The role of air pollution and lung function in cognitive impairment

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ABSTRACT Air pollution has been associated with impaired lung and cognitive function, especially impairment in visuo-construction performance (VCP). In this article, we evaluate whether the effect of air pollution on VCP is mediated by lung function.

We used data from the SALIA cohort (baseline 1985–1994 and follow-up 2007–2010) including 587 women aged 55 years at baseline. Particulate matter (PM) and nitrogen dioxide (NO_2) exposures at baseline were estimated via land-use regression models. Lung function was characterised by averages between baseline and follow-up. We used age- and height-controlled Global Lung Initiative (GLI) z-scores of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC. VCP was assessed at follow-up with the CERAD-Plus neuropsychological test battery and causal mediation analysis was conducted.

An increase of one interquartile range in FEV_1 and FVC was positively associated with VCP (β=0.18 (95% CI 0.02–0.34) and β=0.23 (95% CI 0.07–0.39), respectively). The proportion of the association between NO_2 on VCP mediated by FEV_1 was 6.2% and this was higher in never smokers (7.2%) and non-carriers of the *APOE-ε4* allele (11.2%). However, none of the mediations were statistically significant.

In conclusion, air pollution associated VCP was partially mediated by lung function. Further studies on the mechanisms underlying this pathway are required to develop new strategies to prevent air pollution induced cognitive impairment.

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Introduction

Ambient air pollution exposure has been linked to impaired lung function [1] and chronic obstructive pulmonary disease (COPD) in the elderly [2]. Impaired lung function has also been associated with impaired cognitive function in both adults and children [3, 4]. Accordingly, cognitive decline is highly prevalent in people with impaired lung function and COPD [5, 6]. Various studies investigating the association between midlife pulmonary function and cognitive function in old age have shown that pulmonary dysfunction in midlife is associated with an increased risk of poor cognition later in life [7–9]. The influence of pulmonary function on cognitive decline may result from various factors including hypoxia, reduced neurotransmitter function, increased systemic inflammation, or a combination of these processes [10].

There is emerging epidemiological evidence of an association between exposure to air pollution and cognitive decline [11, 12], especially with impaired visuo-construction performance (VCP; copying geometrical figures) [13]. Epidemiological studies showing a relationship between distance to major roads and cognitive decline suggest that particles from traffic sources can, due either to their size or composition, have detrimental effects on cognition [14, 15].

However, while the associations between respiratory health and cognitive function are well established, the relationships between air pollution, impaired lung function and cognitive decline remain unclear. Air pollution and reduced pulmonary function also inflict high oxidative stress on the body [16] and hence can potentially accelerate age-related changes in the brain. It is possible that air pollution induced impaired lung function causes changes in the central nervous system (CNS) through processes such as vascular diseases resulting from inflammation, impaired fibrinolytic activity, or oxidative stress and other cardiovascular risk factors [4, 17]. A common approach to investigating such a causal pathway in epidemiological studies is to use causal mediation analysis [18].

The objective of the current study was to investigate whether impaired lung function was not only a risk factor for cognitive decline but also if it mediated the association between air pollution exposure and cognitive decline. We used data from the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) cohort.

Methods

Study design and study population

The SALIA study was initiated in the early 1980s by the North Rhine–Westphalia State Government as part of the Clean Air Plan to investigate the effect of air pollution exposure in women. The study population was a sample of women from the Ruhr area and two rural areas in Southern Münsterland. Between 1985 and 1994, health examinations were conducted in 4874 women who were 55 years of age at the time of their baseline investigations. These examinations included lung function measurements in 2785 women and details of the baseline investigation have been described elsewhere [19]. A follow-up examination was conducted between 2007 and 2010 [13]. Women who had lung function measured at baseline were invited in a randomised manner from the Ruhr area cities of Duisburg, Dortmund, Essen and Gelsenkirchen, as well as from the rural county of Borken. In total, 834 women participated who were then aged 70 to 80 years. The Ethical Committee of the University of Bochum approved the study. We received written informed consent from all participants.

Assessment of respiratory health and pulmonary function

Spirometry was performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [20] at both investigations. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured. Three to four manoeuvres were performed under the direction of trained personnel and the values used were those where the maximal FEV_1 was reached. All measuring instruments were calibrated prior to testing, the technical personnel were specially trained and a pulmonary physician reviewed all results. To control for age and height-dependency of lung function, we calculated z-scores from the Global Lung Initiative (GLI) reference values. In a previous publication, we showed that the GLI z-scores fitted cross-sectionally and longitudinally with FEV_1, FVC and FEV_1/FVC measured in our SALIA cohort [21]. To evaluate long term lung function during follow-up and to reduce measurement errors, we calculated the average GLI z-scores between baseline and follow-up investigation.

Assessment of cognitive function

Participants were tested for cognitive function using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery (Memory Clinic University Hospital, Basel, Switzerland, 2005). The CERAD-Plus test battery consists of 18 items which measured 10 subtests: 1) verbal fluency, 2) the Boston naming test, 3) phonetic fluency, 4) word list learning, 5) word list recall,

6) word list recognition discriminability (recognising previously learned words), 7) VCP (copying geometrical figures), 8) recall (recalling previously presented figures), 9) the trail making test (A, B, B/A) and 10) the Mini-Mental State Examination (MMSE). The test battery is described in detail elsewhere [22].

Each subtest examines various cognitive functions in the brain to obtain a complete picture of an individual's cognition. The integrated standardisation programme of the German version of CERAD-Plus transformed subtest scores into normalised z-scores standardised for age and level of education (measured in years). In this publication, we focused on VCP, a subtest which has previously been associated with air pollution [13].

Assessment of potential confounders

We gathered questionnaire-based information about known risk factors. Information was collected regarding age, body mass index (BMI), socio-economic status, current and past smoking habits and passive smoking exposure at home or at work, as well as other risk factors. We classified socio-economic status into three categories at baseline using the highest school level achieved by either the woman or her husband. These were low (<10 years), medium (10 years) or high (>10 years). Additionally, we gathered information regarding depression by using the Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaire with a cut-off of 22 points to indicate a depressive state [23].

The apolipoprotein-ε4 allele (*APOE-ε4*) is the most prevalent genetic risk factor for Alzheimer's disease [24]. DNA was extracted from each individual with a QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) using a standard procedure. DNA amplification and genotyping of the *APOE* polymorphisms rs429358 and rs7412 were performed by LCG/KBioscience (Hoddesdon, UK) using a Kompetitive Allele Specific PCR (KASP) single nucleotide polymorphism (SNP) genotyping system with an error rate of less than 0.3% to define the *APOE-ε4* isoform.

Assessment of air pollution

Outdoor air pollution concentrations were assessed according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocol [25, 26]. Each participant was assigned an annual average concentration of nitrogen dioxide (NO_2) and particulate matter (PM) at home ($PM_{2.5}$ and PM_{10} for particulates, where PM_x indicates particles with a 50% cut-off aerodynamic diameter of x μm). Air pollution was monitored over 1 year (2008–2009) in the Ruhr area and in adjacent Münsterland. Three 2-week measurements were performed at 40 monitoring sites (20 sites for PM measurement), one each in cold, warm and intermediate seasons, and results were adjusted for temporal variation using a reference station which measured during the whole period. The measured concentrations were associated with the characteristics of land-use at the monitoring sites to obtain a regression equation. Data on nearby traffic, ports or industry, as well as population/household density derived from Geographic Information Systems (GIS), were included in the equations. The models reached high adjusted R^2 values of 0.85 for $PM_{2.5}$ mass, 0.66 for PM_{10} mass and 0.88 for NO_2. They were applied to the home addresses of participants to get individual exposure concentrations.

To characterise long-term exposure at baseline (1985–1994) we back-extrapolated these exposure concentrations using the exact recruitment date as well as data for the year before and after. For each study participant's home address, the back-extrapolated concentration was obtained by multiplying the modelled ESCAPE annual mean concentration with the ratio between average annual concentrations as derived from a routine monitoring site for the period in the past and for the ESCAPE measurement period time, which was used as a reference [27].

The implicit assumption of proportional spatial contrasts over time was tested with data from six routine monitoring stations situated in the investigation area and covering the investigation period. The trend concordance was good (R^2 values between 0.42 and 0.84).

Statistical analysis

We analysed the association of individual long-term exposure to air pollution at baseline with average lung function between baseline and follow-up and with VCP at follow-up. Next, we investigated the association between average lung function and VCP at follow-up, as well as the interaction between air pollution exposure and average lung function on VCP. We used multiple linear regression analysis throughout. Linear regression coefficients (β) with corresponding 95% confidence intervals were estimated for increases of one interquartile range in baseline exposure or in the respective lung function parameter.

Furthermore, we analysed whether the average level of lung function between baseline and follow-up mediated the effect of air pollution exposure on VCP. Causal mediation analysis from a counterfactual perspective with possible exposure-mediator interaction was performed by using the R [28] package

"mediation" [29], an approach that relies on the quasi-Bayesian Monte Carlo method based on normal approximation [30]. Using the counterfactual framework allows for definition of direct and indirect effects and a total effect as the sum of direct and indirect effects, even in models with interactions. The indirect effect refers to the effect through the mediator under study. The direct effect refers to the remaining effect that is not through the mediator [18]. The proportion of the indirect effect in the total effect was used to assess the extent to which the association between air pollution and VCP was mediated through impaired lung function as an intermediate pathway [31].

The proportion of air pollution associated VCP mediated by lung function might differ in subgroups defined by the presence of strong risk factors for impaired lung function or Alzheimer's disease. The robustness of the results considering these potential effect modifications was examined through sensitivity analyses in which we excluded smokers and *APOE-ε4* carriers (strong risk factors for impaired lung function and Alzheimer's disease, respectively).

Age, height, BMI, socio-economic status, current and former smoking habits, exposure to second-hand smoke, living in an urban area *versus* a rural area, *APOE-ε4* incidence, physical activity and depression were associated with air pollution, lung function or VCP in univariate analyses and were included as covariates in the models to adjust for potential confounding. All statistical analyses were carried out with R 3.4.1 for Windows [28].

Results

Description of study participants, outcome and air pollution

The characteristics of the study participants are described in table 1. Of the 834 women who participated in the follow-up examination, 520 had complete information about air pollution exposure, lung function at baseline and follow-up, and the covariates included in the statistical analysis. The average age of these women at the time of the baseline investigation (1985–1994) was 54.3 years and at follow-up (2007–2010)

TABLE 1 Description of the Study on the influence of Air pollution on Lung function, Inflammation and Aging (SALIA) population at baseline and at follow-up

Characteristic	Baseline (1985–1994)	Follow-up (2007–2010)
Age years	54.3±0.8	73.3±3.4
BMI kg·m^{-2}	26.6±4.0	27.3±4.5
Height cm	162.5±5.5	163.1±5.9
Educational level[#]		
<10 years	92 (17.7)	92 (17.7)
10 years	246 (47.3)	246 (47.3)
>10 years	182 (35.0)	182 (35.0)
Smoking		
Active smoker	56 (10.8)	17 (3.3)
Ex-smoker	54 (10.4)	88 (16.9)
Never smoker	410 (78.8)	415 (79.8)
Second-hand smoke	245 (47.1)	312 (60.0)
Residential area		
Urban	230 (44.2)	230 (44.2)
Rural	290 (55.8)	290 (55.8)
***APOE-ε4* carrier**[¶,+]		151 (29.0)
Ever sport activity[¶]		222 (42.7)
Depression scale >22[¶]		18 (3.5)
GLI z-score for FEV_1	−0.2±1.0	0.2±1.0
GLI z-score for FVC	0.0±0.9	0.3±0.9
GLI z-score for FEV_1/FVC	−0.4±0.8	−0.2±0.8
Average[§] **GLI z-score for FEV_1**	0.0±0.9	
Average[§] **GLI z-score for FVC**	0.1±0.8	
Average[§] **GLI z-score for FEV_1/FVC**	−0.3±0.7	
VCP		−0.9±1.3

Data are presented as n (%) or mean±SD. The total number of subjects is 520. BMI: body mass index; GLI: Global Lung Initiative; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; VCP: visuo-construction performance (z-score of subtest "figure copying"). [#]: only assessed at baseline investigation; [¶]: only assessed at follow-up investigation; [+]: carrier of at least one ε4 allele; [§]: averaged between the lung function measurements at baseline investigation and follow-up investigation.

it was 73.3 years. The majority of women had a school education of 10 or >10 years. Results from the CES-questionnaire indicated 3.5% of the women were depressed in the last week before the examination. The average GLI z-score for FEV_1 from the baseline and follow-up values was 0.0±0.9 and the average z-score for FVC was 0.1±0.8. The mean z-score of the CERAD subtest (figure copying) was −0.9±1.3.

We compared baseline characteristics of participants with non-participants in a univariate analysis. Significant risk factors for loss to follow-up were a high BMI, a low socio-economic status, high levels of air pollution and low lung function values at baseline (see supplementary table S1). Within the follow-up sample, more women living in the rural area with lower levels of air pollution were included in the analyses (n=520) than those not included (n=314) (see supplementary table S1).

The distributions of air pollutants back-extrapolated to the baseline investigation are presented in table 2. The median of the baseline concentration was 33.0 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, 49.8 $\mu g \cdot m^{-3}$ for PM_{10} and 33.5 $\mu g \cdot m^{-3}$ for NO_2.

Association between air pollution and lung function

Higher concentrations of PM_{10} and $PM_{2.5}$ at baseline were associated with lower average z-scores for FEV_1 and FEV_1/FVC between baseline and follow-up (figure 1). Associations with FVC as well as associations of NO_2 were not significant.

Association between VCP and air pollution or lung function

Air pollution exposure at baseline and average lung function from the baseline and follow-up values (mean GLI z-scores of FEV_1 and FVC) showed an association with the follow-up test of VCP (table 3). Cognitive test performance was decreased with increasing air pollution as well as with decreasing lung function; however, there was no evidence for an association with the FEV_1/FVC ratio. Interactions between air pollution and lung function on VCP were only moderate. Participants with high average levels of FVC were slightly more susceptible to air pollution-induced VCP impairment than participants with low average levels of FVC. None of these interactions (with the exception of FVC and NO_2) was significant.

Mediation of the association between air pollution and VCP by lung function

The mediation analysis focused on the mediating effect of average lung function on the previously shown association between air pollution exposure and the VCP subtest (table 3). The largest mediated proportion was found for FEV_1. For the association between NO_2 and VCP, 6.2% was mediated by FEV_1 (table 4). Mediated proportions were higher in never smokers (7.2%) and non-*APOE-ε4* carriers (11.2%); however, none of the mediations were statistically significant. Mediated proportions did not change when including an exposure-mediator interaction term. The indirect, direct and total effects resulting from the mediation analyses are summarised in supplementary tables S2–S4.

Discussion

In the present study, we showed that average lung function between middle and late adulthood was associated with the development of mild cognitive impairment later in life among elderly women who were followed for more than 20 years. We also showed that the association between air pollution and VCP was partially mediated by impaired lung function (up to 11% for non-*APOE-ε4* carriers).

Our study extends previous epidemiological studies which showed that pulmonary function was an independent risk factor for poor cognitive function [4, 7]. However, most of these studies used either a single lung function parameter, namely FEV_1, or investigated a younger cohort. Poor respiratory function is related to a number of adverse health effects as well as mortality [32] and is associated with

TABLE 2 Distribution of air pollution concentrations back-extrapolated to baseline metrics according to European Study of Cohorts for Air Pollution Effects (ESCAPE) protocols

Exposure	Concentration	
	Median (IQR)	Distribution (min–max)
$PM_{2.5}$ $\mu g \cdot m^{-3}$	33.0 (4.9)	22.0–41.3
PM_{10} $\mu g \cdot m^{-3}$	49.8 (8.0)	32.2–65.1
NO_2 $\mu g \cdot m^{-3}$	33.5 (13.8)	20.3–84.1

The total number of subjects is 520. IQR: interquartile range; PM_x: particles with a 50% cut-off aerodynamic diameter of x µm; NO_2: nitrogen dioxide.

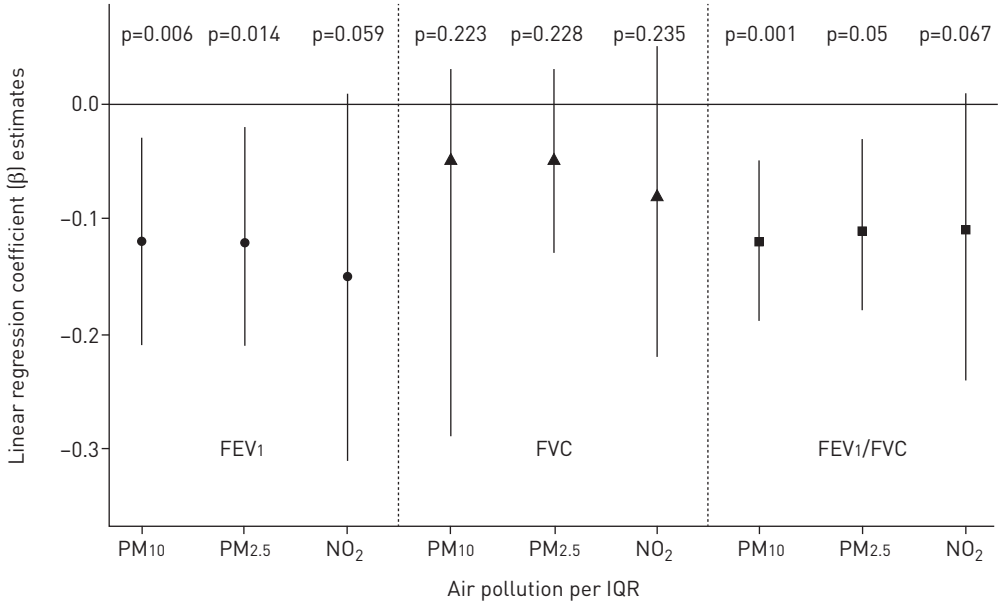

FIGURE 1 Association between air pollution exposure at baseline and average lung function between baseline and follow-up examination (average Global Lung Initiative z-scores for forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC). Linear regression coefficients (β) with corresponding 95% confidence intervals were estimated for increases of one interquartile range (IQR) in baseline exposure. All models were adjusted for age, height, body mass index, socio-economic status, current and former smoking habits, exposure to second-hand smoke, living in an urban area *versus* a rural area and physical activity.

TABLE 3 Association between visuo-construction performance (VCP) and air pollution at baseline, average lung function and the interaction between air pollution and lung function

Exposure	β-estimate	p-value
Air pollution		
PM_{10}	−0.25 (−0.40; −0.11)	0.001
$PM_{2.5}$	−0.21 (−0.36; −0.06)	0.005
NO_2	−0.26 (−0.50; −0.03)	0.030
Lung function		
FEV_1	0.18 (0.02; 0.34)	0.030
FVC	0.23 (0.07; 0.39)	0.005
FEV_1/FVC	−0.04 (−0.20; 0.11)	0.566
Air pollution × lung function		
PM_{10} × FEV_1	−0.05 (−0.15; 0.06)	0.381
$PM_{2.5}$ × FEV_1	−0.07 (−0.18; 0.04)	0.213
NO_2 × FEV_1	−0.10 (−0.26; 0.05)	0.185
PM_{10} × FVC	−0.08 (−0.20; 0.03)	0.142
$PM_{2.5}$ × FVC	−0.10 (−0.22; 0.02)	0.090
NO_2 × FVC	−0.18 (−0.35; −0.01)	0.035
PM_{10} × FEV_1/FVC	0.10 (−0.03; 0.23)	0.123
$PM_{2.5}$ × FEV_1/FVC	0.09 (−0.05; 0.23)	0.208
NO_2 × FEV_1/FVC	0.16 (−0.05; 0.36)	0.130

The total number of subjects is 520. Average lung function between baseline and follow-up examinations. VCP was measured at follow-up examination. Linear regression coefficients (β) with corresponding 95% confidence intervals were estimated for increases of one interquartile range in air pollution or in the respective lung function parameter. All models were adjusted for age, height, body mass index, socio-economic status, current and former smoking habits, exposure to second-hand smoke, living in an urban area *versus* a rural area, *APOE-ε4* incidence, physical activity and depression. PM_x: particles with a 50% cut-off aerodynamic diameter of x µm; NO_2: nitrogen dioxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

TABLE 4 Mediation analysis in all participants, never smokers and non-*APOE-ε4* carriers

Mediator	Exposure	All participants (n=520)		Never smokers (n=410)		non-*APOE-ε4* carriers (n=369)	
		Proportion mediated %	p-value mediation	Proportion mediated %	p-value mediation	Proportion mediated %	p-value mediation
Without exposure × mediator interaction							
FEV_1	PM_{10}	4.92	0.068	4.81	0.064	10.59	0.052
FEV_1	$PM_{2.5}$	5.82	0.066	5.67	0.070	11.65	0.080
FEV_1	NO_2	6.23	0.132	7.19	0.298	11.24	0.328
FVC	PM_{10}	3.33	0.160	4.02	0.114	5.02	0.262
FVC	$PM_{2.5}$	4.16	0.168	5.06	0.114	6.09	0.278
FVC	NO_2	5.83	0.202	7.69	0.324	6.79	0.486
FEV_1/FVC	PM_{10}	−3.61	0.312	−0.74	0.674	−4.48	0.520
FEV_1/FVC	$PM_{2.5}$	−3.35	0.372	−0.46	0.758	−3.77	0.586
FEV_1/FVC	NO_2	−1.81	0.536	−0.13	0.898	−1.90	0.760
With exposure × mediator interaction							
FEV_1	PM_{10}	5.51	0.046	5.22	0.068	10.09	0.078
FEV_1	$PM_{2.5}$	6.47	0.064	6.10	0.084	10.84	0.144
FEV_1	NO_2	7.12	0.096	8.85	0.250	11.02	0.284
FVC	PM_{10}	3.49	0.184	4.02	0.120	4.67	0.290
FVC	$PM_{2.5}$	4.21	0.196	4.86	0.134	5.46	0.322
FVC	NO_2	6.34	0.226	9.48	0.250	6.60	0.466
FEV_1/FVC	PM_{10}	−2.38	0.466	−0.02	0.982	−3.15	0.598
FEV_1/FVC	$PM_{2.5}$	−1.83	0.588	0.13	0.960	−2.06	0.732
FEV_1/FVC	NO_2	−2.14	0.522	−0.19	0.964	−2.91	0.700

Estimated percentage of the association between air pollution exposure and visuo-construction performance (VCP; figure copying) that was mediated by a decrease in lung function. All models were adjusted for age, height, body mass index, socio-economic status, current and former smoking habits (in the analysis of all participants and in the analysis of non-*APOE-ε4* carriers), exposure to second-hand smoke, living in an urban area *versus* a rural area, *APOE-ε4* incidence (in the analysis of all participants and in the analysis of never smokers), physical activity and depression. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PM_x: particles with a 50% cut-off aerodynamic diameter of x µm; NO_2: nitrogen dioxide.

socio-economic status [4] and lifestyle factors such as smoking and air pollution. However, we adjusted for all these factors and the association remained stable.

Poor pulmonary function has also been related to an increased risk of hypertension, atherosclerosis, heart disease and stroke [33, 34], all of which are risk factors for the development of mild cognitive impairment and have been associated with air pollution [11, 35]. A possible biological explanation for the association between impaired lung function and cognitive decline is that impaired pulmonary health can have a detrimental effect on cognitive function later in life through hypoxia and oxidative damage through systemic inflammation. It has been postulated that hypoxia impairs the metabolism of the central neurotransmitters [36]. Chronic undersupply of oxygen to the brain may cause oxidative stress and defective adenosine triphosphate production [7]. However, this explanation might only be plausible for individuals with severe lung impairment and diseases such as COPD [37]. It has been suggested that lung and cognitive function operate under common regulatory processes. Respiratory and cardiovascular control systems require the integrity of brain structures at many levels of the neuraxis [38].

Our mediation analysis suggested that only a small part of the association between air pollution and VCP was mediated by average lung function (6% for NO_2, FEV_1 and VCP). The mediated proportion was slightly higher in never smokers (7% for NO_2, FEV_1 and VCP) and non-*APOE-ε4* carriers (11% for NO_2, FEV_1 and VCP), indicating that after controlling for residual confounding and effect modifications, the mediated proportion increased. One explanation for the small part that was mediated by impaired lung function might be that spirometric measurements are only a rough proxy for lung inflammation and VCP only covers a small aspect of cognitive impairment.

Various pathways have been discussed as to how air pollution can damage the brain. Data from controlled animal studies suggest that PM can infiltrate the brain *via* the circulatory system [39] or translocate *via* the olfactory nerve [40]. Our findings support the hypothesis that at least a portion of the particles might infiltrate the brain *via* the circulatory system. However, the major part of the association between air pollution and VCP could not be explained by air pollution induced lung function impairment.

Strengths and limitations

The strength of our study was the long follow-up period and the availability of repeated lung function measurements as well as a range of potential confounders on which information was collected over a period of time. Furthermore, air pollution exposures were assessed by using state of the art air pollution modelling gained from the ESCAPE campaign in 2009. In addition, we used the most recent spirometric reference values (GLI z-scores) to control for age- and height-dependencies and conducted a prevailing approach for causal mediation analysis allowing an interaction term between exposure and mediator [31]. Furthermore, our long-term cohort study enabled us to consider the chronological order of exposure, mediating event and outcome, which makes our findings more reliable than using only a cross-sectional design.

One limitation of our study was the cross-sectional investigation of cognitive function. It is possible that women with a severe cognitive impairment also performed worse in the lung function testing at follow-up due to a comprehension problem. However, since we evaluated average lung function measurements between baseline and follow-up, this would only have a small impact on our findings. Furthermore, the women who were lost to follow-up were less well educated, smoked more heavily, were exposed to higher levels of air pollution and their respiratory health was worse than those who did participate. These factors have already been shown to be predictors for cardiovascular mortality in the SALIA cohort [19] and this could have led to non-responder bias in the prevalence data. Additionally, there might be some non-responder bias in the air pollution effect and in our mediation analysis. Since air pollution levels in the analysed sample were lower than in the whole baseline sample, the effects of air pollution might have been underestimated in our study. Furthermore, our analysed sample included fewer smokers than the baseline sample and, given that the mediation effect was more pronounced in non-smokers, it might be stronger in our analysed sample than it would have been in the whole baseline sample.

Another limitation of our study is the strong set of assumptions in the causal mediation analysis. This analysis assumes no unmeasured confounding of the treatment–mediator relationship [31]. We considered all potential confounders available in our study sample but we cannot totally exclude the possibility of unmeasured confounding. Furthermore, the sample size of our study population was relatively small, which could reduce the ability to detect significant mediating effects. In this regard, our findings need to be replicated in other cohorts.

Conclusions

Our study provides indications about the mechanisms underlying the association between air pollution and cognitive decline-an association that is partly mediated by impaired lung function. We found that lung function throughout adulthood and later in life was an important predictor for the development of mild cognitive impairment in the elderly. It thus appears that maintenance of good lung function through adulthood is important for healthy brain ageing.

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