to be associated with faster cognitive decline, and a 10-$\mu g/m^3$ increment in long-term particulate matter (both $PM_{2.5}$ and $PM_{2.5-10}$) exposure was cognitively equivalent to aging by approximately 2 years. A cross-sectional study from the Los Angeles Basin examined the associations between modeled air pollution levels at home and cognitive function in middle-aged and older persons, but this found no significant association between NO_2 levels and cognitive functions (Gatto et al 2014). The results from a study from Taiwan with data from a national health insurance database of persons aged 50 or older suggested that concentrations of NO_2 and CO from the measuring station (out of 74 in the country) closest to the health clinic most frequently visited, was associated with a higher risk of dementia (Chang et al. 2014). In the Whitehall II longitudinal cohort study, PM exposure was modeled according to postcode for the years 2003–2009. Cross-sectional associations were observed between PM exposure and reasoning and memory, but not with verbal fluency. PM was also associated with decline over time in cognition. However, the study provided no evidence for differential associations depending on particle source (Tonne et al. 2014). Results from two large cross-sectional studies in older adults in the US suggested associations between both fine particles ($PM_{2.5}$) and cognitive function—primarily episodic memory (Ailshire and Crimmins 2014)—and an association between $PM_{2.5}$ and error rates in cognitive assessments (Ailshire and Clarke 2014). These studies used a neighborhood-based measure of air pollution to represent the regional or urban background levels, not accounting for variability related to local sources of pollutants.

There might also be short-term effects of air pollution on the brain that are related to the last few hours and days of exposure, and these might contribute to, or confound, associations with long-term exposure. As early as 1970, it was reported that mental efficiency decreased when adults tested in London were breathing air pumped from the street compared to clean air (Lewis et al. 1970). A recent study found that short-term exposure to ambient fine PM was associated with lower resting cerebrovascular flow velocity and higher resting cerebrovascular resistance in community-dwelling elderly participants (Wellenius et al. 2013). In the present study, we investigated the relationship between exposure to air pollution and dementia incidence in Umeå, Sweden, by using data from a prospective cohort study.

Methods

Participants

Longitudinal data from the Betula study, described in detail elsewhere (Nilsson et al. 1997; Nilsson et al. 2004) were combined with individual traffic pollution data. The Betula study was initially motivated by the need to explore various aspects of health and cognitive aging, including early signs and potential risk factors of cognitive decline and dementia in adulthood and late life. The Betula study has been carried out with a narrow age cohort design. At the first data collection in 1988–90 (T1), an equal number of men and women, distributed in ten age cohorts (all 35, 40, 45, …80 years), were randomly sampled from the general population in the municipality of Umeå for a final sample of 1,000 participants. On the first follow-up occasion in 1993–95 (T2), two new cohorts were included; sample 2 (S2; n = 995), with the same age and sex distribution as S1 at T1, and sample 3 (S3; n = 963), with the same age and sex distribution as S1 at the time of T2 (all 40, 45, 50, …85 years). Data collections have, to date, been

conducted six times with five-year intervals between the follow-ups (T1 1988–1990, T2 1993–1995, T3 1998–2000, T4 2003–2005, T5 2008–2010 and T6 2013-2014). S1 participants have been tested up to six times (T1-T6) and S3 participants have been tested up to five times (T2–T5). For S2 participants, data were collected at T2 and T3. At each test point (T1-T6), the investigation was split on two occasions where a health survey constituted the first examination and a cognitive evaluation the second. Between the first and the second testing the study participants filled out a fairly extensive battery of self-assessment forms covering various socioeconomic-, health-, biological- aging- and personality traits. The health survey consisted of an health interview, health questionnaires and blood sampling (Hemoglobin, blood glucose, sedimentation rate, urine samples and blood samples for research purpose) as well as investigation of blood pressure, pulse, height, weight, waist-hip-ratio (WHR), grip strength, sight, hearing and odour identification. Research nurses or nursing assistants conducted the health survey according to a specified protocol. In the event of pathological findings the study physician (RA) was consulted and if deemed necessary, a referral were sent to the primary health care for further follow-up.

The cognitive evaluations were conducted by persons with basic training in psychology and especially trained to carry out the Betula cognitive test battery. The battery of cognitive tests is extensive and composed to cover a wide range of cognitive processes and memory systems for the evaluation of how normal memory changes with age. It has also the power to identify and evaluate disease-related cognitive decline. The cognitive test battery includes tasks that assess episodic memory, semantic memory, working memory, perceptual representation system, prospective memory, visual attention, processing speed, problem solving, decision making.

MMSE and a questionnaire assessing subjective experiences of memory function and the subjective experience of memory loss are also included.

All participants in the Betula study gave informed consent, and the study was approved by the Regional Ethical Review Board at Umeå University with DNR: 2012-12-31M.

In the present study, data on participants from samples S1, S2 and S3 gathered at T2 were considered as baseline information (Figure 1). The participants in S1, who prior to T2, were deceased, who had received a dementia diagnosis, who were lost to follow-up, or who had left the study for other reasons were excluded (n = 155). At the present study baseline (T2), the three samples consisted of 2,803 non-demented individuals; S1 (n=845), S2 (n=995) and S3 (n=963). Participants younger than 55 years of age at T2 (n = 973) were thereafter excluded because their low risk of developing dementia within the coming 15-year follow-up period. Participants with an address that could not be geocoded (n = 24) were also excluded from analysis. Thus, the final sample consisted of 1,806 individuals (Figure 1).

Dementia diagnoses

In the Betula study, the dementia status was assessed at baseline and re-assessed every five years to identify new cases and determine the year in which the DSM-IV core criteria for dementia were met, i.e. when cognitive symptoms became sufficiently severe to interfere with social functioning and instrumental activities of daily living (American Psychiatric Association, 2000). The diagnoses were based on observations obtained at the Betula study visits (health- and cognitive evaluations), supplemented with medical record data covering the entire study period (1988-2010). The medical records from all hospital and primary care visits within the county

were thus continuously evaluated. Available clinical results from Magnetic resonance imaging, Computerized tomography scan and autopsy (not part of the Betula protocol), were also taken into account in the diagnostic decision. The Betula study population (n=4445) has thus been evaluated with regard to dementia after each test wave (T1, T2, T3, T4, T5). The diagnostic evaluations were coordinated by the same senior research geropsychiatrist (RA) throughout the study period. In 2011 an extensive quality assurance of the dementia diagnoses in the Betula study was performed. The medical records of those with an established dementia diagnosis were blindly re-evaluated with regard to dementia status, sub-type, and age at onset (Boraxbekk et al., 2015). In total, n=444 individuals, who in previously evaluations had received a dementia diagnosis, were blindly re-evaluated and dementia subtypes were distinguished between; Alzheimer's disease (AD), Vascular dementia (VaD), Parkinson dementia, Lewy body dementia, Alcohol dementia, Frontotemporal dementia and Dementia not otherwise specified. The re-evaluated diagnoses were based on a follow-up time with a minimum of five years additional information about the course of the disease available.

As part of the Betula protocol, the following predetermined criteria, recorded at the health- and cognitive examinations, were used as a guide for an extended evaluation as determined by the senior geropsychiatrist (RA): MMSE score ≤ 23, a decline in cognitive performance compared to a previous test occasion (from high to average/low or from average to low), a decline in daily functional activities or a subjective loss of memory function expressed by the participant in the semi-structured interview, and any other behavioral or cognitive deviations e.g. confusion, disorientation noticed by the testing team. The high/low performance was based on a composite cognitive measure, defined as a summed Z-score of 1.8 above/below the mean of the age group.

Participants in the intermediate range were categorized as "average" in terms of levels of cognitive performance. The composite cognitive measure is based on the principal component analysis presented in Nilsson et al (1997). At test-wave T1 and T2, two geropsychiatrists participated in the evaluation process. At test-wave T3, four geropsychiatrists were involved in the diagnostic evaluation, thereby establishing a solid ground for diagnostic consensus. In case of disagreement, the senior research geropsychiatrist (RA), who coordinated the diagnostic evaluations, was ultimately responsible for the final diagnoses.

Of the 1,806 participants included in the present study, 302 were diagnosed with either Alzheimer's disease (n = 191) or vascular dementia (n = 111) up to T5. In this context, it should be pointed out that a dementia diagnosis given to a participant from the S1 or S3 cohorts was based both on clinical examinations and medical record data obtained between 1993 and 2011, whereas for the S2 participants, a dementia diagnosis given from T4 was based solely on information obtained from medical records.

Study area and exposure measure

The study area included Umeå municipality in northern Sweden with an area of 2,397 km^2 and a population of around 120,000 people in 2014. At baseline, the population was around 100,000. To describe the spatial contrasts in exposure to vehicle exhausts between the study participants, we geocoded all participants' home addresses at baseline (1993-1995) using information from the Swedish Population Registry. We developed a land-use regression (LUR) model for Umeå to estimate the annual average levels of Nitrogen Oxides (NO_x), a commonly used marker of vehicle exhaust. The model was built around 36 measuring sites spread throughout the city of

Umeå. For each site, four weeklong measurements with diffusive samplers (Ogawa samplers) were performed between November 2009 and June 2010 to represent an annual average. For the sake of comparison with other air pollution studies, we constructed our model using the same principles and geographical variables as in the large-scale European Study of Cohorts for Air Pollution Effects (ESCAPE; Beelen et al. 2013). The final LUR model explained 76% (adjusted $r^2 = 0.76$) of the variation in measured NO_x values, and when validating using "leave one out" cross validation, the adjusted r^2 became 0.54. The LUR model was highly correlated ($r = 0.86$) for NO_x (and NO_2) with the ESCAPE LUR model in Umeå, which was developed by the same team but with other and less extensive monitoring data.

We created a concentration grid (50 m × 50 m) covering the entire study area. Because some participants (1.6%) lived in rural areas outside the area of measurements, the intercept was adjusted according to population density to avoid unrealistically high levels in rural locations. In a sensitivity analysis, the modeled NO_x values were rescaled using back extrapolation to better correspond to the levels seen at the start of the follow-up in this study (1993–1995).

The back-extrapolation was done using information regarding the estimated total amount of traffic for each year and national vehicle fleet emission factors for Sweden based on the Artemis model (Sjödin et al. 2006). From this information we calculated scaling factors for each year using 2009 as the baseline year.

The estimated NO_x concentration at the home address at baseline was divided into quartiles (Figure 2). Participants in the lowest NO_x quartile had an annual mean exposure up to 9 $\mu g/m^3$, the 2nd quartile had exposures between 9 and 17 $\mu g/m^3$, the 3rd quartile had exposures from 17

μg/m^3 to 26 μg/m^3, and the 4th quartile had exposures of 26 μg/m^3 and higher, implying quite large exposure contrasts within the study area. When rescaling the exposure with back extrapolation, the quartile limits were 19 μg/m^3, 35 μg/m^3, and 54 μg/m^3 for the 2nd, 3rd, and 4th quartiles, respectively.

Potential confounding variables

All 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 (Fratiglioni et al. 2008). In addition to age at baseline as a categorical variable, we considered several social and lifestyle variables as potential confounding variables (Table 1). Education, an indicator of socioeconomic status, was categorized into elementary school, upper secondary school, and university level education depending on the highest achieved education.

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. Smoking was categorized into present smokers, previous smokers, and non-smokers at baseline. Alcohol consumption was classified into present consumers, previous consumers, and non-consumers at baseline. Body mass index (BMI, kg/m^2) was in a previous study associated with inflammatory effects associated with traffic pollution (Zeka et al. 2006), and BMI was in another study associated with cognitive decline in women in the Betula cohort (Thilers et al. 2010). We

therefore chose to include BMI as a potential confounding variable in the statistical analysis. Following the National Health Institute standards from 1985, (Van Itallie 1985) the BMI cut-offs between normal weight and overweight were 23.8 for women and 25.0 for men. We also considered WHR as a potential confounding variable with a cutoff of 0.8 for women and 1.0 for men (Nilsson and Nilsson 2009).

Diabetes, stroke, and hypertension are risk factors for dementia (Cheng et al. 2012; Sahathevan et al. 2012; Sharp et al. 2011), but also might be intermediate factors on the causal pathway between air pollution exposure and dementia. Therefore we ran models with and without adjustment for a history of diabetes, stroke, and hypertension, respectively, based on each participant's status at baseline. In a study on overweight and cognition, it was considered necessary to include supplementary information on hypertension (Nilsson and Nilsson 2009). We followed the same criteria when defining hypertension in this study: (i) the participant reported the use of at least one of three blood pressure/heart medicines (Anatomic Therapeutic Chemical classification C01, C02, or C07) or (ii) the systolic blood pressure was above 140 mmHg and/or the diastolic blood pressure was above 80 mmHg at the baseline (T2) health examination for inclusion in the Betula study. Also, because being a ε4 carrier of apolipoprotein E (ApoE4) adds substantially to the risk of developing at least Alzheimer's disease (Anttila et al. 2002), the presence of at least one ε4 allele was taken into consideration in the analysis. Details on the methods for the genotyping have been published (Nilsson et al. 2006)

Statistical analyses

Cox proportional hazards models were used with time as the underlying scale to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia incidence in association with long-term exposure to air pollution. Censoring occurred at the time of death, the diagnosis of dementia, loss to follow-up, or the end of follow-up, whichever came first. Censoring due to loss to follow-up occurred if a participant moved outside the Betula catchment area. Participants were censored if they were diagnosed with a dementia disorder of another subtype (for example alcohol-or Parkinson-related dementia). There was no exact date available for dementia diagnosis, only the year of onset. We therefore assume onset at July 1 for all participants with a dementia diagnosis. As a marker for long-term exposure to air pollution, we used the annual mean NO_x concentration (estimated for 2009–2010 using the LUR) at the residential address of the study participants at baseline. The NO_x concentration was used as a categorical variable in quartiles, with the first quartile as a reference category, and tested as a continuous variable. We ran models adjusted for variables defined from baseline data on age, ApoE4, and the potential confounding factors of education, physical activity, smoking, sex, alcohol use, BMI, and WHR as well as models adjusted for the potential intermediate factors of hypertension, diabetes, and stroke (variables described in Table 1). We ran models adjusted for baseline age only (Model 1); models adjusted for age and ApoE4, education, physical activity, smoking, sex, alcohol use, BMI, and WHR at baseline, categorized as shown in Table 1 (Model 2); and models that were additionally adjusted for the potential intermediate factors hypertension, diabetes, and stroke (Model 3) which also were defined at baseline. In addition, we studied the two major diagnoses of Alzheimer's disease and vascular dementia separately. End of follow-up was June 30, 2010.

In a subgroup analysis, we excluded participants who belonged to subsample S2—who were younger than S1 and S3 and who were only re-tested after five years—and in another analysis we adjusted for sample (S1, S2, S3). In a sensitivity analysis we excluded participants who were censored because they moved outside of the Betula catchment area before the end of follow-up. The validity of the inherent proportionality assumption was checked visually (by inspecting Kaplan-Meier plots) as well as with formal statistical testing. We included covariates in the model, entered as the interaction between the covariates and the natural logarithm of time. The time-dependent interaction terms were not statistically significant ($p > 0.1$), neither when tested individually nor when tested together, supporting the assumption of proportional hazards.

We used *a priori*-defined statistical models and backward elimination as a sensitivity analysis.

We calculated the population-attributable fraction, AF_p, according to the formula

$$AF_p = p_c \frac{RR - 1}{RR}$$

where p_c is the exposure prevalence among cases and RR is the relative risk associated with the exposure. We used the HR as a proxy of the RR in this setting and defined "exposed" as belonging to the 3rd or 4th quartile of NO_x exposure, and we defined "unexposed" as belonging to the 1st or 2nd quartile of NO_x exposure. We used the HR for dementia in association with exposure above versus below the median from the model adjusted for education, physical activity, smoking, sex, BMI, WHR, alcohol, age, and ApoE4 for the attributable fraction calculation. All analyses were performed with SAS for Windows version 9.4.

Results

During follow-up, 302 participants were diagnosed with either Alzheimer's disease (n = 191) or vascular dementia (n = 111). There were (n=29) participants who were censored when they were diagnosed with a dementia disorder of other subtype, and (n=49) were censored when they moved from the catchment area and no longer could be followed in local medical records. The mean age at end of follow-up was similar across exposure categories at 79, 79, 80, and 81 years in quartiles 1, 2, 3, and 4, respectively. Dementia risk from T2 (1993–1995) to 2010 (the cumulative dementia incidence) was similar across samples at 15% in S1, 17% in S2, and 18% in S3. The proportion of participants diagnosed with dementia increased with increasing NO_x concentration at home (Table 1).

For the full cohort, participants in the highest exposure group were more likely to be diagnosed with dementia (HR=1.43; 95% CI: 0.998, 2.05 for the highest versus lowest quartile; Table 2), whereas the HR associated with quartile 3 was 1.48 (95% CI: 1.03, 2.11; Table 2). When analyzed linearly, the exposure measure coefficients were not statistically significant (Table 2). Including hypertension, stroke, and diabetes in the statistical models only had a slight effect on the estimates (Table 2). The use of back-extrapolated exposure concentrations only marginally affected the estimates (data not shown). Adjusting for sample, or excluding participants who moved outside the Betula catchment area during follow-up, only marginally altered the HR estimates (data not shown). The assumptions regarding proportional hazards seemed to hold both upon visual inspection of the data and with formal statistical testing (data not shown). The HR associated with exposure (quartile 3 or 4 versus quartile 1 and 2) was 1.37 (95% CI: 1.07, 1.76),

and p_c was 0.6, which resulted in an estimated population attributable fraction (AF_p) of 16% (95% CI: 4, 26).

With the sample re-tested only after 5 years (S2) excluded, the number of events decreased from 275 to 181, the number of study subjects decreased from 1592 to 1065 and the number of person years decreased from 18576 to 12295. In that sample, participants in the highest exposure group were more likely to be diagnosed with dementia (HR = 1.71; 95% CI: 1.08, 2.73 for the highest versus lowest quartile; Table 3).

The analysis stratified by diagnosis yielded estimates of similar magnitude for Alzheimer's disease and vascular dementia, with an HR for Alzheimer's disease of 1.38 (95% CI: 0.87, 2.19; Table 4) and an HR for vascular dementia of 1.47 (95% CI: 0.83, 2.61; Table 4) for the highest versus lowest quartile.

Discussion

Our results suggest an association between air pollution exposure and dementia incidence, with an HR of 1.43 (95% CI: 0.998, 2.05) for the highest versus lowest quartile of exposure, and higher in the sub-analysis excluding the younger sample that was re-tested only after the first 5 years of the follow-up period (HR=1.71. 95% CI: 1.08, 2.73). Our findings are supported by a growing number of epidemiological studies showing an association between air pollution exposure and cognitive impairment in the elderly (Chen and Schwartz 2009; Power et al. 2011; Ranft et al. 2009; Wellenius et al. 2012; Weuve et al. 2012a; Chang et al. 2014; Tonne et al. 2014, Ailshire and Crimmings 2014, Ailshire and Clarke 2014) and by toxicological studies suggesting that air pollution has neuropathological effects (Block and Calderón-Garcidueñas

2009). It should be noted that the size of the estimates associated with quartiles 3 and 4 are similar and that we observe no statistically significant linear association with the exposure measure. Interestingly, Ailshire and Crimmins observed a similar tendency when they studied cognitive function and $PM_{2.5}$, with a higher risk in quartile 3 than in quartile 4 (although not a statistically significant difference). We were not able to control at which floor the residence was, infiltration of outdoor air pollutants, exposure to wood smoke or time spent away from the residence, which may have resulted in exposure misclassification.

Previous studies on air pollution and aging have used cross-sectional data or have been based only on cognitive testing, and studies on cognitive outcomes are especially susceptible to bias from selective attrition (Weuve et al. 2012b).

The present study has a major strength in the longitudinal high quality data from the Betula study and the dementia diagnoses, specified by subtype and age at onset. There are often difficulties to elucidate aetiology/pathophysiology in dementing disorders, particularly if a patient develops dementia in high age, mainly due to an increasing burden of vascular complications. In the Betula study, the primary aim in the diagnostic process was to determine a clinical diagnosis of dementia and become confident that we had identified a progressive course of the disorder. We adopted a conservative taxonomic approach i.e. to establish a diagnosis of AD or VaD and other more uncommon dementia disorders e.g. Frontotemporal lobe dementia, Lewy body dementia, Parkinson dementia. The concept of AD/VaD-mixed dementia type was not of primary interest, mainly due to the high prevalence of risk factors for cardiovascular disease (CVD) present in high age.

Clinically, significant CVD risk factors were recorded during the entire follow-up period, and presence of these favoured a diagnosis of VaD, however, only when these risk factors were sufficiently severe and were combined with neurological signs and symptoms of VaD. It is of importance to stress that the mere presence of CVD risk factors did not automatically lead to a diagnosis of VaD, as these risk factors also are of etiological relevance in AD (e.g. hypertension, diabetes mellitus, hypercholesterolemia). The vascular types of lesions probably also contribute to AD pathology and/or exert additive adverse effects on cognition, however, this is still debated (Attems and Jelling 2014). In autopsy studies comparing VaD and VaD/AD mixed type, a rather similar distribution and frequency of multiple infarcts, subcortical lacunas and strategic infarcts was reported (Jellinger 2013). Not unexpectedly, clinico-pathological studies show only moderate sensitivity using the current criteria for VaD. There is thus also a dilemma with the strictly taxonomic approach (AD, VaD, AD/VaD mixed dementia, and other dementias). Accordingly, it was recently proposed that the complexity encountered in determining the role of CVD in VaD, AD and AD/VaD mixed type should be replaced by a more integrating approach taken multiple pathophysiological mechanisms into account (Kling et al. 2013). Furthermore, there is also a lack of clinical and histopathological consensus regarding the impact of cerebrovascular disorders necessary for a ”pure” VaD or AD/VaD mixed type diagnosis, which give raise to multilevel diagnostic difficulties.

A strength of the present study is the fine-scale LUR model with a high level of precision (adjusted $r^2 = 0.76$) and constructed according to the ESCAPE protocol offering good external validity (Beelen et al. 2013). In most of the previous studies on cognitive outcomes and air pollution, a neighborhood-based measure of air pollution was used. In such studies it is difficult

to investigate the association with traffic emissions near the home. The exposure measure in the present study, which modeled exposure at the home address at baseline, is prone to exposure misclassification because exposure to air pollution in reality is not restricted to when someone is at home. A limitation is that we used information on the home address at inclusion, which however unlikely would create a false association.

Residual confounding, e.g. from traffic noise, is a possible explanation of our findings. We considered a list of potential confounding factors, but only adjustment for age had any substantial influence on the association between traffic pollution and dementia incidence. Factors related to socio-economic status, such as education and smoking, did not influence the observed association. The potential intermediate factors of stroke, hypertension, and diabetes did not generally influence the estimates (Table 2). Interestingly, the estimates became higher when excluding S2 (the sample re-tested only once, after 5 years). Dementia incidence was similar across samples. Diagnostic bias due to fewer cognitive testing occasions therefore does not seem to explain the seemingly higher HRs when removing S2. S2 had the lowest proportion of participants in the highest exposure quartile (20%), perhaps because of the younger age distribution, which might be part of an explanation.

Umeå is a city with very low regional background levels of air pollution, but with rather strong gradients within the city, and yearly violations of the NO_2 limits are reported to the Swedish and European agencies. The levels of NO_2 at monitoring stations have fallen over the course the study period, (Naef and Xhillari 2002) but the spatial patterns are assumed to be rather constant. Back extrapolation of exposure levels only marginally altered the estimates, which is

not surprising because baseline was limited to three different years (1993–1995). The major source of our exposure measure, NO_x, is vehicle exhaust from local traffic. However, road dust shares the same patterns as for NO_x and exhaust particles in Sweden (Johansson et al. 2007).

Conclusions

We observed associations between dementia incidence and local traffic pollution that remained after adjusting for known risk factors. The magnitude of the association was similar for Alzheimer's disease and vascular dementia. However, residual confounding from other environmental factors such as traffic noise, and other potential sources of bias, cannot be ruled out. The results of the present study are thus a strong indication of the need for further research using prospective cohorts.

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Table 1. Distribution of dementia and population characteristics at baseline according to quartiles of NOx exposure.

Characteristic	**NO_x Q1 4.8–9 µg/m^3**	**NO_x Q2 >9–17 µg/m^3**	**NO_x Q3 >17–26 µg/m^3**	**NO_x Q4 >26 µg/m^3**	**All**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
All observations	433	476	459	438	1806
Total dementia	55 (13)	65 (15)	90 (21)	92 (22)	302 (18)
Vascular dementia	23 (5)	22 (5)	31 (7)	35 (8)	111 (6)
Alzheimer's disease	32 (8)	43 (10)	59 (14)	57 (14)	191 (11)
Sex					
Men	205 (47)	205 (43)	189 (41)	174 (40)	773 (43)
Women	228 (53)	271 (57)	270 (59)	264 (60)	1033 (57)
Age					
55	83 (19)	84 (18)	65 (14)	58 (13)	290 (16)
60	65 (15)	94 (20)	72 (16)	55 (13)	286 (16)
65	64 (15)	92 (20)	76 (17)	54 (13)	286 (16)
70	65 (15)	74 (16)	70 (15)	69 (16)	278 (15)
75	71 (16)	65 (14)	76 (17)	62 (14)	274 (15)
80	57 (13)	53 (11)	67 (15)	89 (20)	266 (15)
85	28 (6)	14 (3)	33 (7)	51 (12)	126 (7)
Education					
Compulsory	360 (83)	354 (74)	344 (75)	345 (79)	1403 (78)
High school	31 (7)	46 (10)	34 (7)	22 (5)	133 (7)
University	36 (8)	70 (15)	74 (16)	66 (15)	246 (14)
Missing	6 (1)	6 (1)	7 (1)	5 (1)	24 (1)
Physical activity					
Never	91 (21)	90 (19)	105 (23)	126 (29)	412 (23)
Occasionally	57 (13)	61 (13)	57 (12)	44 (10)	219 (12)
Few times per month	38 (9)	46 (10)	39 (9)	53 (12)	176 (10)
Weekly	148 (34)	165 (35)	154 (34)	121 (28)	588 (33)
Daily	92 (21)	106 (22)	95 (21)	84 (19)	377 (21)
Missing	7 (2)	8 (2)	9 (2)	10 (2)	34 (2)
Smoking					
Non-smoker	236 (55)	278 (57)	249 (54)	238 (55)	1001 (55)
Smoker	60 (14)	50 (11)	59 (13)	56 (13)	225 (12)
Ex-smoker	137 (32)	148 (31)	151 (33)	144 (33)	580 (32)
Alcohol					
Yes	291 (67)	331 (70)	328 (71)	322 (74)	1272 (70)
No, never	122 (28)	122 (26)	103 (22)	99 (23)	445 (25)

No, have quit	19 (4)	21 (4)	28 (6)	17 (4)	85 (5)
Missing	1 (0.2)	2 (0.5)	0 (0)	1 (0.2)	4 (0.2)
BMI[a]					
Overweight	293 (68)	318 (67)	288 (63)	281 (64)	1180 (65)
Missing	8 (2)	22 (5)	15 (3)	15 (3)	60 (3)
WHR[b]					
>Recommended	157 (36)	178 (37)	177 (39)	185 (42)	697 (39)
Missing	34 (8)	39 (8)	35 (8)	38 (9)	146 (8)
Hypertension	146 (34)	161 (34)	174 (38)	142 (32)	623 (34)
Missing	1 (0.2)	2 (0.4)	1 (0.2)	0 (0)	4 (0.2)
Diabetes	39 (9)	35 (7)	25 (5)	20 (5)	119 (7)
Missing	3 (0.7)	3 (0.7)	2 (0.5)	1 (0.2)	9 (0.5)
Stroke	18 (4)	28 (6)	33 (7)	38 (9)	117 (6)
Missing	2 (0.5)	3 (0.6)	2 (0.4)	1 (0.2)	8 (0.4)
ApoE	114 (26)	115 (24)	130 (28)	135 (31)	494 (27)
Missing	11 (3)	21 (4)	16 (3)	13 (3)	61 (3)
Deceased	157 (36)	131 (28)	146 (32)	165 (38)	599 (33)

[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.

Table 2. Hazard ratios (HRs) and 95% Confidence Interval (CI) for dementia in association with baseline annual NOx concentration from Cox proportional hazards models.

NO_x[a] (µg/m^3)	**N (person-years)**	**Cases**	**HR (95% CI)**
Model 1[b]			
4.8–9	433 (5,024)	55	1.0
>9–17	476 (5,787)	65	1.10 (0.77, 1.58)
>17–26	459 (5,182)	90	1.49 (1.07, 2.09)
>26	438 (4,540)	92	1.57 (1.12, 2.19)
Per 10 µg/m^3			1.04 (0.98, 1.11)
Model 2[c]			
4.8–9	381 (4,553)	50	1.0
>9–17	420 (5,286)	59	1.11 (0.76, 1.63)
>17–26	408 (4,700)	82	1.48 (1.03, 2.11)
>26	383 (4,037)	84	1.43 (0.998, 2.05)
Per 10 µg/m^3			1.05 (0.98, 1.12)
Model 3[d]			
4.8–9	378 (4,538)	49	1.0
>9–17	418 (5,264)	59	1.13 (0.77, 1.66)
>17–26	406 (4,677)	81	1.49 (1.04, 2.14)
>26	383 (4,037)	84	1.60 (1.02, 2.10)
Per 10 µg/m^3			1.05 (0.98, 1.12)

[a]The annual non back-extrapolated NO_x baseline concentration at the residence of the participants was used as a proxy for exposure to air pollution.
[b]Model 1: Age-adjusted
[c]Model 2: Adjusted for baseline age, education, physical activity, smoking, sex, BMI (Body Mass Index), WHR (Waist-hip-ratio), alcohol, ApoE4
[d]Model 3: Model 2 plus baseline medical history of diabetes, hypertension, and stroke

Table 3. Hazard Ratios (HRs) and 95% Confidence Interval (CI) for dementia in association with baseline annual NOx concentration from Cox proportional hazards models (sample 2 excluded).

NO_x[a] (µg/m^3)	**N (person-years)**	**Cases**	**HR (95% CI)**
Model 1[b]			
4.8–9	262 (3,065)	32	1.0
>9–17	317 (3,793)	45	1.24 (0.79, 1.96)
>17–26	320 (3,625)	57	1.49 (0.97, 2.30)
>26	315 (3,172)	67	1.72 (1.13, 2.62)
Per 10 µg/m^3			1.05 (0.98, 1.13)
Model 2[c]			
4.8–9	227 (2,757)	27	1.0
>9–17	275 (3,423)	40	1.39 (0.85, 2.28)
>17–26	285 (3,294)	52	1.58 (0.98, 2.53)
>26	278 (2,821)	62	1.71 (1.08, 2.73)
Per 10 µg/m^3			1.08 (1.00, 1.16)

[a]The annual non back-extrapolated NO_x baseline concentration at the residence of the participants was used as a proxy for exposure to air pollution.
[b]Model 1: Age-adjusted
[c]Model 2: Adjusted for education, physical activity, smoking, sex, BMI (Body Mass Index), WHR (Waist-hip-ratio), alcohol, age, ApoE4

Table 4. Hazard Ratios (HRs) and 95% Confidence Interval (CI) for Alzheimer's disease and vascular dementia in association with baseline annual NOx concentration from Cox proportional hazards models.

Alzheimer's disease			
NO_x[a] (µg/m^3)	**N (person-years)**	**Cases**	**HR (95% CI)**
Model 1[b]			
4.8–9	381 (4,553)	30	1.0
>9–17	420 (5,286)	39	1.15 (0.72, 1.86)
>17–26	408 (4,700)	52	1.51 (0.96, 2.37)
>26	383 (4,037)	52	1.38 (0.87, 2.19)
Per 10 µg/m^3			1.05 (0.97, 1.15)
Vascular dementia			
NO_x[a] (µg/m^3)	**N (person-years)**	**Cases**	**HR (95% CI)**
Model 1[b]			
4.8–9	381 (4,553)	20	1.0
>9–17	420 (5,286)	20	1.15 (0.62,2.11)
>17–26	408 (4,700)	30	1.46 (0.83, 2.61)
>26	383 (4,037)	32	1.47 (0.83, 2.61)
Per 10 µg/m^3			1.02 (0.92, 1.14)

[a]The annual non back-extrapolated NO_x baseline concentration at the residence of the participants was used as a proxy for exposure to air pollution
[b]Model 1: Adjusted for education, physical activity, smoking, sex, BMI (Body Mass Index), WHR (Waist-hip-ratio), alcohol, age, ApoE4.

Figure Legends

Figure 1. Flow-chart from study inclusion to end of follow-up. The concept of ”Termination" is used for those participants from S1 that did not want to, or could not participate at T2 e.g. due to illness.

Figure 2. The study area of Umeå municipality illustrated with gradients in annual mean NO_x concentration at the home address at baseline. The lines of higher exposure radiating out from the central area (Umeå city center) correspond to major roads in the area. The smaller map shows borders between the quartiles.

Figure 1.

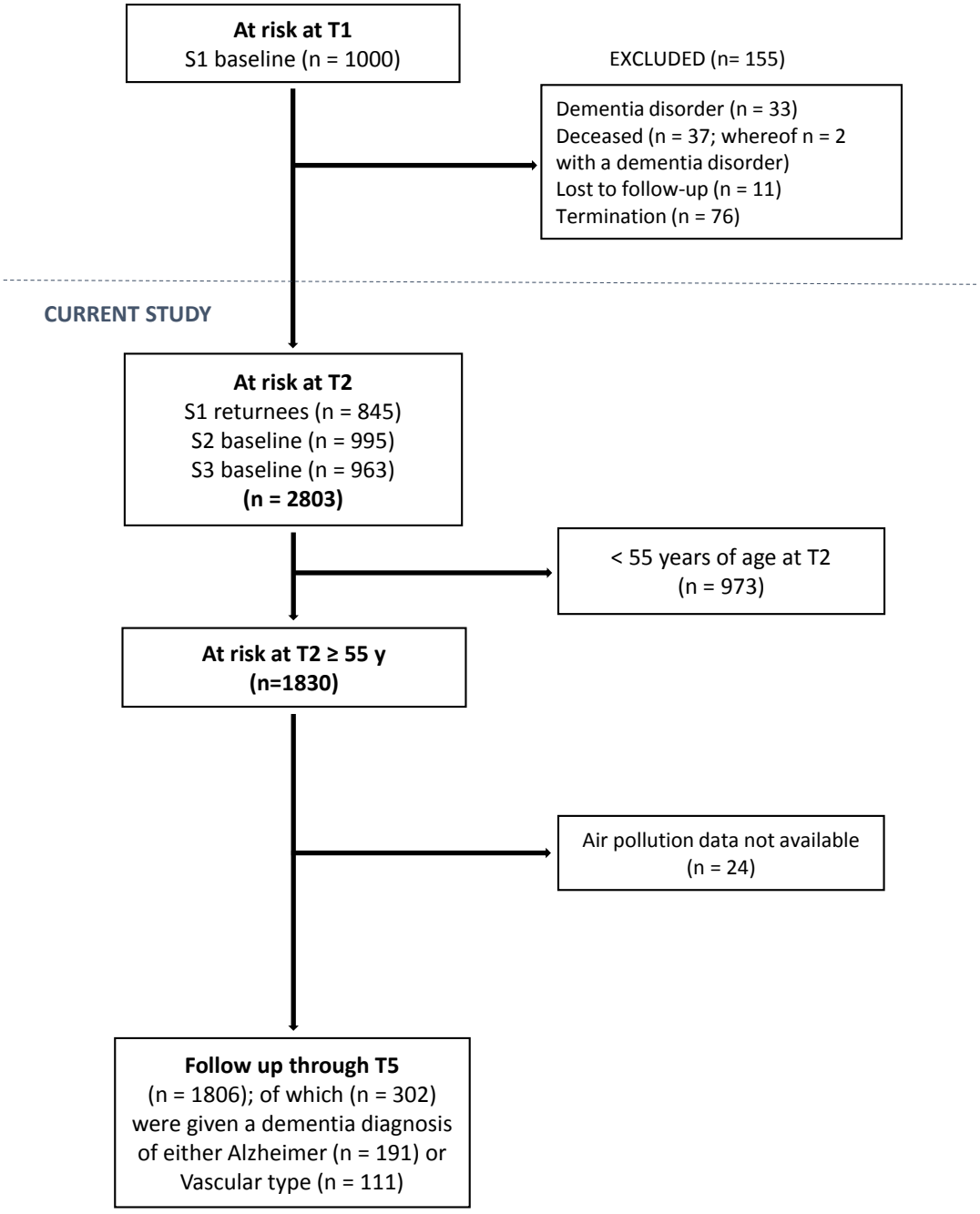
At risk at T1
S1 baseline (n = 1000)
EXCLUDED (n= 155)
Dementia disorder (n = 33)
Deceased (n = 37; whereof n = 2 with a dementia disorder)
Lost to follow-up (n = 11)
Termination (n = 76)
CURRENT STUDY
At risk at T2
S1 returnees (n = 845)
S2 baseline (n = 995)
S3 baseline (n = 963)
(n = 2803)
< 55 years of age at T2 (n = 973)
At risk at T2 ≥ 55 y (n=1830)
Air pollution data not available (n = 24)
Follow up through T5
(n = 1806); of which (n = 302) were given a dementia diagnosis of either Alzheimer (n = 191) or Vascular type (n = 111)

Figure 2.