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Air pollution as a risk factor for Cognitive Impairment no Dementia (CIND) and its progression to dementia: A longitudinal study

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ABSTRACT

Background and aim: Accumulation of evidence has raised concern regarding the harmful effect of air pollution on cognitive function, but results are diverging. We aimed to investigate the longitudinal association of long-term exposure to air pollutants and cognitive impairment and its further progression to dementia in older adults residing in an urban area.

Methods: Data were obtained from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). Cognitive impairment, no dementia (CIND) was assessed by a comprehensive neuropsychological battery (scoring ≥1.5 standard deviations below age-specific means in ≥1 cognitive domain). We assessed long-term residential exposure to particulate matters ($PM_{2.5}$ and PM_{10}) and nitrogen oxides (NO_x) with dispersion modeling. The association with CIND was estimated using Cox proportional hazards models with 3-year moving average air pollution exposure. We further estimated the effect of long-term air pollution exposure on the progression of CIND to dementia using Cox proportional hazards models.

Results: Among 1987 cognitively intact participants, 301 individuals developed CIND during the 12-year follow-up. A 1-μg/m^3 increment in $PM_{2.5}$ exposure was associated with a 75% increased risk of incident CIND (HR = 1.75, 95 %CI: 1.54, 1.99). Weaker associations were found for PM_{10} (HR for 1-μg/m^3 = 1.08, 95 %CI: 1.03–1.14) and NO_x (HR for 10 μg/m^3 = 1.18, 95 %CI: 1.04–1.33). Among those with CIND at baseline (n = 607), 118 participants developed dementia during follow-up. Results also show that exposure to air pollution was a risk factor for the conversion from CIND to dementia ($PM_{2.5}$: HR for 1-μg/m^3 = 1.90, 95 %CI: 1.48–2.43; PM_{10}: HR for 1-μg/m^3 = 1.14, 95 %CI: 1.03–1.26; and NO_x: HR for 10 μg/m^3 = 1.34, 95 %CI: 1.07–1.69).

Conclusion: We found evidence of an association between long-term exposure to ambient air pollutants and incidence of CIND. Of special interest is that air pollution also was a risk factor for the progression from CIND to dementia.

1. Introduction

Driven by the increasing life expectancy in the last decades, the rapid global aging of populations leads to a higher prevalence of age-related cognitive dysfunctions. The subtle pathological changes in the brains of older adults start even decades before a clinical diagnosis of dementia (Bateman et al., 2012; Whalley et al., 2006). Cognitive impairment, no dementia (CIND) describes individuals whose cognitive functioning falls below normal but does not meet dementia criteria. Importantly, CIND potentially identifies a subgroup at higher risk of developing dementia

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(Grande et al., 2019; Giulia Grande et al., 2020; Plassman et al., 2011). Although a certain degree of decline in cognitive functions can be considered a normal consequence of aging, the identification of modifiable risk factors for mild cognitive changes should be urgently prioritized, as these may be essential for the prevention or postponement of dementia development.

Exposure to air pollution can cause substantial adverse health effects at all stages of life, and especially in the more vulnerable people such as the children and elderly (Clifford et al., 2016). Around twenty years ago, Oberdörster and colleagues suggested the potential adverse effects of air pollution on the nervous system (Oberdörster and Utell, 2002). At that time, the majority of research has focused on the adverse effect on cognitive function in childhood and adolescence (Clifford et al., 2016). The effects of air pollution on adult cognitive function, on the other hand, have yet to be extensively studied. Later, in older adults, the effect of air pollution on cognitive functioning (Cacciottolo et al., 2017; Kulick et al., 2020; Weuve et al., 2012) and dementia incidence (Chen et al., 2017; G. Grande et al., 2020; Ilango et al., 2020; Oudin et al., 2016) have been studied with mixed or sometimes contradictory findings (Peters et al., 2019). Some studies suggested that particulate matter (PM) may adversely affect cognitive performance (Cacciottolo et al., 2017; Kulick et al., 2020; Weuve et al., 2012), but others did not observe such association (Loop et al., 2013; Tonne et al., 2014), and there is contradicting evidence regarding an association between nitrogen oxide species (NO_x) exposure and cognitive decline (Oudin et al., 2017; Paul et al., 2020). The inconsistent results may be due to differences in assessment of cognitive performance, types of air pollutants, and length of the exposure period.

Using a well-characterized population-based study with high-resolution dispersion modeling and longitudinal clinical assessments, our objectives were to: 1. assess the impact of long-term exposure to PM and NO_x on incident cognitive impairment; 2. explore whether exposure to air pollution accelerates the progression from CIND to dementia.

2. Material and methods

2.1. Study population

For the present study, we used data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), which is an ongoing community-based longitudinal study of participants aged 60 and above, living at home or in an institution in the Kungsholmen district of Stockholm (Lagergren et al., 2004). Participants are followed up every six years between age 60 and 72 years and every three years from age 78 years and onwards. At baseline (between 2001 and 2004), 3363 (73.3% response rate) of all eligible individuals were assessed. We formed a study sample of 2594 individuals who at baseline performed a complete neuropsychological assessment (n = 2689) and were not then found to suffer from dementia (n = 83), schizophrenia (n = 11), or developmental disorder (n = 1). The detailed flowchart of the study population is described in Supplementary Fig. 1.

The results were reported following the Strengthening the reporting of observational studies in epidemiology (STROBE) Recommendations (von Elm et al., 2008).

2.2. Data collection

A comprehensive assessment following standard questionnaires, medical examinations, and interviews was performed by trained nurses and physicians to collect demographic, clinical, and functional measures from all participants. Neuropsychological assessment was performed by psychologists in all waves of the SNAC-K study (Laukka et al., 2020). Participants who agreed to participate but were not able to come to the center were assessed by home visits. All waves of the study were approved by the Regional Ethical Review Board in Stockholm, Sweden. Participants have provided written informed consents, or from a proxy, in case of severe cognitive impairment.

2.3. Assessment of long-term air pollution

Participants' residential addresses were updated during follow-up assessments. Long-term air pollution levels at the residential addresses were assessed using spatiotemporal dispersion modeling, based on local emission inventories and meteorological data, as previously described (Segersson et al., 2017). Briefly, emissions of fine particulate matter with a diameter < 2.5 μm ($PM_{2.5}$), respirable particulate matter with a diameter < 10 μm (PM_{10}), and nitrogen oxides (NOx) were documented through local emission inventories for the years 1990, 1995, 2000, 2005 and 2011. Gaussian dispersion models with a quadtree receptor grid ranging from 35 to 500 m side squares were applied to the emissions together with climatologies. The maps of PM and NOx concentrations in the Kungsholmen district, Stockholm, from 1990 to 2011 are presented in Supplementary Figs. 2–4. For the period 1990–2011, annual average levels of pollutants were obtained from linear interpolation over the four years between each model simulation. We compared the calculated levels of air pollutants with yearly measurements at three curbsides (traffic) monitoring sites and one urban background site in Stockholm City for the period 1990–2011, resulting r^2-values were 0.99 for $PM_{2.5}$, 0.99 for PM_{10}, and 0.99 for NOx. Due to stable pollution levels at urban background stations, levels for 2012 and 2013 were set as for 2011.

2.4. Assessment of cognitive impairment, no dementia (CIND)

CIND diagnosis at baseline and during the follow-up examinations was assigned following Graham et al (Graham et al., 1997) criteria. Diagnosis required the absence of dementia and the presence of an objective cognitive impairment in at least one of the following domains: memory, executive function, language, visuospatial or perceptual speed function. Impairment in each domain was operationalized as scoring 1.5 standard deviations (SDs) below age-specific means based on the baseline SNAC-K cohort. The same procedure was used to create CIND at follow-up, using the baseline cut-offs.

The following cognitive tests were administered: free recall (episodic memory), Trail Making Test Part B (executive function), Category and Letter Fluency (language), mental rotation (visuospatial ability), and digit cancellation and pattern comparison (perceptual speed). For domains including more than one cognitive test, we created a domain score by averaging the z-scores of the included tests. The detailed description of the neuropsychological tests battery is presented in Supplementary Table 8.

2.5. Assessment of dementia

Diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and followed a 3-step procedure. A first diagnosis was made by the examining physician and followed by a second diagnosis by a reviewing physician, who also was involved in the data collection. In case of disagreements on the diagnoses, a neurologist external to the data collection made the final diagnosis. To account for the dementia cases among those who died between follow-up evaluations, we also included dementia cases diagnosed from the Swedish National Cause of Death Register and clinical medical records.

2.6. Assessment of covariates

Potential confounders were identified a *priori* in the literature. Education level was categorized as elementary, high school, or university or above. Socioeconomic status (SES) was assessed using the longest-held occupation, which was categorized as blue-collar and white-collar workers. Smoking habits were categorized as never, former, or current smokers. Early retirement was defined as retirement before age 65. The level of physical activity was based on a questionnaire administered to

the participants, which assesses both the frequency and the intensity of these activities. Physical inactivity was defined as being physically active less than once a week in light and/or intensive activity. The neighborhood household mean income at baseline was retrieved from Statistic Sweden (Pyko et al., 2019).

2.7. Statistical methods

Firstly, we investigated the associations of long-term exposure to air pollution and incident CIND in participants who were cognitively intact at baseline (n = 1987). Participants were considered at risk until the first CIND diagnosis, death, dementia, or last assessment, whichever came first. Next, in participants with a diagnosis of CIND at baseline (n = 607), we evaluated the association of long-term air pollution exposure with progression to dementia. Participants were considered at risk until dementia diagnosis, death, or last assessment.

In our main analysis, to consider the long-term cumulative effect and temporal changes of air pollution, we included exposure to air pollution as a time-varying variable between assessment occasions. Following the approximate 3-year interval between testing cycles, we assigned air pollution exposure using three-year moving averages of air pollution levels prior to the end of follow-up. To testify the robustness of the results, we then repeated the analyses by including air pollution levels at different averaging periods: 1) average levels of air pollutants from baseline assessment to the end of follow-up; 2) yearly exposure with lag 1–3 years prior to the disease onset. The departures from linearity for air pollution exposure were fitted as cubic splines with three knots at fixed percentiles (10th, 50th, 90th) of its distribution, as an alternative to the linear term.

Hazard ratio (HR) and 95% confidence interval (CI) for both outcomes were estimated using Cox proportional hazard models. The proportional hazards assumption was tested by describing the survival curves and Schoenfeld residuals. To account for the effect of the competing risk of death, we estimated the subdistribution hazard ratio (sHR) using the Fine and Gray competing risk regression models (Andersen et al., 2012). All models were adjusted for potential confounders that were identified based on reviewing the literature and according to the definition of a confounding variable: age, sex, SES, education, smoking, physical activity, neighborhood household mean income, and early retirement. We also included the number of cognitive test occasions to control for the potential retest effect in the study design.

We conducted additional sensitivity analyses to assess whether loss to follow-up might affect the results. Initially, we ran logistic regression models for dropouts and included participants, considering their sex, age, and education levels. An inverse probability weight (IPW) was estimated to create a pseudo-population, mimicking the total population before censoring (Mansournia and Altman, 2016). We, therefore, ran the marginal structural Cox proportional hazards models in the uncensored population, including the IPW weight. The potential temporal trends in exposure and outcome were investigated by adjusting the models for the year of baseline assessment and using age as the underlying timescale. We then excluded from the analysis those who developed dementia without preceding CIND (n = 58) diagnosis to take into account the possible informative censoring.

All analyses were performed in Stata SE, version 16 (StataCorp LLC).

3. Results

3.1. Effect of air pollution on cognitive impairment

Among 1987 cognitively intact participants at baseline, 301 developed CIND during 12 years of follow-up. Participants who developed CIND during follow-ups were older, had lower education levels, earlier retirement, and lower SES status, as compared with those who did not develop CIND (Table 1).

The associations between the air pollution exposures at different time lags with CIND incidence, adjusting for potential confounders, are shown in Table 2. When using 3-year moving average air pollution exposure, we observed a higher hazard of incident CIND per 1 μg/m^3 increment of $PM_{2.5}$ (HR = 1.75, 95% CI: 1.54, 1.99), PM_{10} (HR = 1.08, 95% CI 1.03, 1.14) and per 10 μg/m^3 of NOx exposure (HR = 1.18, 95 CI % 1.04, 1.33) (Table 2, model 1). Similar estimates were observed when using the average levels from baseline to end of follow-up of $PM_{2.5}$ (HR for 1-μg/m^3 = 1.73, 95% CI 1.50, 1.99), PM_{10} (HR for 1-μg/m^3 = 1.07, 95 %CI 1.01, 1.12) and NOx (HR for 10-μg/m^3 = 1.13, 95 %CI 1.00, 1.28). Exposure to $PM_{2.5}$ at 1 year prior to disease onset was associated with about 54% increased hazard for CIND incidence (HR for 1-μg/m^3 = 1.54, 95 %CI 1.42, 1.67). Exposure to $PM_{2.5}$ at yearly lag 2 (HR for 1-μg/m^3 = 1.54, 95 %CI 1.41, 1.69) and yearly lag 3 (HR for 1-μg/m^3 = 1.75, 95 %CI 1.59, 1.93) showed 54% and 75% increased hazards for CIND incidence, respectively. The yearly lags of PM_{10} and NOx showed consistent estimates for CIND onset. Results for the competing risk analysis are reported in Table 2, model 2. Exposure to 3-year moving average $PM_{2.5}$, PM_{10}, and NOx were associated to respectively 64% (sHR for 1-μg/m^3 = 1.64, 95 %CI 1.46, 1.84), 8% (sHR for 1-μg/m^3 = 1.08, 95 %CI 1.03, 1.12), and 15% (sHR for 10-μg/m^3 = 1.15, 95 %CI 1.03, 1.29) increased sub-hazard for CIND after considering competing risk of death. We also observed similar effects by repeating the competing risk analysis used average levels from baseline to end of follow-up of $PM_{2.5}$ (sHR for 1-μg/m^3 = 1.66, 95 %CI 1.46, 1.89), PM_{10} (sHR for 1-μg/m^3 = 1.06, 95 %CI 1.01, 1.11), and NOx (sHR for 10-μg/m^3 = 1.12, 95 % CI 0.99, 1.25).

Table 1
Baseline characteristics of the overall sample and stratified by cognitive impairment no dementia (CIND) participants status.

	Total (N = 1987)	Incident CIND (N = 301)	No CIND (N = 1686)
Age (years)	71.6 ± 9.8	74.2 ± 9.0	71.1 ± 9.9
Female, n (%)	1188 (59.8)	196 (65.1)	992 (58.8)
Education, n (%)			
Elementary	214 (10.8)	44 (14.6)	170 (10.1)
High school	946 (47.6)	156 (51.8)	790 (46.9)
University or above	827 (41.6)	101 (33.5)	726 (43.1)
Early retirement, n (%)	1501 (75.5)	253 (84.1)	1248 (74.0)
SES status, n (%)			
Blue collar workers	333 (16.8)	66 (21.9)	267 (15.8)
White collar workers	1653 (83.2)	235 (78.1)	1418 (84.1)
Smoking, n (%)			
Never smoker	890 (44.8)	142 (47.2)	748 (44.4)
Former smoker	814 (41.0)	117 (38.9)	697 (41.3)
Current smoker	274 (13.8)	41 (13.6)	233 (13.8)
Physically inactive, n (%)	1396 (70.3)	218 (72.4)	1178 (69.9)
3-year average levels of $PM_{2.5}$ before baseline (μg/m^3, mean ± SD)	8.8 ± 0.7	8.8 ± 0.6	8.8 ± 0.7
3-year average levels of PM_{10} before baseline (μg/m^3, mean ± SD)	15.6 ± 2.2	15.6 ± 2.0	15.6 ± 2.3
3-year average levels of NOx before baseline (μg/m^3, mean ± SD)	29.4 ± 10.4	29.5 ± 9.1	29.4 ± 10.6
Free recall (mean ± SD)	7.5 ± 2.2	7.0 ± 2.1	7.6 ± 2.2
Trail Making Test Part B (mean ± SD)	11.9 ± 0.7	11.9 ± 0.6	11.8 ± 0.7
Letter Fluency (mean ± SD)	14.6 ± 4.6	14.0 ± 4.5	14.7 ± 4.6
Category Fluency (mean ± SD)	19.5 ± 5.2	18.3 ± 4.7	19.7 ± 5.3
Mental rotation (mean ± SD)	6.5 ± 1.7	6.1 ± 1.6	6.6 ± 1.7
Digit cancellation (mean ± SD)	18.1 ± 4.0	17.0 ± 3.7	18.2 ± 4.1
Pattern comparison (mean ± SD)	14.5 ± 3.7	13.4 ± 3.4	14.6 ± 3.8

Abbreviations: SES, socioeconomic status; CIND, cognitive impairment no dementia; SD, standard deviation; PM, particulate matter; NOx, nitrogen oxide.
Missing values: 9 in smoking, 17 in retirement, 1 in SES, 104 in physical activity; 4 in $PM_{2.5}$, 4 in PM_{10}, 4 in NOx.

Table 2
Hazard ratio (HR) and sub-HR (sHR) with 95% confidence interval of cognitive impairment, no dementia (CIND) by levels of air pollutants.

Air pollutants	Model 1 HR of CIND (95% CI)	Model 2 sHR of CIND (95% CI)
$PM_{2.5}$ (per 1 μg/m^3 increment)	–	–
3-year moving average prior to event	1.75 (1.54, 1.99)	1.64 (1.46, 1.84)
Average levels from baseline to end of follow-up	1.73 (1.50, 1.99)	1.66 (1.46, 1.89)
Yearly exposure with 1-year lag	1.54 (1.42, 1.67)	1.51 (1.40, 1.63)
Yearly exposure with 2-year lag	1.54 (1.41, 1.69)	1.53 (1.42, 1.65)
Yearly exposure with 3-year lag	1.75 (1.59, 1.93)	1.75 (1.59, 1.91)
PM_{10} (per 1 μg/m^3 increment)	–	–
3-year moving average prior to event	1.08 (1.03, 1.14)	1.08 (1.03, 1.12)
Average levels from baseline to end of follow-up	1.07 (1.01, 1.12)	1.06 (1.01, 1.11)
Yearly exposure with 1-year lag	1.13 (1.08, 1.18)	1.12 (1.08, 1.17)
Yearly exposure with 2-year lag	1.14 (1.09, 1.18)	1.13 (1.09, 1.17)
Yearly exposure with 3-year lag	1.15 (1.11, 1.20)	1.15 (1.11, 1.19)
NOx (per 10 μg/m^3 increment)	–	–
3-year moving average prior to event	1.18 (1.04, 1.33)	1.15 (1.03, 1.29)
Average levels from baseline to end of follow-up	1.13 (1.00, 1.28)	1.12 (0.99, 1.25)
Yearly exposure with 1-year lag	1.40 (1.25, 1.58)	1.34 (1.21, 1.50)
Yearly exposure with 2-year lag	1.34 (1.19, 1.50)	1.29 (1.16, 1.43)
Yearly exposure with 3-year lag	1.31 (1.17, 1.46)	1.27 (1.15, 1.40)

HR was derived from the Cox-proportional hazard model (Model 1). sHR was derived from the Fine and Gray model (Model 2) considering death as the competing risk event. Air pollutants were modeled as time-varying variables. Models are adjusted for age, sex, SES, education, smoking, physical activity, early retirement, neighborhood household mean income, and the number of cognitive test occasions.

The concentration-response relationships of air pollution exposure for CIND are presented in Fig. 1. We observed a significant linear relationship for time-varying PM concentrations from low to approximately mean levels, followed by attenuated associations at higher levels (Fig. 1, panel A and B). A similar concentration-response shape was observed for low to mean levels of NOx exposure followed by flattened and less precise associations at higher levels (Fig. 1, panel C).

3.2. Effect of air pollution on the progression of CIND to dementia

There were 118 out of 607 participants with CIND at baseline that developed dementia during the 12 years follow-up (Table 3). The incident dementia cases were older, had lower education levels, earlier retirement, lower SES status, fewer smokers, and were more physically inactive than those who did not develop dementia.

Table 4 presents the association between time-varying ambient $PM_{2.5}$, PM_{10}, and NOx and the progression of CIND to dementia. A higher hazard of dementia appeared for 1 μg/m3 increase of $PM_{2.5}$ (HR = 1.90, 95 %CI: 1.48, 2.43), and PM_{10} (HR = 1.14, 96 %CI: 1.03, 1.26), and for 10 μg/m^3 increase of NOx (HR = 1.34, 95 %CI: 1.07, 1.69) (Table 4, model 1). Every 1 μg/m^3 increase in average $PM_{2.5}$ and PM_{10} during the entire follow-up was associated with respectively over 2- and 1.15-fold higher hazards of incident dementia among CIND individuals. The results from exposures to air pollution at yearly exposure with 1–3 years lag showed the robust associations between exposure to air pollution and conversion from CIND to dementia incidence. When considering death as a competing risk event, we observed increased sub-hazards of air pollution exposure on dementia (Table 4, model 2).

3.3. Sensitivity analyses

We compared the baseline characteristics of the two study subsamples and dropouts (Supplementary Tables 1 & 2). The dropouts had similar levels of air pollution exposure compared to included study populations. In comparison to the cognitively intact study subsample,

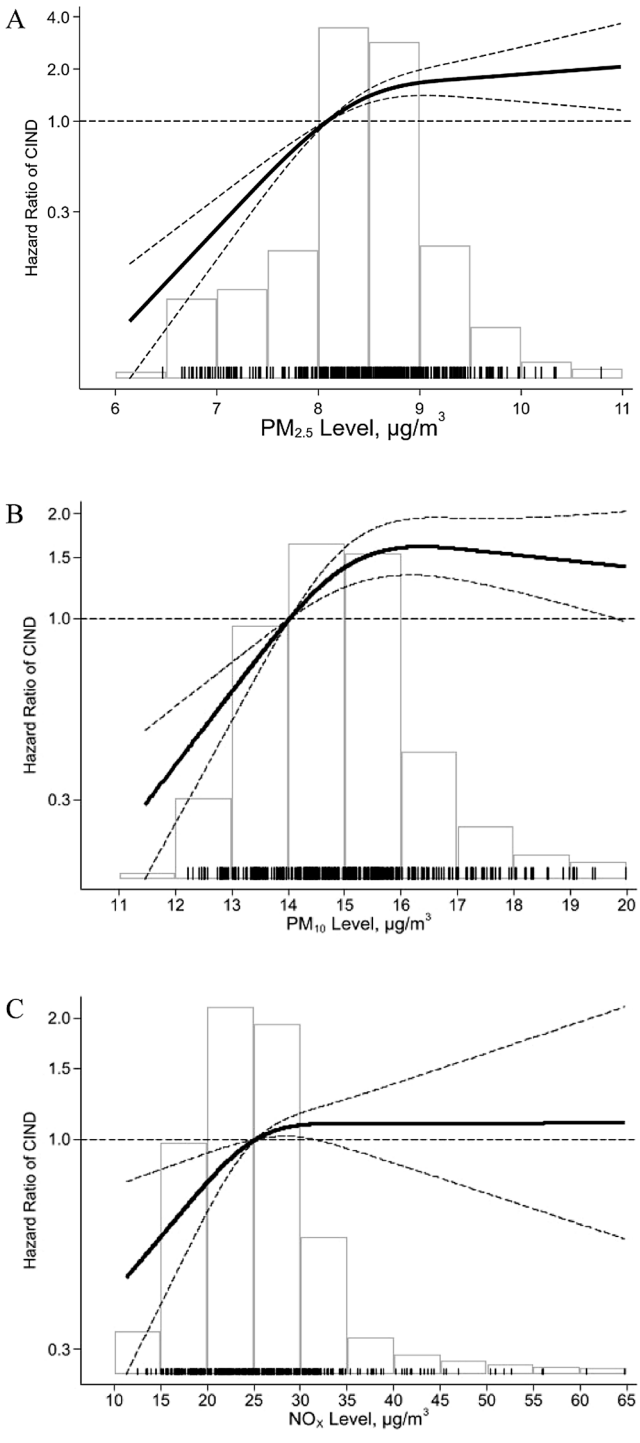

Fig. 1. Concentration-response curves of the association between long-term air pollution exposure and hazards for cognitive impairment, no dementia (CIND). Hazard ratios were estimated from Cox hazard proportional regression models according to air pollution levels. Air pollutants were included as a time-varying covariate and modeled by restricted cubic splines with three knots at 10th, 50th, 90th percentiles of its distribution with 95% CI (dash lines). Models were adjusted for age, sex, education, smoking, socioeconomic status, early retirement, physical activity, neighborhood household mean income, and the number of cognitive test occasions. The reference group is considered 8 μg/m^3 of $PM_{2.5}$, 14 μg/m^3 of PM_{10}, and 25 μg/m^3 of NOx in the entire population (mean level). The spikes represent CIND cases.

Table 3
Baseline characteristics of the prevalent CIND subsample and stratified by dementia status at follow-up.

	Total (N = 607)	Dementia (N = 118)	No dementia (N = 489)
Age (years)	74.2 ± 9.9	80.7 ± 6.9	72.6 ± 9.8
Female, n (%)	404 (66.6)	83 (70.3)	321(65.6)
Education, n (%)			
Elementary	145 (23.9)	33 (28.0)	112 (22.9)
High school	325 (53.5)	67 (56.8)	258 (52.8)
University or above	137 (22.6)	18 (15.2)	119 (24.3)
Early retirement, n (%)	524 (86.3)	117 (99.2)	407 (83.2)
SES status, n (%)			
Blue collar workers	201 (33.1)	44 (37.3)	157 (32.1)
White collar workers	405 (66.7)	73 (61.9)	332 (67.9)
Smoking, n (%)			
Never smoker	274 (45.1)	62 (52.5)	212 (43.4)
Former smoker	219 (36.1)	37 (31.4)	182 (37.2)
Current smoker	109 (18.0)	18 (15.2)	91 (18.6)
Physically inactive, n (%)	416 (68.5)	84 (71.2)	332 (67.9)
3-year average levels of $PM_{2.5}$ before baseline ($\mu g/m^3$, mean ± SD)	8.8 ± 0.6	8.8 ± 0.6	8.8 ± 0.6
3-year average levels of PM_{10} before baseline ($\mu g/m^3$, mean ± SD)	15.7 ± 1.8	15.7 ± 1.7	15.7 ± 1.9
3-year average levels of NOx before baseline ($\mu g/m^3$, mean ± SD)	30.0 ± 8.7	30.4 ± 7.9	29.9 ± 8.9
Free recall (mean ± SD)	5.4 ± 2.5	4.0 ± 2.1	5.7 ± 2.4
Trail Making Test Part B (mean ± SD)	9.7 ± 3.3	8.4 ± 3.9	10.0 ± 3.1
Letter Fluency (mean ± SD)	11.0 ± 4.9	9.6 ± 4.4	11.4 ± 5.0
Category Fluency (mean ± SD)	15.3 ± 5.5	11.8 ± 4.2	16.1 ± 5.5
Mental rotation (mean ± SD)	4.8 ± 2.1	4.9 ± 1.8	4.8 ± 2.2
Digit cancellation (mean ± SD)	15.3 ± 4.5	12.8 ± 4.1	15.9 ± 4.4
Pattern comparison (mean ± SD)	11.8 ± 4.1	8.6 ± 3.5	12.5 ± 3.9

Abbreviations: SES, socioeconomic status; CIND, cognitive impairment no dementia; SD, standard deviation; PM, particulate matter; NOx, nitrogen oxide.
Missing values: 5 in smoking, 2 in retirement, 1 in SES, 82 in physical activity; 2 in $PM_{2.5}$, 2 in PM_{10}, 2 in NOx.

Table 4
Hazard ratio (HR) and sub-HR (sHR) with a 95% confidence interval (CI) of dementia by levels air pollutants for participants with a diagnosis CIND at baseline (n = 607).

Air pollutants	Model 1 HR of dementia (95% CI)	Model 2 sHR of dementia (95% CI)
$PM_{2.5}$ (per 1 $\mu g/m^3$ increment)	–	–
3-year moving average prior to event	1.90 (1.48, 2.43)	1.27 (1.02, 1.58)
Average levels from baseline to end of follow-up	2.26 (1.73, 2.95)	1.68 (1.29, 2.20)
Yearly exposure with 1-year lag	1.76 (1.50, 2.05)	1.39 (1.21, 1.60)
Yearly exposure with 2-year lag	1.74 (1.49, 2.02)	1.46 (1.27, 1.67)
Yearly exposure with 3-year lag	1.95 (1.65, 2.31)	1.70 (1.42, 2.02)
PM_{10} (per 1 $\mu g/m^3$ increment)	–	–
3-year moving average prior to event	1.14 (1.03, 1.26)	1.05 (0.95, 1.16)
Average levels from baseline to end of follow-up	1.15 (1.04, 1.27)	1.08 (0.98, 1.19)
Yearly exposure with 1-year lag	1.20 (1.10, 1.31)	1.11 (1.02, 1.21)
Yearly exposure with 2-year lag	1.21 (1.12, 1.31)	1.14 (1.05, 1.22)
Yearly exposure with 3-year lag	1.25 (1.16, 1.34)	1.17 (1.09, 1.26)
NOx (per 10 $\mu g/m^3$ increment)	–	–
3-year moving average prior to event	1.34 (1.07, 1.69)	1.14 (0.90, 1.43)
Average levels from baseline to end of follow-up	1.36 (1.08, 1.71)	1.20 (0.96, 1.51)
Yearly exposure with 1-year lag	1.85 (1.51, 2.28)	1.42 (1.15, 1.76)
Yearly exposure with 2-year lag	1.73 (1.42, 2.12)	1.38 (1.13, 1.69)
Yearly exposure with 3-year lag	1.66 (1.38, 2.01)	1.36 (1.12, 1.65)

HRs were derived from the Cox-proportional hazard model (Model 1). sHR derived from the Fine and Gray model (Model 2) considering death as the competing risk event. Air pollutants were modeled as a time-varying variable. Models are adjusted for age, sex, SES, education, smoking, physical activity, early retirement, neighborhood household mean income, and number of assessment occasions.

the prevalent CIND participants tended to be older, had lower education levels, earlier retirements and lower SES status, and were more likely to be smokers.

All sensitivity analyses showed similar results to the main analyses when considering the dropouts using IPW weight (Supplementary Tables 3 & 4). We observed a similar pattern but slightly decreased estimations after adjusting for baseline year and using age as the timescale compared to the main analysis (Supplementary Tables 5 & 6). Additionally, the results remained similar after excluding participants who developed dementia without preceding CIND diagnosis (Supplementary Table 7).

4. Discussion

Our findings suggest that older individuals exposed to long-term ambient air pollution experience an increased risk for cognitive impairment, even after considering death as a competing event. Interestingly, we also observed that air pollution was a risk factor for the progression of CIND to dementia.

An increasing number of studies have investigated the association between long-term air pollution exposure and cognitive function in older adults, but yielded inconsistent results (Peters et al., 2019). A recent systematic review has suggested that, among others, different measurements of cognitive function and insufficient follow-up time are the main reasons for such variation (Peters et al., 2019). In the present study, we included a long follow-up period of up to 12 years and air pollution exposure over 10 years. The strongest effects of long-term exposure to $PM_{2.5}$ on cognition were reported by Monongahela-Youghiogheny Healthy Aging Team (MYHAT) cohort, showing that 1-$\mu g/m^3$ increase in 5-year average $PM_{2.5}$ exposure was associated with about an over 3-fold increased risk (HR = 3.42, 95% CI: 2.81, 4.16) of mild cognitive impairment (the Clinical Dementia Rating = 0.5) and a 2-fold increased risk (HR = 2.08, 95% CI: 1.53, 3.02) of incident dementia among 1572 US old population (Sullivan et al., 2021). The Women's Health Initiative Memory Study (WHIMS) found an 81% increased risk (HR = 1.81, 95 %CI: 1.42–2.32) of cognitive impairment (8-point reduction on the Modified Mini-Mental State Examination) for exposure to high levels of $PM_{2.5}$ (over 12 $\mu g/m^3$) versus low, among older women (Cacciottolo et al., 2017), which is broadly consistent with our results. Conversely, previous analyses from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) project measured cognitive impairment using a Six-item telephone screener, which failed to identify the effects of $PM_{2.5}$ on cognitive impairment (Loop et al., 2013). Our results showed a slightly weaker effect, about 11% increased hazard for CIND incidence per 10 $\mu g/m^3$ increase of NO_x, as compared with the effect observed in the Sacramento Area Latino Study on Aging (SALSA) study, which reported a 21% elevated hazard for the combined outcome dementia/CIND per interquartile range (2.31 ppb ≈ 3.5 $\mu g/m^3$) increase of traffic-related NOx exposure among the older Mexican American population (Paul et al., 2020). Additional cohort studies investigated cognitive decline longitudinally, and while some were supporting the association of air pollution exposure and faster cognitive decline (Kulick et al., 2020; Weuve et al., 2012), others did not (Oudin et al., 2017; Tonne et al., 2014).

The extent to which air pollution influences domain-specific cognitive decline is still unclear as results are inconsistent. Results from The Washington Heights Inwood Community Aging Project (WHICAP) showed that air pollution was associated with both decreased global cognition and domain-specific deterioration including memory,

language executive function (Kulick et al., 2020). However, the Whitehall II cohort (Tonne et al., 2014) showed long-term air pollution to be associated with lower scores in reasoning and memory, but not with verbal fluency, whereas The San Diego site of the Hispanic Community Health Study/Study of Latinos (Ilango et al., 2021) showed that air pollution was only cross-sectionally associated to verbal fluency and executive function, but not with other tests.

Importantly, our results were confirmed when we considered the competing event of death, supporting the impact of air pollution on CIND. In one previous study from our group, we observed a significant association between low to mean levels of long-term $PM_{2.5}$ exposure and faster cognitive decline among older-old adults (Grande et al., 2021). In the present study, we used a comprehensive neuropsychological battery consisting of various domains that reflecting early detection of insidious but were not influenced by education levels. Taken together, with the competing risk of death and comprehensive neuropsychological assessments, our results are clinically insightful for future prevention of dementia as people with mild cognitive impairment have a greater tendency of developing dementia.

We observed a deviation from linearity in the concentration-response with a steep increase in the hazards from low to mean levels of air pollution exposure followed by a plateau in the CIND risk. However, the results should be cautiously interpreted, given the limited number of observations in high-level ranges of exposure. The weakened hazards at mean to high levels of exposure might be due to a "healthy survivor" effect because these participants who were exposed to higher levels of air pollution are more likely to experience premature mortality before exhibiting cognitive change (Stayner et al., 2003). Our data showed that people who were alive and exposed to higher air pollution levels were more physically active and had higher education levels in comparison to those people who died and were exposed to higher air pollution levels. It was interesting that we observed the associations even with relatively low levels of exposure, so future studies are warranted to study the mechanisms behind the flattening of effects at higher levels of exposure.

Our study also suggested long-term exposure to air pollution was not only linked to increased CIND incidence but also associated with the progression of CIND to dementia. To date, there is limited evidence available on the effect of air pollution in older individuals with cognitive impairment and their progression to dementia (Paul et al., 2020). Thereby, these results might shed light on future studies to better understand the role of air pollution on the relationship between cognitive impairment and developing dementia.

Several biological mechanisms underlying the relationship between air pollution and cognition have been proposed, including neuroinflammation, oxidative stress, and vascular damage (Block and Calderón-Garcidueñas, 2009; Hahad et al., 2020). Air pollutants might pass the blood-brain barrier and enter the central nervous system via the olfactory bulb (Block and Calderón-Garcidueñas, 2009). Exposure to air pollution may also stimulate the inflammatory response and increase cytokine release to the circulation (Hahad et al., 2020). Findings revealed that ambient air pollution may also influence cognition via vascular damage, for instance, by increasing the carotid intima-media thickness and arterial stiffness (Aguilera et al., 2016; Wu et al., 2010), which are inversely associated with cognitive function.

Our study has several strengths. Notably, a major difference between our study and existing literature is that we used a comprehensive neuropsychological examination including various cognitive domains for CIND diagnosis, which can more accurately capture subtle cognitive change compared to self-administered questionnaires or single scores. We also benefitted from a long follow-up of up to 12 years in a large cohort and were able to examine the relationship between air pollution and two clinically relevant cognitive outcomes as CIND and dementia. To our best of knowledge, this is the first longitudinal study that has not only investigated the impact of air pollution on CIND but also its progression to dementia, considering various air pollutants. Moreover, we were able to assess long periods of air pollution exposure from the detailed spatiotemporal model also considering the moving status during follow-ups.

Some limitations need to be acknowledged. Potential informative dropouts during 12-year follow-ups may need to be addressed. However, we used IPW in the sensitivity analyses and observed similar effect estimates of air pollution exposure, indicating the selection bias due to dropouts were subtle. Although we were able to obtain moving status during follow-ups, some level of exposure misclassification may bias effect estimates towards the null when assigning air pollution exposure derived based on the participant's residential address and we were not able to assess the indoor air pollution levels. However, our study population consisted mainly of retired individuals, and older adults are more prompt to spend more time in and around their residences on a daily basis (Hjorthol et al., 2010). Also, since diagnosis of CIND was only assessed at periodic follow-up visits, for participants who were free from CIND at their last visit before death, CIND status at death was unknown which may have led to an underestimation of CIND incidence. Lastly, we were not able to adjust for unmeasured confounding due to inaccessible data sources, for example, green space accessibility and noise exposure.

5. Conclusion

Long-term exposure to air pollution was associated with higher CIND incidence and we also report novel evidence that air pollution is a risk factor for the progression from CIND to dementia. Our study identified air pollution as a modifiable risk factor for CIND, which sheds light on future primary prevention. Future studies are warranted to investigate the mechanism underlying the risk of air pollution for cognitive impairment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.107067.

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