Long-Term Air Pollution and Traffic Noise Exposures and Mild Cognitive Impairment in Older Adults: A Cross-Sectional Analysis of the Heinz Nixdorf Recall Study

Lilian Tzivian,1 Martha Dlugaj,2 Angela Winkler,2 Gudrun Weinmayr,1 Frauke Hennig,1,3 Kateryna B. Fuks,1 Mohammad Vossoughi,1 Tamara Schikowski,1,4,5 Christian Weimar,2 Raimund Erbel,6 Karl-Heinz Jöckel,3 Susanne Moebus,3 and Barbara Hoffmann,7 on behalf of the Heinz Nixdorf Recall study Investigative Group

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 simultaneous exposure to noise are scarce.

OBJECTIVES: We analyzed the cross-sectional associations of long-term exposure to AP and traffic noise with overall MCI and amnestic (aMCI) and nonamnestic (naMCI) MCI.

METHODS: At the second examination of the population-based Heinz Nixdorf Recall study, cognitive assessment was completed in 4,086 participants who were 50–80 years old. Of these, 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-fractionated particulate matter (PM) and nitrogen oxides with land use regression, and for traffic noise [weighted 24-hr (LDEN) and night-time (Lnight) means]. Logistic regression models adjusted for individual risk factors were calculated to estimate the association of environmental exposures with MCI in single- and two-exposure models.

RESULTS: Most air pollutants and traffic noise were associated with overall MCI and aMCI. For example, an interquartile range increase in PM2.5 and a 10-A-weighted decibel [dBA(i)] increase in LDEN were associated with overall MCI as follows [odds ratio (95% confidence interval)]: 1.16 (1.05, 1.27) and 1.40 (1.03, 1.91), respectively, and with aMCI as follows: 1.22 (1.08, 1.38) and 1.53 (1.05, 2.24), respectively. In two-exposure models, AP and noise associations were attenuated [e.g., for aMCI, PM2.5 1.13 (0.98, 1.30) and LDEN 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.

CITATION: Tzivian L, Dlugaj M, Winkler A, Weinmayr G, Hennig F, Fuks KB, Vossoughi M, Schikowski T, Weimar C, Erbel R, Jöckel KH, Moebus S, Hoffmann B, on behalf of the Heinz Nixdorf Recall study Investigative Group. 2016. Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: a cross-sectional analysis of the Heinz Nixdorf Recall Study. Environ Health Perspect 124:1361–1368; http://dx.doi.org/10.1289/ehp.1509824

Introduction

Age-related cognitive decline is becoming increasingly important because of aging populations in developed countries. Since 1980, the prevalence of dementia has 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 way of characterizing the 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 Disease (AD) stage, and nonamnestic 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 a normal consequence of aging (Glicky 2007), the identification of risk factors for dementia is of great importance for prevention and future treatment options. Several factors are related to dementia, such as age, ethnicity, sex, genetic factors, physical activity, smoking, drug use, education level, alcohol consumption, and body mass index (Chen et al. 2009). Approximately a decade ago, adverse effects of environmental exposures, such as air pollution, on the central nervous system were proposed (Oberdörster and Ustel 2002). However, the effects of air pollution on the cognitive function of adults has not yet been thoroughly investigated (Block et al. 2012; Tzivian et al. 2015). The majority of studies investigating the effects 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, until now, most studies have generally supported 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. Because of their common source, air pollution and traffic noise often occur simultaneously in time and space. Although air pollution and cognitive function have been studied repeatedly, the association of ambient noise with the cognitive function of adults has rarely been investigated (Clark and Stansfeld 2007; Tzivian et al. 2015). Most studies on ambient noise have 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, for example, anxiety and annoyance. To our knowledge, there have been no long-term studies on the effects of traffic noise exposure on the cognitive function of adults. Furthermore, there are a limited number of studies that have investigated simultaneous co-exposures of air pollution and traffic noise on the 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 diagnosed with MCI 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 was a cross-sectional analysis based on data from the first follow-up examination (2006–2008) of the Heinz Nixdorf Recall (Risk factors, Evaluation of Coronary 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 elsewhere (Schmemund et al. 2002). Briefly, 4,814 randomly chosen men and women who were 45–75 years old at baseline were enrolled into the study between December 2000 and August 2003. After 5 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 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 for 4,086 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 1 min) 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 meeting the following criteria received an MCI diagnosis: (a) presence of a subjective cognitive complaint (participants were asked if their cognitive performance had changed during the past 2 years. A complaint was considered present if the participant reported a decline in cognitive performance over time); (b) presence of an objective cognitive impairment that was (c) insufficient to fulfill criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) and reflected (d) generally intact activities of daily living. Presence of objective cognitive impairment (criterion b) 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 if the participant received 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 who showed objective cognitive impairment without subjective cognitive complaint (n = 1,452) were excluded from the main analyses (Figure 1).

We also excluded participants with a physician’s diagnosis of dementia or AD, with intake of cholinesterase inhibitors [Anatomic Therapeutic Chemical (ATC) classification code N06DA or other anti-dementia drugs (N06DX) as issued by the World Health Organization (WHO) (WHO 2004)], or who fulfilled the DSM-IV dementia diagnosis (and did not meet 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 2004). If only nonmemory domains were impaired (at least one), the participant received a diagnosis of nonamnestic 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 with aerodynamic diameter measured in μm—less than 10 μm (PM10), > 2.5 to ≤ 10 μm (PMcoarse), less than 2.5 μm (PM2.5), and PM2.5 absorbance (blackness of the PM2.5-exposed filter, determined by measurement of light reflectance as a marker for soot and black carbon)—was measured at 20 sites, and nitrogen oxides (NOx and NO2) were measured at 40 sites in three separate 2-week periods (to cover different seasons) over 1 year (Beelen et al. 2013). Air pollution measurements were performed between October 2008 and October 2009, and the 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 NO2 was modeled including the data from background measurement stations only while excluding traffic stations from the model (ESCAPE Project 2010). Annual averages (October 2008—September 2009) of measured pollutant concentrations at the monitoring sites and predictor variables, derived from Europe-wide and local geographic information system (GIS) 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 PM10, 77% of that for PM10, 66% of that for PMcoarse, 97% of that for PM2.5, 84% of that for NO2, 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 the weighted 24-hr mean (L10DENV) and the night-time (2200–0600 hours) mean (L10NIGHT) 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 constructed for 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 2007 European noise exposure assessment (European Commission Working Group Assessment of Exposure to Noise 2007).

In addition to air pollution and noise exposure estimates, we used small-scale noise indicators. The total traffic load at major roads (> 5,000 vehicles/day) in a 100-m buffer (vehicles × meters/day) was obtained from local road networks with traffic intensity data. Additional sensitivity analyses were performed using exposure variables from the European Air Pollution Dispersion and Chemistry Transport Model (EURAD-CTM) (Memmesheimer et al. 2004). This model used input data from official emission inventories on a spatial resolution of 1 km2 grid cells and included industrial sources, household heating, traffic and agriculture, and data on hourly meteorology and regional topography. Furthermore, pollutants entering the area by long-range transport were taken into account (Memmesheimer et al. 2004). The model output reflected the long-term urban background concentrations in the 1 km2 grid cell of the residential address of the participant. We used modeled averages of PM2.5, PM10, and NO2 for the years 2001–2003 to represent long-term exposure to air pollution.

**Covariates**

Individual-level characteristics including age, sex, socioeconomic status (SES, assessed as education level, classified by the International Standard Classification of Education (ISCED) as total years of formal education, combining school and vocational training), 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 sports activities) were assessed in standardized interviews and questionnaires. Anthropometry was measured according to standardized protocols, and body mass index (BMI) was calculated (kilograms per meters squared). Further intermediates included coronary heart disease (CHD), which was 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 as categorized according to the Anatomical Therapeutic Chemical (ATC) classification index (WHO 2004) during the 7 days before examination. Apolipoprotein E (APOE) genotypes were investigated because the APOE ε4 allele has been shown to increase the risk for Alzheimer disease. Genotyping was performed using 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, and 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 Baler 1993).

**Statistical Analysis**

All air pollution components estimated with ESCAPE-LUR were obtained as continuous variables and included in the models per interquartile range (IQR). Noise exposure was investigated as a continuous variable with a threshold at 60 A-weighted decibels (dB(A)) for L10DENV and 55 dB(A) for L10NIGHT, respectively, and calculated per 10 dB(A) increase. Threshold values were selected as those at which cardiovascular health effects have previously been 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 NO2. 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, medium, and high according to ≤ 10, 11–13, and ≥ 14 years of education), alcohol consumption (categorized as 0, 1–3, > 3 and ≤ 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 nonlinear 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 R2 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 ε4 (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—one at the median and the second at the 75th percentile—and
constructed product terms of air pollution (dichotomous) \times noise. Noise variables were dichotomized on the threshold values [60 dB(A) for \text{L}_\text{DEN} and 55 dB(A) for \text{L}_\text{NIGHT}] for interaction analysis with continuous air pollution variables. We also evaluated possible effect modification by age (< 65 vs. \geq 65 years), sex, SES (low and medium vs. high education), BMI (\leq 30 vs. > 30), smoking status (non-smoker vs. current and former smoker), alcohol consumption (\leq 6 drinks per week vs. > 6 drinks per week), APOE ε4 (carrier vs. non-carrier), and depression (< 18 vs. \geq 18 on the CES-D scale).

**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-CITM (Mennemheimer 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 with 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 \text{L}_\text{DEN} and 50 dB(A) for \text{L}_\text{NIGHT}] with a continuous noise variable without a threshold (per IQR of exposure). We also analysed noise variables in 10 dB(A) categories [≥ 45 to < 55 dB(A); ≥ 55 to < 65 dB(A); ≥ 65 to < 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 the latter group, 309 had aMCI, and 283 had 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 approximately one-quarter of all participants reporting exposure to environmental tobacco smoke (ETS). Medication for hypertension was used by 45% of the unimpaired participants and 55% of those with MCI, and statin use was reported by 18% and 24%, respectively (Table 1).

The mean concentrations of PM₂.₅ and PM₁₀ were 18.4 μg/m³ and 27.7 μg/m³, 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).

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

| Variable/subgroups          | Total population, \( n = 2,050 \) | Unimpaired group, \( n = 1,458 \) | Overall MCI, \( n = 592 \) | Amnestic MCI, \( n = 309 \) | Non-amnestic MCI, \( n = 283 \) |
|-----------------------------|-----------------------------------|----------------------------------|---------------------------|---------------------------|---------------------------|
| Age (years), mean ± SD     | 64.1 ± 7.7                        | 63.2 ± 7.4                       | 66.3 ± 7.9                | 66.0 ± 8.0                | 66.6 ± 7.7                |
| Men, n (%)                 | 1,007 (49.1)                      | 718 (49.2)                       | 289 (48.8)                | 169 (54.7)                | 120 (42.4)                |
| Education level, n (%)     |                                    |                                  |                           |                           |                           |
| Low                         | 191 (9.3)                         | 122 (8.4)                        | 69 (11.7)                 | 38 (12.3)                 | 31 (10.9)                 |
| Medium                      | 1,142 (55.7)                      | 785 (53.8)                       | 357 (60.3)                | 184 (59.5)                | 173 (61.1)                |
| High                        | 716 (34.9)                        | 551 (37.8)                       | 165 (27.9)                | 86 (27.8)                 | 79 (27.9)                 |
| Alcohol consumption, n (%) |                                    |                                  |                           |                           |                           |
| Never                       | 726 (35.4)                        | 468 (32.1)                       | 258 (43.6)                | 152 (49.2)                | 106 (37.5)                |
| 1–3 drinks/week             | 400 (19.5)                        | 284 (19.5)                       | 116 (19.6)                | 55 (17.8)                 | 61 (21.5)                 |
| > 3,≤ 6 drinks/week         | 151 (7.4)                         | 117 (8.0)                        | 34 (5.7)                  | 5 (1.8)                   | 9 (6.7)                   |
| > 6 drinks/week             | 738 (36.0)                        | 570 (39.1)                       | 168 (28.4)                | 77 (24.9)                 | 91 (32.2)                 |
| Smoking, n (%)              |                                    |                                  |                           |                           |                           |
| Current                     | 462 (22.5)                        | 327 (22.4)                       | 135 (22.8)                | 75 (24.3)                 | 60 (21.2)                 |
| Former smokers              | 720 (35.1)                        | 520 (35.7)                       | 200 (33.8)                | 112 (36.2)                | 88 (31.1)                 |
| Never smokers               | 886 (42.3)                        | 611 (41.9)                       | 257 (43.4)                | 122 (39.5)                | 135 (47.7)                |
| Environmental tobacco smoke, n (%) | 521 (25.4) | 380 (26.1) | 141 (23.8) | 76 (24.8) | 65 (23.0) |
| Any regular physical activity, n (%) | 1,192 (57.7) | 891 (61.1) | 291 (49.2) | 132 (42.7) | 159 (56.2) |
| BMI (kg/m²), mean ± SD      | 28.1 ± 4.8                        | 28.0 ± 4.6                       | 28.4 ± 5.2                | 28.7 ± 5.3                | 28.0 ± 5.1                |
| Diabetes, n (%)             | 369 (18.0)                        | 238 (16.3)                       | 131 (22.1)                | 74 (23.9)                 | 57 (20.1)                 |
| CHD, n (%)                  | 106 (5.2)                         | 58 (4.0)                         | 48 (8.1)                  | 29 (9.4)                  | 19 (6.7)                  |
| Medicated hypertension, n (%) | 986 (48.1) | 659 (45.2) | 327 (55.2) | 182 (58.9) | 145 (51.2) |
| Medications – statins, n (%) | 405 (19.8) | 264 (18.1) | 141 (23.8) | 78 (25.2) | 63 (22.3) |
| Cholesterol (mg/dL), mean ± SD | 224.5 ± 40.8 | 225.0 ± 39.5 | 223.2 ± 43.9 | 222.6 ± 46.4 | 223.8 ± 41.1 |
| Depression (CES-D score), mean ± SD | 8.0 ± 6.6 | 6.9 ± 6.6 | 11.5 ± 7.6 | 12.0 ± 8.0 | 11.0 ± 7.1 |
| APOE ε4, n (%)              | 505 (24.6)                        | 337 (23.1)                       | 168 (28.4)                | 91 (29.4)                 | 77 (27.2)                 |
| City, n (%)                 | 650 (31.7)                        | 443 (30.8)                       | 207 (35.0)                | 93 (30.1)                 | 97 (34.3)                 |
| Bochum                      | 584 (28.5)                        | 427 (29.3)                       | 157 (26.5)                | 90 (29.1)                 | 64 (22.6)                 |
| Mülheim                     | 742 (36.2)                        | 536 (36.8)                       | 206 (34.8)                | 93 (30.1)                 | 113 (39.9)                |

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression scale; CHD, coronary heart disease; APOE, apolipoprotein E.
of L\textsubscript{NIGHT} with MCI and its subtypes were slightly lower than those obtained with L\textsubscript{DEN} (Table 3). All AP and noise exposures were more strongly associated with aMCI than with overall MCI or naMCI. Traffic indicator variables were not associated with MCI or its subtypes.

Point estimates for associations with PM\textsubscript{2.5} and L\textsubscript{DEN} were robust to different model specifications (Figure 2). Results for associations with other air pollutants and with L\textsubscript{NIGHT} were also 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 variables (CHD diagnosis, LDL cholesterol) did not change the association of PM\textsubscript{2.5} with MCI and aMCI and the association of L\textsubscript{DEN} with MCI remained significant after adjustment for PM\textsubscript{2.5} (Figure 2).

Additional adjusted for background NO\textsubscript{2}.

Conclusion analysis of noise variables showed similar results to those of the main analysis (see Table S3). Categorical analysis of noise variables revealed elevated estimates > 65 dB(A) (see Table S3).

Discussion
We found that long-term exposure to both air pollution and road traffic noise was associated with overall MCI, particularly with the amnestic subtype, in this middle- and older-aged German study population. In two-exposure models including both PM\textsubscript{2.5} and noise, we observed a trend towards a higher susceptibility in carriers of the APOE risk allele (OR = 1.30, 95% CI: 0.89, 2.05) compared with other participants (OR = 1.10, 95% CI: 0.83, 1.49). The results of sensitivity analyses for noise variables with a 65-dB(A) threshold for L\textsubscript{DEN} and a 50-dB(A) threshold for L\textsubscript{NIGHT} and for continuous noise variables showed similar results to those of the main analysis (Table S2). Categorical analysis of noise variables revealed elevated estimates > 65 dB(A) (Table S3).
and LDEN, effect estimates for both exposures remained positive and the association with noise remained statistically significant for overall MCI and aMCI. Our results also indicated that the two investigated environmental exposures may interact with each other. Specifically, associations of PM$_{2.5}$ with overall MCI were stronger among those exposed to higher levels of noise, and the association of LDEN 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 the findings of previous studies that have reported associations 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 LDEN and L NIGHT) was positively associated with MCI. Similar to the association with air pollutants, the association with ambient noise (both LDEN and L NIGHT) was stronger for aMCI than for naMCI. This is a novel finding; studies investigating the association between ambient noise and cognitive functions in the general adult population are scarce (Wright et al. 2014; Basner et al. 2014). Importantly, our results showed that positive associations of environmental exposures with MCI continued to be evident when adjusted for confounding by the other exposure. If corroborated by other studies, this finding 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 associations between PM$_{2.5}$, O$_3$, and NO$_2$ with attention, memory, and executive functions in 1,496 residents of Los Angeles, California (Gatto et al. 2014), and in a longitudinal study investigating the effects of PM$_{2.5}$ and PM$_{10}$ on the decline of inductive reasoning, verbal fluency, and verbal memory in 2,867 older residents of London, U.K. (Tonne et al. 2014), air pollution was associated with reduced verbal and logical memory, respectively, and in a cross-sectional analysis of NHANES data for 1,764 U.S. adults (Chen and Schwartz 2009), the association of PM$_{10}$ with memory function disappeared after adjustment for personal covariates. In line with the findings reported by Gatto et al. (2014) and by Tonne et al. (2014), we found highly consistent associations of air pollution and traffic noise with memory-related aMCI. This outcome is potentially of great public health importance because aMCI may be associated with an elevated risk of developing AD (Petersen 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 high exposure to air pollution (Calderón-Garcidueñas et al. 2008). Furthermore, an experimental study of rats exposed to diesel exhaust by inhalation over 4 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 an animal study, Arnsten and Goldman-Rakic (1998) reported that in monkeys, mild noise exposure significantly impaired performance in spatial working memory, which is dependent on prefrontal cortex function, and elicited excessive dopamine release (Arnsten and Goldman-Rakic 1998). Because there is a lack of evidence regarding the 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.

Figure 2. Associations between environmental exposures and overall mild cognitive impairment (MCI), amnestic MCI (aMCI), and nonamnestic MCI (naMCI) for crude, main and extended models. (A) Association of PM$_{2.5}$ (per interquartile range [IQR]) with overall MCI, aMCI, naMCI. (B) Association of weighted 24-hr average (LDEN) (per 10 A-weighted decibels [dB(A)]) with overall MCI, aMCI, naMCI. Main model adjusted for age, sex, socioeconomic status, alcohol consumption, smoking status, self-reported environmental tobacco smoke, any regular physical activity, and body mass index. Covariates classified as “intermediates” were coronary heart disease diagnosis, low-density lipoprotein cholesterol level, diabetes mellitus and intake of statin or anti-hypertensive medication.
We did not find a significant association between air pollution and naMCI, although the odds ratios were elevated. In contrast, in a longitudinal study by Kiomourtzoglou et al. (2016) that assessed the effects 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 disease, which is closely related to naMCI (Costello et al. 2011). In turn, naMCI 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 of the Heinz Nixdorf Recall study population found associations between long-term PM air pollution and risk factors for or manifestations of atherosclerosis and cardiovascular 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.

In general, we found the 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. Although some studies have reported strong associations of cognitive function with smaller particles or with traffic-related exposures and soot (Loop et al. 2013; Ranft et al. 2009), others observed associations with larger particle fractions (Chen and Schwartz 2009). Only a few studies have comprehensively compared the associations between cognitive outcomes and different particle size fractions and air pollution components (Chen and Schwartz 2009; Weuve et al. 2012), and these studies have yielded different results. For example, in a cohort study by Weuve et al. (2012) that investigated the effects of PM$_{2.5}$, PM$_{2.5-10}$, and PM$_{10}$ on global cognition, verbal memory, and executive function in 10,409 participants in a 7-year follow-up examination, an association of PM$_{2.5-10}$, but not of PM$_{2.5}$ or of PM$_{10}$, with global cognitive decline was found, and in a 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 a database of a middle- and older-age population in the highly urbanized German Ruhr area. Unless more studies with other study populations and methods are conducted in different areas of the world, the generalizability of the present findings cannot be assessed. One important limitation of this study is its cross-sectional design, which prevented us from establishing a temporal relationship between air pollution/noise and MCI. In addition, cognitively impaired people were probably less likely to have participated in the study, which could have led to selection bias. Another limitation of our study is the absence of detailed information on room location, type of windows, and other factors that can contribute to misclassification of both noise- and air-pollution exposure. Additionally, some of the personal variables (alcohol consumption, physical activity, smoking status) 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 because they share a common source and are moderately correlated.

Our study has several strengths. To our knowledge, this is the first study that has investigated the association of different air pollutants and noise with cognitive function in two-exposure models. Additionally, this is the first study that has assessed the effects of air pollution and noise in participants with MCI. Because 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 with both clinically important MCI subtypes, aMCI and naMCI. Furthermore, we excluded all participants with either only objective impairment or only subjective cognitive complaints, 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 enabled good control of confounding factors. The population-based nature of this study and the standardized outcome assessment methods, as well as the large sample size, are additional strengths.

**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**

Arbsten AFT, Goldman-Rakic PS. 1998. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatry 55(4):382–388.

Babisch W. 2008. Road traffic noise and cardiovascular risk. Noise Health 10:27–33.

Basner M, Babisch W, Davis A, Brink M, Clark C, Janssen S, et al. 2014. Auditory and non-auditory effects of noise on health. Lancet 383:1325–1332.

Beelen R, Hoek G, Fischer P, van den Brandt PA, Brunekreef B. 2007. Estimated long-term outdoor air pollution concentrations in a cohort study. Atmos Environ 41:1343–1358.

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X, et al. 2013. Development of NO$_2$ and NO$_x$ land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project. Atmos Environ 72:10–23.

Block ML, Calderón-Garcidueñas L. 2009. Air pollution: mechanisms of neuroinflammation and CNS disease trends. Nueroscosi 30(9):506–516.

Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. 2012. The outdoor air pollution and brain health workshop. Neurotoxicology 33:972–984.

Brook RD, Rajagopalan S, Pope CA III, Brook JR, Bhatnagar A, Drez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121:2331–2378.

Calderón-Garcidueñas L, Reed W, Maronpot RR, Henríquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, et al. 2004. Brain inflammation and Alzheimer’s-like pathology in individuals exposed to severe air pollution. Toxicol Pathol 32:650–658.

Calderón-Garcidueñas L, Soft AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, et al. 2008. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. Toxicol Pathol 36(2):289–310.

Chen JC, Schwartz J. 2009. Neurobehavioural effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology 30:231–239.

Chen JH, Lin KP, Chen YC. 2010. Risk factors for dementia. J Formos Med Assoc 108:754–764.

Clark C, Stansfeld SA. 2007. The effect of transportation noise on health and cognitive development: a review of recent evidence. Int J Comp Psychol 20:145–158.

Costello A, Al Khames H, Moriarty J, Hulse N, Malik I, Selway R, et al. 2011. Non-annemic mild cognitive impairment is a prominent aspect in Parkinson’s disease patients being considered for deep brain stimulation. Basal Ganglia 1:213–220.

Dlugaj M, Weimar C, Wege N, Verde PE, Gerwig M, Dragoanu N, et al. 2010. Prevalence of mild cognitive impairment and its subtypes in the Heinz Nixdorf Recall study cohort. Dement Geriatr Cogn Disord 30:382–393.

Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for PM$_{2.5}$, PM$_{10}$ and PM$_{coarse}$ in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46:1195–1120.

Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. 2010. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical
coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 58:1297–1406.

ESCAPE Project. 2010. ESCAPE Exposure Assessment Manual. http://www.escapeproject.eu/manuals/ESCAPE_Exposure MANUALV9.pdf [accessed 8 August 2016].

European Commission. 2002. Directive 2002/49/EC of the European Parliament and of the Council of 25 June 2002 relating to the assessment and management of environmental noise. OJ L 189:0012–0026.

European Commission Working Group Assessment of Exposure to Noise (WG-AEN). 2007. Position paper: Good practice guide for strategic noise mapping and the production of associated data on noise exposure. Version 2. https://www.lfu.bayern.de/laerm/eg_umgebungslaermrichtlinie/doc/good_practice_guide_2007.pdf [accessed 8 August 2016].

Gatto NM, Henderson WV, Hodis HN, St John JA, Lurmann F, Chen JC, et al. 2014. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology 40:1–7.

Glisky EL. 2007. Changes in cognitive function in human aging. In: Brain Aging: Models, Methods, and Mechanisms (Riddle DR, ed). Boca Raton, FL:CRC Press/Taylor & Francis, 1–15.

Guxens M, Sunyer J. 2012. A review of epidemiological studies on neuropsychological effects of air pollution. Swiss Med Wkly 141:w13322, doi:10.4414/smw.2011.13322.

Hautzinger M, Baillier M. 1993. Allgemeine Depressions Skala – ADS [in German]. Weinheim:Beltz.

Hoffmann B, Moebus S, Möhlenkamp S, Stang A, Lehmann N, Dragoanu N, et al. 2007. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 116:495–496.

Hygge S, Boman E, Enmarker I. 2007. The effects of road traffic noise and meaningful irrelevant speech on different memory systems. Scand J Psychol 44:13–21.

Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. 2016. Long-term PM2.5 exposure and neurological hospital admission in the northeastern United States. Environ Health Perspect 124:23–28, doi:10.1289/ehp.1408973.

Levesque S, Taetzsch T, Lull ME, Kodavanti U, Statler K, Wagner A, et al. 2011. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotranscytosis. Environ Health Perspect 119:1149–1155, doi:10.1289/ehp.1002986.

Loop MS, Kent ST, Al-Hamdan MZ, Crosson WL, Estes SM, Estes MG Jr, et al. 2013. Fine particulate matter and incident cognitive impairment in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. PLoS One 8:e75001, doi:10.1371/journal.pone.0075001.

Memesheimer M, Friese E, Ebel A, Jakobs HJ, Feldmann H, Kessler C, et al. 2004. Long-term simulations of particulate matter in Europe on different scales using sequential nesting of a regional model. Int J Environ Pollut 22:108–132.

Oberdörster G, Utell MJ. 2002. Ultrafine particles in the urban air: to the respiratory tract—and beyond? [Editorial]. Environ Health Perspect 110:A440–A441.

Paciaroni M, Bogousslavsky J. 2013. Connecting cardiovascular disease and dementia: future evidences. J Am Heart Assoc 2:e000856, doi:10.1161/JAHA.113.000856.

Petersen RC. 2004. Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. 1999. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56:303–308.

Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A III, Schwartz J. 2011. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect 119:682–687, doi:10.1289/ehp.1002767.

Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. 2013. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 9:63–75e2.

R Core Team. 2013. R: A Language and Environment for Statistical Computing. Vienna, Austria:R Foundation for Statistical Computing. http://www.R-project.org/ [accessed 8 August 2016].

Ranft U, Schikowski T, Sugiri D, Krumtum J, Krämer U. 2009. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environ Res 109:1004–1011.

Schapkin SA, Falkenstein M, Marks A, Graftein B. 2006. Executive brain functions after exposure to nocturnal traffic noise: effects of task difficulty and sleep quality. Eur J Appl Physiol 96:693–702.

Schmerrmund A, Möhlenkamp S, Stang A, Grönnemeyer D, Seibel R, Hrche H, et al. 2002. Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Am Heart J 144:212–218.

Stansfeld SA, Haines MM, Burr M, Berry B, Lercher P. 2000. A review of environmental noise and mental health. Noise Health 2:1–8.

Tonne C, Elbaz A, Beesers S, Sigh-Manoux A. 2014. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 25:674–681, doi:10.1097/EDE.0000000000000144.

Tzivian L, Winkler A, Dlugaj M, Schikowski T, Vossoughi M, Fuku K, et al. 2015. Effect of long-term outdoor air pollution and noise on cognitive and psychological functions in adults. Int J Hyg Environ Health 218:1–11.

Wege N, Dlugaj M, Siegrist J, Dragoanu N, Erbel R, Jöckel KH, et al. 2011. Population-based distribution and psychometric properties of a short cognitive performance measure in the population-based Heinz Nixdorf Recall Study. Neuroepidemiology 37:13–20.

Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. 2012. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 172:219–227.

World Health Organization (WHO). 2004. The anatomical, therapeutic, and chemical classification system with defined daily doses. http://www.whoccs.nic.in/cccddd_index/ [accessed 8 August 2016].

Wright B, Peters E, Ettinger U, Kuipers E, Kumari V. 2014. Understanding noise stress-induced cognitive impairment in healthy adults and its implications for schizophrenia. Noise Health 16:166–176.