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http://dx.doi.org/10.1289/ehp.1509824

Received: 13 February 2015
Accepted: 15 January 2016
Advance Publication: 5 February 2016
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Lilian Tzivian1, Martha Dlugaj2, Angela Winkler2, Gudrun Weinmayr1, Frauke Hennig1,3, Kateryna B. Fuks1, Mohammad Vossoughi1, Tamara Schikowski1,4,5, Christian Weimar2, Raimund Erbel6, Karl-Heinz Jöckel3, Susanne Moebus3, and Barbara Hoffmann7, on behalf of the Heinz Nixdorf Recall Study Investigative Group

1IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany; 2Department of Neurology, University Hospital of Essen, University of Duisburg-Essen, Essen, Germany; 3Institute for Medical Informatics, Biometry and Epidemiology, University Duisburg-Essen, Essen, Germany; 4Swiss Tropical and Public Health Institute, Switzerland; 5University of Basel, Basel, Switzerland; 6Clinic of Cardiology, West-German Heart Center, University Hospital of Essen, University Duisburg-Essen, Essen, Germany; 7Medical Faculty, Deanery of Medicine, Heinrich Heine University of Düsseldorf, Düsseldorf, Germany

Address correspondence to Lilian Tzivian, Environmental Epidemiology of Cardiovascular Aging and Allergies, IUF – Leibniz Research Institute for Environmental Medicine, Auf’m Hennekamp 50, Düsseldorf, D-40225, Germany. E-mail: Liliana.Tzivian@IUF-Duesseldorf.de

Running title: Air pollution, traffic noise and MCI

Acknowledgment: We thank the Heinz Nixdorf Foundation (chairman: M. Nixdorf; former chairman: †Dr. jur. Schmidt) for the generous support of this study. We are indebted to
investigative group and the study personnel of the Heinz Nixdorf Recall study. We also thank the North Rhine-Westphalia State Agency for Nature, Environment and Consumer Protection for providing emission and land use data for North Rhine-Westphalia.

We gratefully acknowledge the work of Environmental Health Perspectives science editor. This study is also supported by the German Ministry of Education and Science and by the German Research Council (DFG; JO 170/8-1, HO 3314/2-1, ER 155/6-2, HO 3314/4-3). Lilian Tzivian gratefully acknowledges support by a post-doctoral fellowship from the Environmental and Health Fund, Jerusalem, Israel.

**Competing financial interests:** The authors declare they have no actual or potential competing financial interests.
Abstract

Background: Mild cognitive impairment (MCI) describes the intermediate state between normal cognitive aging and dementia. Adverse effects of air pollution (AP) on cognitive functions have been proposed, but investigations of the simultaneous exposure to noise are scarce.

Objectives: To analyze the cross-sectional associations of long-term exposure to AP and traffic noise with overall MCI, amnestic (aMCI) and non-amnestic (naMCI) MCI.

Methods: At the second examination of the population-based Heinz Nixdorf Recall study cognitive assessment was completed in 4086 participants aged 50 – 80 years. Of them 592 participants were diagnosed as having MCI (aMCI n=309; naMCI n=283) according to previously published criteria using five neuropsychological subtests. We assessed long-term residential concentrations for size-fractioned particulate matter (PM) and nitrogen oxides with land use regression, and traffic noise (weighted 24-h (L_{DEN}) and night-time (L_{NIGHT}) means) according to the EU directive 2002/49/EC. Logistic regression models adjusted for individual risk factors were calculated to estimate the association of environmental exposures with MCI in single and in two-exposure models.

Results: Most air pollutants and traffic noise were associated with overall MCI and aMCI. For example, an interquartile range increase in PM_{2.5} and a 10 dB(A) increase in L_{DEN} were associated with overall MCI (odds ratio (95% confidence interval)=1.16 (1.05, 1.27) and 1.40 (1.03, 1.91), respectively) and with aMCI (1.22 (1.08, 1.38) and 1.53 (1.05, 2.24), respectively). In two-exposure models, AP and noise associations were attenuated (i.g., for aMCI: PM_{2.5} 1.13 (0.98, 1.30) and L_{DEN} 1.46 (1.11, 1.92)).

Conclusions: Long-term exposures to air pollution and traffic noise were positively associated with MCI, mainly with the amnestic subtype.
Introduction

Age-related cognitive decline is becoming more and more important due to aging populations in developed countries. During the last two decades, prevalence of dementia doubled each 5.5 – 6.7 years (Prince et al. 2013). The estimated prevalence of dementia will reach 42.7 – 48.1 million worldwide in 2020 (Prince et al. 2013). One possibility to characterize early stages of cognitive decline in elderly populations is mild cognitive impairment (MCI). MCI describes the stage between normal cognitive changes in aging and early dementia (Petersen et al. 1999). MCI can be classified as amnestic MCI (aMCI) where memory domains are affected and which most likely reflects the prodromal Alzheimer’s Disease (AD) stage, and non-amnestic MCI (naMCI), which has been linked to the prodromal stages of vascular and other forms of dementia (Petersen 2004).

Although a decline in cognitive functions is considered as a normal consequence of aging (Glisky 2007), the identification of risk factors for dementia is of great importance for prevention and future treatment options. Several factors are related to dementia, e.g. age, ethnicity, sex, genetic factors, physical activity, smoking, drug use, education level, alcohol consumption and body mass index (Chen et al. 2009). About a decade ago, adverse effects of environmental exposures, such as air pollution, on the central nervous system have been proposed (Oberdörster and Utell 2002). However, the effect of air pollution on cognitive function of adults has not yet been well investigated (Block et al. 2012; Tzivian et al. 2015). A major part of the studies investigating the effect of different pollutants on cognitive function are focused on childhood and adolescence (Guxens and Sunyer 2012). In adults, associations of air pollution with different aspects of cognitive function, mood disorders, and neurodegenerative diseases have been studied with partially inconsistent or even controversial results (Block et al. 2012). However, most
studies so far generally support the hypothesis that ambient air pollution is associated with
cognitive function in long-term exposed persons (Tzivian et al. 2015).

An important inner-urban source of air pollution is traffic, which also emits ambient
noise. Due to their common source, air pollution and traffic noise often occur simultaneously in
time and space. While air pollution and cognitive function have been studied repeatedly, the
association of ambient noise with cognitive function of adults has rarely been investigated
(Clark and Stansfeld 2007; Tzivian et al. 2015). Most studies on ambient noise examined short-
term effects (Hygge et al. 2003; Schapkin et al. 2006; Stansfeld et al. 2000), suggesting a clinical
impact of noise on psychological outcomes, e.g. anxiety and annoyance. To our knowledge, no
long-term studies exist on the effect of traffic noise exposure on cognitive function of adults.
Furthermore, there is a limited amount of studies that have investigated the co-exposures of air
pollution and traffic noise simultaneously on cognitive function of adults.

The aim of this study was to investigate the independent cross-sectional associations of
long-term exposure to air pollution and traffic noise in adults with MCI diagnosis and its
subtypes (amnestic and non-amnestic) using data from the first follow-up examination of the
population-based Heinz Nixdorf Recall study in Germany.

Materials and Methods

Study population

This study is a cross-sectional analysis based on data from the first follow-up
Calcium and Lifestyle) study, a population-based cohort study located in three adjacent cities
(Bochum, Essen and Mülheim/Ruhr) in the highly urbanized German Ruhr Area. The study
design has been described in detail before (Schmermund et al. 2002). In short, 4814 randomly
chosen men and women aged between 45 and 75 years at baseline were enrolled into the study between December 2000 and August 2003. After five years (2006-2008) the first follow-up examination was performed (response rate of 90.2%). The Heinz Nixdorf Recall study was approved by the ethics committee of the University Hospital Essen. All participants gave their written informed consent.

Cognitive assessment - MCI diagnosis

At the 5 year follow up examination, a cognitive performance assessment was implemented and completed in 4086 participants. The cognitive performance assessment has been previously described in detail (Wege et al. 2011; Dlugaj et al. 2010). Briefly, it consists of established measures of immediate and delayed verbal memory (eight word list, performance measured as number of words recalled in each trial), problem solving/speed of processing (labyrinth test, time in seconds needed to complete the task), verbal fluency (semantic category “animals”, number of recalled words within one minute) and abstraction (as an executive function)/visual-spatial organization (clock-drawing test). The short cognitive performance assessment reached a good accuracy (area under the curve =0.82, 95% confidence interval (CI) =0.78, 0.85) against a detailed neuropsychological and neurological examination assessing MCI in a previous study (Wege et al. 2011). The raw data for each subtest were z-transformed (mean = 0, standard deviation (SD) ± 1) according to three age groups (50–59 years, 60–69 years, and 70–80 years) and within every age group according to three education groups (≤ 10 years, 11-13 years, ≥14 years).

MCI was diagnosed according to the Petersen/International Working Group on MCI criteria (Petersen 2004). Participants had to meet the following criteria to receive an MCI diagnosis: (1) presence of a subjective cognitive complaint (participants were asked if their
cognitive performance had changed during the past two years. A complaint was considered present if the participant reported a decline in cognitive performance over time), (2) presence of an objective cognitive impairment that is (3) insufficient to fulfill criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) and reflects (4) generally intact activities of daily living. Presence of objective cognitive impairment (criterion 2) was assessed using the results of all five cognitive subtests. Cognitive function was rated as impaired if the performance of at least one of cognitive subtests was more than one standard deviation (SD) below the age and education-specific mean (age- and education-specific z-scores), or a score of ≥3 in the clock drawing test. Participants with missing information on subjective cognitive complaints (n=14) and participants who reported either a subjective cognitive complaint (without objective cognitive impairment, n=548) or showed objective cognitive impairment (without subjective cognitive complaint, n=1,452) were excluded from the main analyses (Figure 1). We also excluded participants due to a physician’s diagnosis of dementia or AD, with intake of cholinesterase inhibitors (ATC, anatomic-therapeutic-chemical classification issued by the World Health Organization (WHO), code: N06DA) or other anti-dementia drugs (N06DX), or fulfilling the DSM-IV dementia diagnosis (not meeting criterion 3 for Petersen MCI diagnosis) (n=22).

Participants presenting an objective impairment in at least one memory domain (immediate and/or delayed verbal memory subtests) with or without impairment in any other cognitive domain received a diagnosis of amnestic MCI (aMCI) (Petersen et al. 2004). If only non-memory domains were impaired (at least one), the participants received a diagnosis of non-amnestic MCI (naMCI). Participants who presented neither a subjective cognitive complaint nor objective impairment were defined as ‘cognitively normal’.
Exposure assessment

We used the land use regression model (LUR) according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) standardized procedure (ESCAPE-LUR) (Beelen et al. 2007). Briefly, particulate matter of varying sizes in aerodynamic diameter measured in µm - that is less than 10 µm (PM$_{10}$), > 2.5 to ≤ 10 µm (PM$_{coarse}$), less than 2.5 µm (PM$_{2.5}$), and PM$_{2.5}$ absorbance (blackness of the PM$_{2.5}$ exposed filter, determined by measurement of light reflectance as a marker for soot and black carbon) - was measured in 20 sites, and nitrogen oxides (NOx and NO$_2$) was measured at 40 sites in three separate two week periods (to cover different seasons) over one year (Beelen et al. 2013). Air pollution measurements were performed between October, 2008, and October 2009, and resulting LUR models were applied to estimate long-term exposure of concentrations at the baseline year of the study (Beelen et al. 2013; Eeftens et al. 2012). Background NO$_2$ was modeled including the data from background measurement stations only whilst excluding traffic stations from the model (http://www.escapeproject.eu/manuals/ESCAPE_Exposure-manualv9.pdf). Annual averages (10/2008-09/2009) of measured pollutant concentrations at the monitoring sites and predictor variables, derived from Europe-wide and local Geographic Information System databases, were used to develop the study-specific LUR model and to predict concentrations at each participant’s address. In the Ruhr Area, the models explained 88% of the variability in the annual concentrations of PM$_{2.5}$, 77% of that for PM$_{10}$, 66% of that for PM$_{coarse}$, 97% of that for PM$_{2.5}$ absorbance, 84% of that for NO$_2$, and 78% of that for NOx (Beelen et al. 2013; Eeftens et al. 2012).

Long-term exposure to traffic noise was modeled according to the European Directive 2002/49/EC (European Commission 2002) as weighted 24-h mean (L$_{DEN}$) and night-time (10pm
– 6 am) mean (L_{NIGHT}) at the baseline address, with consideration of the following determinants:
small-scale topography of the area, dimensions of buildings, noise barriers, street axis, vehicle
type specific traffic density, speed limit, and type of street surface. Noise models were performed
on behalf of the cities and traffic noise values were supplied as source-specific facade values
from local city administrations. We used the most exposed facade values estimated at the
residential addresses from the European noise exposure assessment in 2007.

In addition to air pollution and noise exposure estimates, we used small-scale traffic
indicators. The total traffic load at major roads (>5000 vehicles/day) in 100 m buffer
vehicles*m/day was obtained from local road networks with traffic intensity data. Additional
sensitivity analysis was performed using exposure variables form the European Air Pollution
Dispersion and Chemistry Transport (EURAD-CTM) model (Memmesheimer et al. 2004). This
model uses input data from official emission inventories on a spatial resolution of 1 km² grid
cells, including industrial sources, household heating, traffic and agriculture and data on hourly
meteorology and regional topography. Furthermore, pollutants coming into the area by long-
range transport are taken into account (Memmesheimer et al. 2004). The model output reflects
the long-term urban background concentrations in the 1 km² grid cell of the residential address of
the participant. We used modeled averages of PM_{2.5}, PM_{10} and NO₂ for years 2001 – 2003 as
long-term exposure to air pollution.

Covariates

Individual-level characteristics including age, sex, socio-economic status (SES, assessed
as education level, classified by the International Standard Classification of Education as total
years of formal education, combining school and vocational training (UNESCO (1997)
International standard classification of education (ISCED)), alcohol consumption in drinks per
week (one drink defined as 0.25 L beer, 0.1 L wine, or 0.02 L spirits), smoking status, environmental tobacco smoke (ETS, assessed as regular exposure to tobacco smoke at work, at home or at other places), and any regular physical activity (regularly performing any type of sport activities) were assessed in standardized interviews and questionnaires. Anthropometry was measured according to standardized protocols and body mass index (BMI) was calculated as weight in kilogram divided by squared height in meters (kg/m²). Further intermediates included coronary heart disease (CHD) defined as a self-reported history of a myocardial infarction or coronary intervention at baseline or documented incidence of CHD during follow-up (Erbel et al. 2010); low-density lipoprotein (LDL)-cholesterol level measured using standard enzymatic methods; type 2 diabetes mellitus defined as fasting blood glucose greater than 125 mg/dl or blood glucose greater than 200 mg/dl or reported use of insulin or oral hypoglycemic agents within the last 7 days before examination; and use of statins and anti-hypertensive medication during 7 days before examination assessed categorized according to the Anatomical Therapeutic Chemical (ATC) classification index (http://www.whocc.no/, ATC 2006). APOE genotypes were investigated, since APOE ε4 allele has been shown to increase the risk for Alzheimer disease. Genotyping was performed on Cardio-Metabochip BeadArrays (Illumina, San Diego, CA, USA). Genotypes of two single nucleotide polymorphisms (SNPs, rs7412 and rs429358) that distinguish between the three APOE alleles ε2, ε3, ε4 were extracted from the whole Metabochip data set. Genotyping was not available for 197 (4.86%) participants. Depressive symptoms were assessed using the German version of the Center for Epidemiologic Studies Depression scale (CES-D) short form (Hautzinger and Bailer 1993).
Statistical analysis

All air pollution components estimated with ESCAPE-LUR were obtained as continuous variables and included in the models per inter-quartile range (IQR). Noise exposure was investigated as a continuous variable with a threshold at 60 dB(A) for $L_{DEN}$, and 55 dB(A) for $L_{NIGHT}$, respectively, and calculated per 10 dB(A) increase. Threshold values were selected as those where cardiovascular health effects were previously seen (Babisch 2008). All noise values lower than the defined threshold value were equated to the threshold value. Total traffic load in major roads was adjusted for background NO$_2$. Spearman correlation coefficients were calculated between estimated levels of air pollution and noise.

Multiple logistic regression models were constructed for each exposure. The main model included age, sex, SES (three categories: low, median and high according to $\leq$ 10, 11 - 13, and $\geq$ 14 years of education), alcohol consumption (categorized as 0, 1–3, > 3 and $\leq$ 6, > 6 drinks per week), smoking status (never, former, current), self-reported ETS (yes or no), any regular physical activity (yes or no) and BMI (continuous). To check potential non-linear associations of age and BMI with MCI we used quadratic and cubic polynomials, and the best model was chosen according to model fit using the adjusted $R^2$ criterion. In an extended analysis, the main model was adjusted for possible intermediate variables and potential risk factors: CHD diagnosis, LDL cholesterol level, intake of statin medications, diabetes mellitus, intake of anti-hypertensive medications, and city of residence. Additional adjustments of the main model were performed with APOE $\varepsilon$4 (carrier/non-carrier) and degree of depressive symptoms (continuous variable of CES-D score).

Two-exposure models for associations of noise and air pollution were developed to investigate the independent association of the two exposures.
Effect modification

We dichotomized air pollution concentrations at two cut-points – once at the median and secondly at the 75-percentile, and constructed product terms of air pollution (dichotomous)*noise. Noise variables were dichotomized on the threshold values (60 dB(A) for L\text{DEN} and 55 dB(A) for L\text{NIGHT}) for interaction analysis with continuous air pollution variables. We also evaluated possible effect modification by age (< 65, vs. ≥65 years), sex, SES (low and median versus high education), BMI (≤ 30, vs. > 30), smoking status (non-smokers vs. current and former smokers), alcohol consumption (≤ 6 drinks per week vs. > 6 drinks per week), APOE ε4 (carrier vs. non-carrier), and depression (< 18, vs. ≥ 18 on the CES-D score).

Sensitivity analysis

We performed sensitivity analyses for the main models excluding participants who changed their residential addresses between the baseline examination (2000 – 2003) and the first follow-up (2006 – 2008). Additionally, we performed a sensitivity analysis using the EURAD-CTM (Memmesheimer et al.2004) air pollution model instead of the LUR exposure values.

We performed several sensitivity analyses to assess the degree of possible outcome misclassification. First, we added participants with objective impairment only to the group of participants classified as having overall MCI, and added those with subjective complaints only to the cognitively healthy group. Second, we compared participants with overall MCI to all other participants combined, including participants with objective impairment only and those with subjective impairment only, in addition to those classified as cognitively healthy.

For noise variables we performed a sensitivity analysis using different threshold values (65 dB(A) for L\text{DEN} and 50 dB(A) for L\text{NIGHT}), and a with continuous noise variable without a
threshold (per IQR of exposure). We also analysed noise variables in 10 dB(A) categories (≥45 - <55 dB(A); ≥55 – <65 dB(A); ≥65 - <75 dB(A); ≥75 dB(A)).

We considered a p-value of 5% as statistically significant. We used SAS version 9.2; (SAS Institute Inc., Cary, NC, USA), and R version 2.13.1 (R Core Team 2013) software for analysis and processing of all databases.

Results

We included 1,458 cognitively normal participants and 592 participants with MCI in our analyses, of them 309 with aMCI and 283 with naMCI (Figure 1). The mean age of all participants combined was 64 years (63 years for the unimpaired group and 66 years for those with overall MCI) (Table 1). Proportions of men and women were generally consistent among the different outcome groups (unimpaired, all MCI, aMCI, and naMCI), and the majority had medium education. Most did not consume alcohol (32–49%) or had > 6 drinks /week (25–39%), and most were never smokers or ex-smokers, with about one-quarter reporting exposure to environmental tobacco smoke (ETS). Medication for hypertension was used by 45% of the unimpaired and 55% of those with MCI, while statin use was reported by 18% and 24%, respectively (Table 1).

Mean concentrations of PM$_{2.5}$ and PM$_{10}$ were 18.4 µg/m$^3$ and 27.7 µg/m$^3$, respectively (Table 2). Air pollution variables (ESCAPE-LUR) and noise variables correlated moderately (Spearman correlation coefficient, $r_s$ 0.30 - 0.48) (see Table S1).

Associations between air pollution, noise and MCI

We found positive associations of most exposures with overall MCI and aMCI (Table 3). For example, an IQR increase in PM$_{2.5}$ and PM$_{2.5}$ absorbance, and a 10 dB(A) increase in $L_{DEN}$ were significantly associated with overall MCI with odds ratios (OR) of 1.16 (95% CI 1.05,
1.27), 1.11 (95% CI 1.03, 1.19) and 1.40 (95% CI 1.03, 1.91), respectively, in the main model. For aMCI, these associations were slightly stronger with ORs of 1.22 (95% CI 1.08, 1.38), 1.17 (95% CI 1.03, 1.35), and 1.53 (95% CI 1.05, 2.24), respectively. Associations of MCI and its subtypes with other investigated air pollutants were similar, but slightly lower than associations with PM$_{2.5}$. Association of LNIGHT with MCI and its subtypes were slightly higher than those obtained with LDEN (Table 3). All AP and noise exposures were more strongly associated with aMCI than with overall MCI and naMCI. Traffic indicator variables were not associated with MCI or its subtypes.

Point estimates for associations with PM$_{2.5}$ and LDEN were robust to different model specifications (Figure 2). Results for associations with other air pollutants and with LNIGHT also were robust to adjustment (data not shown). Additional adjustment of the main model with potential intermediate variables (CHD diagnosis, LDL cholesterol level, diabetes mellitus, and intake of statin or anti-hypertensive medication) did not change the association of PM$_{2.5}$ with MCI and its subtypes, but slightly attenuated the association of LDEN with overall MCI and aMCI (Figure 2). Adjustment for APOE slightly decreased the association of PM$_{2.5}$ with MCI and aMCI, and the association of LDEN with aMCI (Figure 2). Adjustment for depressive symptoms did not change the association between PM$_{2.5}$ and MCI and its subtypes, but the point estimate for the association of LDEN with aMCI decreased after adjustment for depressive symptoms (Figure 2).

Associations of PM$_{2.5}$ with overall MCI and aMCI were positive but became non-significant after adjustment for noise (LDEN or LNIGHT), whereas positive associations of LDEN with MCI and aMCI remained significant after adjustment for PM$_{2.5}$ (Figure 2). ORs for other air pollutants and overall MCI or aMCI also remained positive but were not significant when
adjusted for noise (data not shown). For example, in the two-pollutant model for NO$_2$ adjusted for $L_{DEN}$ the association with aMCI was $OR = 1.12; 95\% CI 0.97, 1.28$.

**Effect modification**

Associations between PM$_{2.5}$ and MCI were stronger in participants with no or moderate alcohol consumption ($OR = 1.27; 95\% CI 1.07, 1.50$) compared to higher alcohol consumption ($OR = 0.96; 95\% CI 0.75, 1.21; p_{inter} = 0.05$) and in former and current smokers ($OR = 1.39; 95\% CI 1.12, 1.71$) compared to non-smokers ($OR = 1.01; 95\% CI 0.85, 1.21; p_{inter} = 0.02$) (see Figure S1). Other interactions were non-significant, but associations between PM$_{2.5}$ and MCI were stronger in participants with high noise exposure (e.g., $OR = 1.30; 95\% CI 1.01, 1.67$ compared with $OR = 1.10; 95\% CI 0.93, 1.29$; for $L_{DEN} \geq 60$ and $< 60$, respectively; $p_{inter} = 0.28$) and for participants with depressive symptoms ($OR = 1.35; 95\% CI 0.89, 2.05$) compared with other participants ($OR = 1.13; 95\% CI 0.97, 1.31; p_{inter} = 0.43$). For the association of $L_{DEN}$ with MCI, we observed a tendency towards a higher susceptibility in carriers of the APOE risk allele ($OR = 1.99; 95\% CI 1.11, 3.56$) compared with others ($OR = 1.21; 95\% CI 0.83, 1.78; p_{inter} = 0.17$) and in those participants with high PM$_{2.5}$ exposure ($OR = 1.53; 95\% CI 1.17, 2.00$) compared with those exposed to low PM$_{2.5}$ ($OR = 1.08; 95\% CI 0.73, 1.62; p_{inter} = 0.17$).

**Sensitivity analysis**

After excluding participants who changed their residential addresses between the baseline and the first follow-up examination, the group of participants with overall MCI contained 511 participants (86.3% of the whole MCI sample), of them 259 with aMCI, and 252 with naMCI. Restricting the sample to non-movers did not change the effect estimates and the significance level of the observed associations.
Correlation between air pollution variables modeled using ESCAPE-LUR and EURAD-CTM models was moderate to high ($r_s=0.44-0.77$). PM$_{10}$ modeled according to the EURAD-CTM was associated with naMCI (OR=$1.20$ (95%CI 0.98, 1.49) per IQR ($4.19 \, \mu g/m^3$) in the main model. However, PM$_{2.5}$ modeled with EURAD-CTM was not associated with MCI (data not shown).

In sensitivity analyses adding participants with only objective impairment to the MCI cases and adding participants with only subjective complaints to the cognitively healthy group, we observed slightly lower associations than those obtained in the main analysis, and results partly became non-significant. For example, for the associations of PM$_{2.5}$ and L$_{DEN}$ with objective impairment the ORs were $1.10$ (95%CI 1.01, 1.21) and $1.18$ (95%CI 0.98, 1.44), respectively. Results for participants with overall MCI versus all other participants (adding all unclear cases to the cognitively healthy group) were similar. For example, for the associations of PM$_{2.5}$ and L$_{DEN}$ we obtained ORs of $1.10$ (95%CI 0.97, 1.26) and $1.19$ (95%CI 0.91, 1.56), respectively.

Results of sensitivity analysis for noise variables with 65 dB(A) threshold for L$_{DEN}$ and 50 dB(A) threshold for L$_{NIGHT}$, and for continuous noise variables showed similar results as the main analysis (see Table S2). Categorical analysis of noise variables revealed elevated estimates above 65 dB(A) (see Table S3).

**Discussion**

We found that both, long-term exposure to air pollution and to road traffic noise, were associated with overall MCI, particularly the amnestic subtype, in this middle- and older-aged German study population. In two-exposure models including both PM$_{2.5}$ and L$_{DEN}$, effect estimates for both exposures stayed positive and the association with noise remained statistically significant for overall MCI and aMCI. Our results also indicate that the two investigated environmental exposures may interact with each other. Specifically, associations of PM$_{2.5}$ with
overall MCI were stronger among those with higher levels of noise, and the association of $L_{DEN}$
with overall MCI appeared to be limited to those with high exposure to PM$_{2.5}$. However,
differences between groups defined by high or low noise or PM$_{2.5}$ were not significant.

The association between long-term exposure to air pollution and MCI confirms prior studies,
which have reported an association of different air pollutants with accelerated neurocognitive
decline in longitudinal studies (Tonne et al. 2014; Weuve et al. 2012) and in cross-sectional
studies (Chen and Schwartz 2009; Loop et al. 2013; Power et al. 2011). We also found that long-
term exposure to traffic noise (both $L_{DEN}$ and $L_{NIGHT}$) was positively associated with MCI.
Similar to air pollutants, the association of ambient noise (both $L_{DEN}$ and $L_{NIGHT}$) was stronger
for aMCI than for naMCI. This is a novel finding, since studies investigating the association
between the ambient noise and cognitive functions in general adult population are scarce (Wright
et al. 2014; Basner et al. 2014). Importantly, our results show that positive associations of
environmental exposures with MCI were still evident when adjusted for confounding by the
other exposure. If corroborated by other studies, this has important public health implications
regarding protection of the public.

Previous studies on air pollution and subtypes of MCI or specific domains of
neurocognitive function are scarce and their results are inconsistent. In a cross-sectional study
investigating the association between PM$_{2.5}$, O$_3$ and NO$_2$ with attention, memory and executive
functions in 1,496 Los Angeles residents (Gatto et al. 2014), and in a longitudinal study
investigating the effect of PM$_{2.5}$ and PM$_{10}$ on decline of inductive reasoning, verbal fluency, and
verbal memory in 2,867 older London residents (Tonne et al. 2014), air pollution was associated
with lower verbal and logical memory, respectively, while in the cross-sectional analysis of
NHANES data for 1,764 US adults (Chen and Schwartz 2009), the association of PM$_{10}$ with
memory function disappeared after adjustment for personal covariates. In line with the findings by Gatto et al. and Tonne et al., we found most consistent associations of air pollution and traffic noise with memory-related aMCI. This is potentially of great public health importance, because aMCI may be associated with higher risk for developing AD (Petersen et al. 2004). An association of air pollution with AD was previously reported in an animal study by Calderón-Garcidueñas et al. (2004).

The association between aMCI as a prodromal AD stage and air pollution seems plausible from a biological perspective. There is evidence for increased brain accumulation of beta-amyloid, a hallmark of AD, in dogs with higher air pollution exposure (Calderón-Garcidueñas et al. 2008). Furthermore, an experimental study of rats exposed to diesel exhaust by inhalation over four weeks or as a single intratracheal administration reported a link between air pollution and neuroinflammation (Levesque et al. 2011), which also plays an important role in the development of AD (Block and Calderón-Garcidueñas 2009). Additionally, in the animal study by Arnsten and Goldman-Rakic (1998) it was shown that in monkeys mild noise exposure significantly impaired the performance in spatial working memory, which is dependent on prefrontal cortex function, and elicits excessive dopamine release (Arnsten and Goldman-Rakic 1998). Since there is a lack of evidence about mechanisms of long-term noise exposure, we can only speculate whether these mechanisms could also be responsible for long-term effects of noise on cognitive function.

We did not find a significant association of air pollution and naMCI, although the odds ratios were elevated. In contrast, in the longitudinal study by Kioumourtzoglou et al. (2015) that assessed the effect of PM$_{2.5}$ on neurological hospital admissions among Medicare enrollees in the northeastern United States, city-wide long-term exposure to PM$_{2.5}$ was associated with hospital
admission for Parkinson’s disease, which is closely related to naMCI (Costello et al. 2011).
NaMCI in turn is related to vascular dementia (Petersen 2004), which is strongly associated with cardiovascular disease (Paciaroni and Bogousslavsky, 2013). Chronic exposure to air pollution has been linked to an elevated risk of cardiovascular disease (Brook et al. 2010), and our own previous study on Heinz Nixdorf Recall study population has reported associations of long-term PM air pollution with risk factors or manifestations of atherosclerosis and cardio-vascular disease (Hoffmann et al. 2007), suggesting that one possible pathway from air pollution to naMCI and vascular dementia could be mediated via cardiovascular disease. However, we did not find strong evidence to support this pathway in the present analysis.

We generally found strongest associations for PM$_{2.5}$, and less clear associations for PM$_{10}$. The particle fraction that might be responsible for potential effects on neurocognition is not clear. While some studies report stronger associations of cognitive function with smaller particles or with traffic-related exposures and soot (Loop et al. 2013; Ranft et al. 2009), others observe associations with larger particle fractions (Chen and Schwartz 2009). Only few studies have comprehensively compared the associations of cognitive outcomes with different particle size fractions and air pollution components (Chen and Schwartz 2009; Weuve et al. 2012), yielding different results. For example, in the cohort study by Weuve et al. (2012) that investigated effects of PM$_{2.5}$, PM$_{2.5-10}$, and PM$_{10}$ on global cognition, verbal memory and executive function of 10,409 participants in a 7-year follow-up examination, an association of PM$_{2.5-10}$, but not of PM$_{2.5}$ and PM$_{10}$, with global cognitive decline was found, while in the study by Chen and Schwartz (2009) such an association was found only for PM$_{10}$. Clearly more combined toxicological and epidemiological research is needed to identify the most pathogenic
components of air pollution and to enhance our understanding of the biology of adverse air pollution effects.

Strengths and limitations of the study

This study was performed using the database of a middle- and older-age population in the highly urbanized German Ruhr Area. Unless more studies with other study populations, methods and in different areas of the world are conducted, generalizability cannot be assessed. One important limitation of this study is its cross-sectional design, which prevents us from establishing a temporal relation between air pollution/noise and MCI. In addition, cognitively impaired people were probably less likely to participate in the study, which could lead to selection bias. Another limitation of our study is the absence of detailed information on room location, the kind of windows and other factors which contribute to misclassification of both noise and air pollution exposure. Additionally, some of the personal variables (alcohol consumption, physical activity, smoking behavior) were obtained from questionnaires, which can lead to residual confounding in case of imprecision and underreporting. We also cannot exclude possible exposure misclassification and residual confounding between air pollution and noise exposures, since they share a common source and are correlated moderately.

Our study has several strengths. To our knowledge this is the first study that investigated the association of different air pollutants and noise with cognitive function in two-exposure models. Additionally, this is the first study that assessed the effect of air pollution and noise in participants with MCI. As these participants have a higher risk of developing dementia, the longitudinal follow-up will allow us to examine the relationship between air pollution and cognitive decline. In our study we investigated associations of air pollutants and noise on both clinically important MCI subtypes – aMCI and naMCI. Furthermore, we have excluded all
participants with either only objective impairment or only subjective cognitive complaint resulting in a reference group of cognitively healthy participants. The large range of pollutants and the extensive adjustment for covariates in this extremely well-characterized population-based study sample enables good control of confounding factors. The population-based nature and standardized outcome assessment methods, as well as the large sample size are additional strengths of this study.

Conclusions

Long-term exposures to air pollution and traffic noise were both associated with MCI, particularly the amnestic subtype, in this middle- and older-age German study population. In two-exposure models including both PM$_{2.5}$ and traffic noise, positive associations persisted for both exposures, and associations with noise remained statistically significant for overall MCI and aMCI.
References


**Table 1. Main characteristic of the whole study population and its subgroups by outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroups</th>
<th>Total population, N=2050</th>
<th>Unimpaired group, N=1458</th>
<th>Overall MCI, N=592</th>
<th>Amnestic MCI, N=309</th>
<th>Non-amnestic MCI, N=283</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td></td>
<td>64.1 ± 7.7</td>
<td>63.2 ± 7.4</td>
<td>66.3 ± 7.9</td>
<td>66.0 ± 8.0</td>
<td>66.6 ± 7.7</td>
</tr>
<tr>
<td>Men, N (%)</td>
<td></td>
<td>1007 (49.1)</td>
<td>718 (49.2)</td>
<td>289 (48.8)</td>
<td>169 (54.7)</td>
<td>120 (42.4)</td>
</tr>
<tr>
<td>Education level, N (%)</td>
<td>Low</td>
<td>191 (9.3)</td>
<td>122 (8.4)</td>
<td>69 (11.7)</td>
<td>38 (12.3)</td>
<td>31 (10.9)</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1142 (55.7)</td>
<td>785 (53.8)</td>
<td>357 (60.3)</td>
<td>184 (59.5)</td>
<td>173 (61.1)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>716 (34.9)</td>
<td>551 (37.8)</td>
<td>165 (27.9)</td>
<td>86 (27.8)</td>
<td>79 (27.9)</td>
</tr>
<tr>
<td>Alcohol consumption, N (%)</td>
<td>Never</td>
<td>726 (35.4)</td>
<td>468 (32.1)</td>
<td>258 (43.6)</td>
<td>152 (49.2)</td>
<td>106 (37.5)</td>
</tr>
<tr>
<td></td>
<td>1-3 drinks/week</td>
<td>400 (19.5)</td>
<td>284 (19.5)</td>
<td>116 (19.6)</td>
<td>55 (17.8)</td>
<td>61 (21.5)</td>
</tr>
<tr>
<td></td>
<td>&gt; 3, ≤ 6 drinks/week</td>
<td>151 (7.4)</td>
<td>117 (8.0)</td>
<td>34 (5.7)</td>
<td>15 (4.8)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td></td>
<td>&gt; 6 drinks/week</td>
<td>738 (36.0)</td>
<td>570 (39.1)</td>
<td>168 (28.4)</td>
<td>77 (24.9)</td>
<td>91 (32.2)</td>
</tr>
<tr>
<td>Smoking, N (%)</td>
<td>Current</td>
<td>462 (22.5)</td>
<td>327 (22.4)</td>
<td>135 (22.8)</td>
<td>75 (24.3)</td>
<td>60 (21.2)</td>
</tr>
<tr>
<td></td>
<td>Ex-smokers</td>
<td>720 (35.1)</td>
<td>520 (35.7)</td>
<td>200 (33.8)</td>
<td>112 (36.2)</td>
<td>88 (31.1)</td>
</tr>
<tr>
<td></td>
<td>Never smokers</td>
<td>868 (42.3)</td>
<td>611 (41.9)</td>
<td>257 (43.4)</td>
<td>122 (39.5)</td>
<td>135 (47.7)</td>
</tr>
<tr>
<td>Environmental tobacco smoke, N (%)</td>
<td></td>
<td>521 (25.4)</td>
<td>380 (26.1)</td>
<td>141 (23.8)</td>
<td>76 (24.6)</td>
<td>65 (23.0)</td>
</tr>
<tr>
<td>Any regular physical activity, N (%)</td>
<td></td>
<td>1182 (57.7)</td>
<td>891 (61.1)</td>
<td>291 (49.2)</td>
<td>132 (42.7)</td>
<td>159 (56.2)</td>
</tr>
<tr>
<td>BMI (kg/m), mean ± SD</td>
<td></td>
<td>28.1 ± 4.8</td>
<td>28.0 ± 4.6</td>
<td>28.4 ± 5.2</td>
<td>28.7 ± 5.3</td>
<td>28.0 ± 5.1</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td></td>
<td>369 (18.0)</td>
<td>238 (16.3)</td>
<td>131 (22.1)</td>
<td>74 (23.9)</td>
<td>57 (20.1)</td>
</tr>
<tr>
<td>CHD, N (%)</td>
<td></td>
<td>106 (5.2)</td>
<td>58 (4.0)</td>
<td>48 (8.1)</td>
<td>29 (9.4)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Medicated hypertension, N (%)</td>
<td></td>
<td>986 (48.1)</td>
<td>659 (45.2)</td>
<td>327 (55.2)</td>
<td>182 (58.9)</td>
<td>145 (51.2)</td>
</tr>
<tr>
<td>Medications – statins, N (%)</td>
<td></td>
<td>405 (19.8)</td>
<td>264 (18.1)</td>
<td>141 (23.8)</td>
<td>78 (25.2)</td>
<td>63 (22.3)</td>
</tr>
<tr>
<td>Cholesterol (mg/dl), mean ± SD</td>
<td></td>
<td>224.5 ± 40.8</td>
<td>225.0 ± 39.5</td>
<td>223.2 ± 43.9</td>
<td>222.6 ± 46.4</td>
<td>223.8 ± 41.1</td>
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<tr>
<td>Depression (CES-D score), mean ± SD</td>
<td></td>
<td>8.0 ± 6.6</td>
<td>6.6 ± 5.6</td>
<td>11.5 ± 7.6</td>
<td>12.0 ± 8.0</td>
<td>11.0 ± 7.1</td>
</tr>
<tr>
<td>APOE-ε4, N (%)</td>
<td></td>
<td>505 (24.6)</td>
<td>337 (23.1)</td>
<td>168 (28.4)</td>
<td>91 (29.4)</td>
<td>77 (27.2)</td>
</tr>
<tr>
<td>City, N (%)</td>
<td>Essen</td>
<td>650 (31.7)</td>
<td>443 (30.8)</td>
<td>207 (35.0)</td>
<td>93 (30.1)</td>
<td>97 (34.3)</td>
</tr>
<tr>
<td></td>
<td>Bochum</td>
<td>584 (28.5)</td>
<td>427 (29.3)</td>
<td>157 (26.5)</td>
<td>90 (29.1)</td>
<td>64 (22.6)</td>
</tr>
<tr>
<td></td>
<td>Mülheim</td>
<td>742 (36.2)</td>
<td>536 (36.8)</td>
<td>206 (34.8)</td>
<td>93 (30.1)</td>
<td>113 (39.9)</td>
</tr>
</tbody>
</table>
Table 2. Descriptive statistics of exposure variables.

<table>
<thead>
<tr>
<th>Exposure variables</th>
<th>Minimum</th>
<th>25th percentile</th>
<th>Median</th>
<th>75th percentile</th>
<th>Maximum</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Air pollution variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PM$_{2.5}$ (µg/m$^3$)</td>
<td>16.04</td>
<td>17.65</td>
<td>18.29</td>
<td>19.08</td>
<td>21.45</td>
<td>18.39 ± 1.05</td>
</tr>
<tr>
<td>PM$_{2.5}$ absorbance (10$^{-5}$/m)</td>
<td>1.01</td>
<td>1.37</td>
<td>1.52</td>
<td>1.72</td>
<td>3.39</td>
<td>1.58 ± 0.35</td>
</tr>
<tr>
<td>PMcoarse (µg/m$^3$)</td>
<td>0.84</td>
<td>9.29</td>
<td>10.14</td>
<td>11.13</td>
<td>15.00</td>
<td>10.13 ± 1.53</td>
</tr>
<tr>
<td>PM$_{10}$ (µg/m$^3$)</td>
<td>23.97</td>
<td>26.54</td>
<td>27.43</td>
<td>28.62</td>
<td>34.68</td>
<td>27.74 ± 1.84</td>
</tr>
<tr>
<td>NO$_2$ (µg/m$^3$)</td>
<td>19.81</td>
<td>26.79</td>
<td>29.47</td>
<td>32.90</td>
<td>62.44</td>
<td>30.12 ± 4.85</td>
</tr>
<tr>
<td>NOx (µg/m$^3$)</td>
<td>24.30</td>
<td>41.97</td>
<td>49.28</td>
<td>57.66</td>
<td>126.63</td>
<td>50.47 ± 11.70</td>
</tr>
<tr>
<td>Traffic load at major roads (veh*m/d) per 100,000</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>13.50</td>
<td>268.19</td>
<td>9.54 ± 21.20</td>
</tr>
<tr>
<td><strong>Noise variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$L_{DEN}$ (dB(A))</td>
<td>0.00</td>
<td>46.70</td>
<td>52.13</td>
<td>60.87</td>
<td>84.56</td>
<td>53.74 ± 9.49</td>
</tr>
<tr>
<td>$L_{NIGHT}$ (dB(A))</td>
<td>0.00</td>
<td>38.15</td>
<td>43.54</td>
<td>51.75</td>
<td>76.29</td>
<td>44.88 ± 9.17</td>
</tr>
</tbody>
</table>

*Descriptive statistics for the noise exposures are based on continuous variables, without a threshold
Table 3. Association of air pollution and noise with MCI\(^a\), OR (95%CI)

<table>
<thead>
<tr>
<th>Cognitive criterion</th>
<th>PM(_{10}) (IQR=2.09µg/m(^3))</th>
<th>PMcoarse (IQR=1.00µg/m(^3))</th>
<th>PM(_{2.5}) (IQR=1.44µg/m(^3))</th>
<th>PM(_{2.5}) absorbance (IQR=0.35(10^{-5})/m)</th>
<th>NO(_{2}) (IQR=6.11µg/m(^3))</th>
<th>NO(_{x}) (IQR=15.70µg/m(^3))</th>
<th>Traffic load at major roads (veh(*)m/d)(^b)</th>
<th>L(_{DEN}) (threshold 60dB(A))</th>
<th>L(_{NIGHT}) (threshold 55dB(A))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall MCI</td>
<td>1.11 (0.99,1.23)</td>
<td>1.11 (0.98,1.26)</td>
<td>1.16 (1.05,1.27)</td>
<td>1.11 (1.03,1.19)</td>
<td>1.10 (0.97,1.25)</td>
<td>1.10 (0.96,1.26)</td>
<td>1.00 (0.94,1.07)</td>
<td>1.40 (1.03,1.91)</td>
<td>1.80 (1.07,3.04)</td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td>1.17 (1.07,1.35)</td>
<td>1.26 (0.95,1.33)</td>
<td>1.22 (1.08,1.38)</td>
<td>1.17 (1.03,1.35)</td>
<td>1.13 (0.96,1.34)</td>
<td>1.13 (0.96,1.11)</td>
<td>1.03 (0.96,1.11)</td>
<td>1.53 (1.05,2.24)</td>
<td>2.25 (1.23,4.12)</td>
</tr>
<tr>
<td>Non-amnestic MCI</td>
<td>1.04 (0.90,1.21)</td>
<td>1.09 (0.92,1.29)</td>
<td>1.10 (0.92,1.31)</td>
<td>1.03 (0.90,1.19)</td>
<td>1.01 (0.85,1.20)</td>
<td>1.05 (0.85,1.05)</td>
<td>0.95 (0.82,1.93)</td>
<td>1.26 (0.60,2.85)</td>
<td>1.31 (0.60,2.85)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for age, sex, SES, alcohol consumption, smoking status, self-reported ETS, any regular physical activity, BMI

\(^b\)Additionally adjusted for background NO\(_{2}\)
**Figure Legends**

**Figure 1.** Derivation of the study population from participants of the Heinz Nixdorf Recall study.

**Figure 2.** Associations between environmental exposures and overall MCI, aMCI, and ncMCI for crude, main and extended models. Panel A. Association of PM2.5 (per IQR) with overall MCI, aMCI, naMCI. Panel B. Association of LDEN (per 10 dB(A)) with overall MCI, aMCI, naMCI. Main model adjusted for age, sex, SES, alcohol consumption, smoking status, self-reported ETS, any regular physical activity and BMI. Covariates classified as “intermediates” were CHD diagnosis, LDL cholesterol level, diabetes mellitus and intake of statin or anti-hypertensive medication.
Figure 1. Derivation of the study population from participants of the Heinz Nixdorf Recall study
Figure 2.