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Long-term exposure to fine particulate matter, lung function and cognitive performance: A prospective Dutch cohort study on the underlying routes☆

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ABSTRACT

Background: Exposure to fine particulate matter and black carbon is related to cognitive impairment and poor lung function, but less is known about the routes taken by different types of air pollutants to affect cognition.
Objectives: We tested two possible routes of fine particulate matter ($PM_{2.5}$) and black carbon (BC) in impairing cognition, and evaluated their importance: a direct route over the olfactory nerve or the blood stream, and an indirect route over the lung.
Methods: We used longitudinal observational data for 49,705 people aged 18+ from 2006 to 2015 from the Dutch Lifelines cohort study. By linking current home addresses to air pollution exposure data from ELAPSE in 2010, long-term average exposure to $PM_{2.5}$ and BC was assessed. Lung function was measured by spirometry and Global Initiative (GLI) z-scores of forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC) were calculated. Cognitive performance was measured by cognitive processing time (CPT) assessed by the Cogstate Brief Battery. Linear structural equation modeling was performed to test direct/indirect associations.
Results: Higher exposure to $PM_{2.5}$ but not BC was related to higher CPT and slower cognitive processing speed [Total Effect $PM_{2.5}$: FEV_1 model = 8.31×10^{-3} (95% CI: 5.71×10^{-3}, 10.91×10^{-3}), FVC model = 8.30×10^{-3} (95% CI: 5.69×10^{-3}, 10.90×10^{-3})]. The direct association of $PM_{2.5}$ constituted more than 97% of the total effect. Mediation by lung function was low for $PM_{2.5}$ with a mediated proportion of 1.32% (FEV_1) and 2.05% (FVC), but higher for BC (7.01% and 13.82% respectively).
Discussion: Our results emphasise the importance of the lung acting as a mediator in the relationship between both exposure to $PM_{2.5}$ and BC, and cognitive performance. However, higher exposure to $PM_{2.5}$ was mainly directly associated with worse cognitive performance, which emphasises the health-relevance of fine particles due to their ability to reach vital organs directly.

1. Introduction

Air pollution contributes substantially to the global burden of disease; it is responsible for 4.2 million deaths, about 8,000 deaths per year in Europe (Lelieveld et al., 2019), and for 103.1 million lost years of healthy life globally in 2015 (Cohen et al., 2017).

There is also recent evidence that exposure to air pollution is associated with lower cognitive performance (Zhang et al., 2018) and a higher incidence of dementia (Carey et al., 2018). A cohort study from Germany investigated the relationship between air pollution and cognitive functioning as well as local brain atrophy measured by magnetic resonance imaging (Nuβbaum et al., 2020). In this study, higher

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exposure to $PM_{2.5}$ and $PM_{2.5\ absorbance}$ was related to lower cognitive functioning, and higher $PM_{2.5}$ was additionally associated with local brain atrophy. A double-cross over experiment suggested that short-term exposure to $PM_{2.5}$ had adverse effects on cognitive functioning measured by the Mini-Mental State Examination (MMSE) (Shehab and Pope, 2019). A prospective cohort study among older Chinese adults, which also measured cognitive performance by using the MMSE, found that each 10-μg/m^3 increase in $PM_{2.5}$ was associated with a 5.1% increase in the risk of poor cognitive functioning (Wang et al., 2020). In the US, a doubling in BC level was related to 1.57 times higher odds of low MMSE scores (Colicino et al., 2017). A study, which explored the relationship between exposure to different constituent of $PM_{2.5}$ and cognitive functioning among older Puerto Rican in the US, found that long-term exposure to BC, nickel, sulfur, silicon, and $PM_{2.5}$ in general were related to slower mental speed or decreased recognition (Wurth et al., 2018).

Although, we know more about the negative effects of particulate matter on cognitive performance, the exact routes by which air pollutants may unfold their neurotoxic effects have barely been tested empirically, and there are substantial gaps in the knowledge of the underlying causal mechanisms (Griffiths and Mudway, 2018). Commonly, two hypotheses are discussed (Block and Calderón-Garcidueñas, 2009).

First, air pollutants may damage the brain directly by entering through the olfactory nerve or the lung, with subsequent entry into the blood stream providing access to the brain (Fig. 1, path 1). It is mainly very fine particles which are assumed to follow this route (Block and Calderón-Garcidueñas, 2009; González-Maciel et al., 2017).

Second, air pollutants may enter the lung by inhalation, thus impairing lung function or causing pulmonary inflammation (Fig. 1, path 2). After inhalation, especially fine particles can penetrate the deepest parts of the lung, e.g. the alveoli, due to their small size (Xing et al., 2016). Impaired lung function may cause lower (abnormal) blood oxygen levels (hypoxemia) leading to systemic inflammation, oxidative stress, cerebral arterial stiffness and small-vessel damage (Lutsey et al., 2018). Air pollutants also cause inflammatory responses of immune cells residing in the lung, e.g. pulmonary macrophages, thereby adding to or causing a substantial systemic presence of inflammatory mediators (Guarnieri and Balmes, 2014).

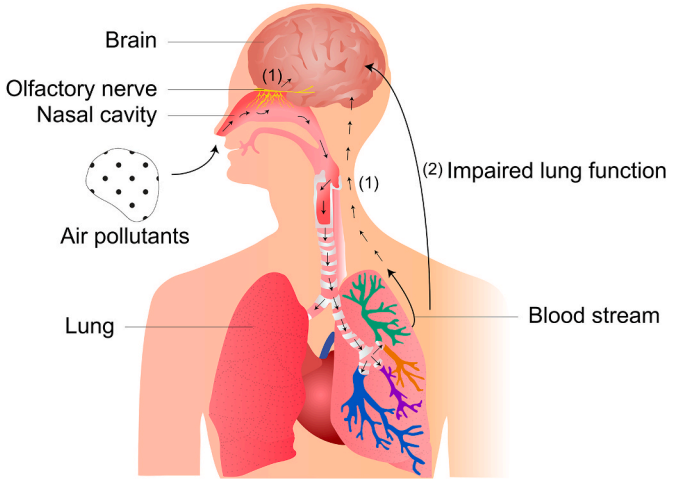

Fig. 1. Routes taken by inhaled fine particles to cause subsequent cognitive impairments. Description: Mainly smaller air pollutants (fine particles) may damage the brain directly by entering through the olfactory nerve or the lung, with subsequent entry into the blood stream providing access to the brain (path 1). Air pollutants may also enter the lung by inhalation, thus impairing lung function or causing pulmonary inflammation (path 2). Impaired lung function may cause lower (abnormal) blood oxygen levels (hypoxemia) leading to systemic inflammation, oxidative stress, cerebral arterial stiffness and small-vessel damage. Air pollutants also cause inflammatory responses of immune cells residing in the lung, e.g. pulmonary macrophages, thereby adding to or causing a substantial systemic presence of inflammatory mediators.

In accordance with this second hypothesis, previous research showed that ambient air pollution is a major health risk contributing substantially to respiratory mortality (Lelieveld et al., 2019), and air pollution is related to lower pulmonary function (Adam et al., 2015), higher COPD prevalence (Bloemsma et al., 2016), higher asthma prevalence (Zheng et al., 2015), higher lung cancer mortality (Dimakopoulou et al., 2014), and a higher burden of COPD (Cohen et al., 2015). But, the negative effect of small particulate matter on lung function, however, is still contested. A meta-analysis of five cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE) observed that higher levels of NO_2, but not of PM_{10} and $PM_{2.5}$, were associated with lower levels of forced expiratory flow in 1 s (FEV_1) and forced expiratory flow (FVC) among adults (Adam et al., 2015). On the contrary, the Framingham Heart Study found that also relatively low levels of $PM_{2.5}$ were related to lower FEV1 and FVC, and an accelerated decline in lung function (Rice et al., 2015). For Black Carbon (BC), there is evidence from a women's cohort from Boston, Massachusetts, that higher levels of BC were associated with decreased lung function in terms of FEV_1 and FVC (Suglia et al., 2008).

Although the hypothesised direct and indirect pathways taken by inhaled air pollutants, there are hardly any cohort studies which explored the interrelations between air pollution, lung function and cognition. To our knowledge, only one cohort study exists that explored the mediating role of FEV_1 and FVC in cognitive impairment caused by long-term exposure to NO_2, PM_{10}, and $PM_{2.5}$ (Hüls et al., 2018). However, this study observed just a small, female cohort in Germany and did not find any significant mediation by lung function. But it showed that there was a total effect/a general relationship in the way that higher exposure to fine particulate matter was related to poor cognitive performance.

Due to the existing lack of research in exploring the interrelation between air pollution, lung function and cognition, this new cohort study has thus two objectives. First, it empirically tests the hypothesised routes taken by fine particulate matter in general ($PM_{2.5}$) and Black Carbon (BC), which is, next to the ultrafine particles (UFP), a major component of $PM_{2.5}$., to impair people's cognitive performance. Second, it evaluates the importance of the found routes in impairing cognition.

2. Methods

2.1. Study population and design

We explored data from the Netherlands, a low pollution setting, and used longitudinal observational data for people aged 18+ from 2006 to 2015 from the Dutch Lifelines cohort study. Lifelines is a multigenerational prospective cohort study on multifactor risks for diseases, which recruited about 10% of the population in the three provinces of the Northern Netherlands, from whom 110,908 adults had a baseline and a follow-up assessment (Scholtens et al., 2015). Current (and for a sensitivity analysis past) residential addresses of each participant were obtained from municipal administration data. The Lifelines Cohort Study is conducted according to the principles of the Declaration of Helsinki and is approved by the medical ethical committee of the University Medical Center Groningen, The Netherlands.

In our study design, we tackled the issue of correct causal time order between the mediator (lung function) and outcome (cognitive performance) of interest. For this purpose, we distinguished between two time periods. The first time period is the baseline (2006–2012), at which the participants were recruited for the Lifelines cohort study and the exposure to fine particulate matter at participants' residential address as well as the lung function was assessed. And the second time period is the follow-up (2014–2015), at which the participants' cognitive performance was assessed.

All participants aged 18+ with data available on residential

addresses at baseline, with valid air pollution exposure data, a valid lung function measurement at baseline (2006–2012), and a valid measurement of cognitive performance at follow-up (2014–2015) were included (Supplementary Figure S1). Our final sample size was 49,705 people (see Supplementary Table S3 for a comparison of the descriptive statistics among participants with complete and incomplete data).

2.2. Outcome assessment: cognitive performance measured by cognitive processing time (CPT)

To measure the participants' cognitive performance in our follow-up period (2014–2015), we used the Cogstate Brief Battery (CBB), which is an age-specific validated standardised computerised tool to measure four domains of cognitive performance: psychomotor speed (reaction time = primary outcome), visual attention (reaction time = primary outcome), visual learning (reaction time and accuracy = primary outcomes), and working memory (accuracy = primary outcome) (Lim et al., 2013).

The CBB has been used in several studies to detect (mild) cognitive impairment (Maruff et al., 2009) and Alzheimer's disease (Maruff et al., 2013; Lim et al., 2012), and has shown to have good test-retest reliability (Darby et al., 2002) and validity (Hammers et al., 2012). The CBB measures were either used as single speed measures from four domains of cognitive performance, or they were used as composite scores, which are constructed by aggregating the single primary outcome measures for reaction time or accuracy (Lim et al., 2012). Composite scores seem to have a greater sensitivity to cognitive impairment than the single CBB measures (Lim et al., 2012; Maruff et al., 2013).

The CBB comprises four card tasks in the space of 11 min, reflecting the four cognitive domains: detection (2 min), identification (2 min), visual learning and memory (5 min), and working memory (2 min). Each task displays a textual instruction screen with a description of the task requirements. Each consists of several exercises (e.g. related to speed or accuracy) to be solved by selecting the "Yes" or "No" buttons on the screen (Lim et al., 2013). The CBB can be conducted un-supervised, which was also shown by evidence from clinical practice (Cromer at al. 2015). The participants should be able to use a computer keyboard or mouse with one hand and should be able to see the computer screen. In Lifelines, the CBB was provided in a systematic fashion. Participants completed the CBB during a visit to the Lifelines location under supervision.

Clinical practice has shown that the cognitive processing speed, defined as the ability to process information rapidly, is closely associated with the ability to solve (complex) cognitive tasks (Lichtenberger et al., 2013) and is thus one of the most important domains of cognitive performance (Salthouse and Ferrer-Caja, 2003). Accordingly, we obtained a speed composite score using the speed measures from detection, identification and working memory task as primary outcomes in consultation with the Cogstate research team.

Each speed measure reflects the mean time for correct responses in each domain and was log (10)-transformed for better normality. A composite score measuring the overall cognitive processing time (CPT) was computed by summing up the speed scores of the three tasks. Positive scores mean that people had higher CPT (= higher reaction time and thus lower speed) and worse cognitive performance, and negative scores that they had lower CPT (= lower reaction time and thus faster speed) and thus better cognitive performance. To control our cognitive speed outcome (CPT) for the accuracy of responses given, we accounted for the composite score of accuracy of given responses and the total number of trials per participant in the three CBB domains we used.

2.3. Exposure assessment: fine particulate matter and black carbon

We used exposure data (spatial resolution = 100 × 100 m) on two ambient air pollutants available in the Lifelines dataset: particulate matter (PM) of particulates with diameters of 2.5 μm and smaller ($PM_{2.5}$) and the black carbon (BC) proportion in the $PM_{2.5}$. By using land-use regression models for the year 2010, which were developed in the project "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) (see de Hoogh et al., 2018 for a detailed description), the 2010 annual mean $PM_{2.5}$ and BC concentrations were estimated. These estimated concentrations were allocated to the participants home addresses in Lifelines at baseline (2006–2012).

In brief, satellite-derived and chemical transport model estimates were used to develop fine spatial scale land use regression (LUR) models for Western Europe for 2010. $PM_{2.5}$ concentrations were derived from the European Air Quality Database (AirBase v8) and BC annual means from the monitoring campaign conducted in the "European Study of Cohorts for Air Pollution Effects" (ESCAPE) (Eeftens et al., 2012). The developed LUR models in ELAPSE for all included sites explained 62% of the variance $PM_{2.5}$, whereas for BC 54% was explained. Spatiotemporal stability was relatively high. Stability tests at country level showed that the agreement between $PM_{2.5}$ levels estimated with the model developed for 2010 and that developed for 2013 was 70.1% for the Netherlands. The relationship between measured average concentrations for the AirBase stations showed an agreement of 68.3% over time (2010–2013) for the Netherlands (de Hoogh et al., 2018).

For a second type of exposure assessment used as a sensitivity analysis, Lifelines linked the current and past home addresses of the individuals to the average annual concentrations for $PM_{2.5}$ and BC, which were estimated for 2010 and came from the LUR developed in ELAPSE. The purpose of this time-weighted average (TWA) exposure model was to investigate if the results change when we take exposure history into account. For this purpose, Lifelines used the Municipal Personal Record Database (Zijlema et al., 2016) that contains the home addresses and thus the geolocations of all individuals who live or have lived in the Netherlands so that residential mobility and length of exposure can be traced. For each air pollutant and individual, we calculated time-weighted average concentrations by using the residential locations of the participants' address history and the allocated average exposure concentrations in 2010, and weighting them by the duration of residence at a specific location (exposure time of the data) (Cohen et al., 1996). This was done for every location of the participants' address history up to baseline. For example, a person had lived in Groningen from 1998 to 2003 (residence duration of five years), moved from Groningen to Drenthe and lived in Drenthe for five years. The baseline of this person was in the year 2008 (and the person was still living at the same address in Drenthe) so that the residence duration in Drenthe up to baseline was again five years. Then, the 2010 exposure values from the ELAPSE project for the Groningen and Drenthe home addresses of this participant were multiplied each with the duration of five years, summed up, and then divided by the total duration (10 years). In this TWA-model, we included participants with available address history of at least ten years only (exposure time $\geq$ 10 years).

2.4. Mediator assessment: lung function

The indirect route assumed that higher exposure to fine particulate matter was related to lower lung function and less oxygen saturation causing worse cognition subsequently. Previous studies found that both FEV_1 and FVC were associated with the oxygen saturation in blood in people with lung diseases (Ardestani and Abbaszadeh, 2014), e.g. COPD, but also in the general adult population (Vold et al., 2012). Both lung function measures FEV_1 and FVC thus reflect the proposed indirect route properly why we treated them as potential mediators in our study.

Lung function at baseline (2006–2012) was assessed by Lifelines through spirometry, performed by trained medical staff according to American Thoracic Society guidelines using a Welch Allyn Version 1.6.0.489 PC-based SpiroPerfect with CardioPerfect workstation software. We used two volume measures, the forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC), as outcome variables. To come up with interpretable scores, we used age-, sex-and height-specific

Table 1
Descriptive statistics of the study participants (n = 49,705) at baseline (2006–2012) and at follow-up (2014–2015) in the study population based on the Dutch Lifelines Cohort Study.

Characteristic	Baseline (2006–2012)	Follow-up (2014–2015)
Sex, No. (%)		
Women	29,422 (59.19)	
Men	20,283 (40.81)	
Age, mean (SD)	44.77 (11.41)	48.94 (11.35)
Province of residence, No. (%)		
Drenthe	10,065 (20.25)	10,117 (20.35)
Friesland	22,279 (44.82)	22,087 (44.44)
Groningen	16,721 (33.64)	16,402 (33.00)
Other	640 (1.29)	1,099 (2.21)
Educational level, No. (%)		
No education	124 (0.25)	130 (0.26)
Primary education	565 (1.14)	426 (0.86)
Lower or preparatory vocation	5,549 (11.16)	5,302 (10.67)
Junior general secondary education	6,728 (13.54)	6,805 (13.69)
Secondary vocational education	15,386 (30.95)	15,006 (30.19)
Senior general secondary education	4,538 (9.13)	4,101 (8.25)
Higher vocational education	12,803 (25.76)	13,635 (27.43)
University education	3,175 (6.39)	3,517 (7.08)
Other	837 (1.68)	783 (1.58)
Net income per month, No. (%)		
Lower than 1500 Euro	6,497 (13.07)	
1500 to 2500 Euro	13,413 (26.99)	
Higher than 2500 Euro	23,302 (46.88)	
Do not know/do not want to tell	6,493 (13.06)	
Pack-years of cigarettes smoked, No. (%)[a]		
Never smokers	23,773 (47.83)	
Lower/equal than the 50th percentile of ever smokers	13,184 (26.52)	
Higher than the 50th percentile of ever smokers	12,748 (25.65)	
BMI, No. (%)		
Lower than 25	22,750 (45.77)	22,211 (44.69)
25 to lower than 30	19,892 (40.02)	19,877 (39.99)
Higher/equal than 30	7,063 (14.21)	7,617 (15.32)
Hypertension, No. (%)[b]		
Yes	8,597 (17.30)	11,074 (22.28)
No	41,108 (82.70)	38,631 (77.72)
Asthma, No. (%)[c]		
Yes	3,803 (7.65)	
No	45,902 (92.35)	
COPD, No. (%)[c]		
Yes	2,332 (4.69)	
No	47,373 (95.31)	
Diabetes, No. (%)[c]		
Yes	3,528 (7.10)	
No	46,177 (92.90)	
Depression, No. (%)[c]		
Yes	4,865 (9.79)	
No	44,840 (90.21)	
Stroke, No. (%)[c]		

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Baseline (2006–2012)	Follow-up (2014–2015)
Yes	262 (0.53)	
No	49,443 (99.47)	
Multiple Sclerosis, No. (%)[c]		
Yes	114 (0.23)	
No	49,591 (99.77)	
Long-term air pollution (one-year annual mean concentrations), mean (SD)[d]		
PM2.5 (in μg/m^3) from ELAPSE, year 2010	14.92 (1.01)	
BC (in μg/m^3) from ELAPSE, year 2010	1.22 (0.22)	
Lung function, mean (SD)[e]		
FEV_1 (L), % predicted	3.50 (0.82), 96.54 (12.72)	
FVC (L), % predicted	4.56 (1.03), 100.78 (12.14)	
Number of total CBB trials, mean (SD)[f]		140.26 (24.65)
Accuracy of given CBB responses, mean (SD)[g]		3.76 (0.47)
Less accurate (lower values) than the mean, No. (%)		21,958 (44.18)
More accurate (higher values) than the mean, No. (%)		27,747 (55.82)
Cognitive processing time (CPT), log10-transformed milliseconds, mean (SD)[h]		8.37 (0.34)
Faster CPT (lower values) than the mean, No. (%)		25,915 (52.14)
Slower CPT (higher values) than the mean, No. (%)		23,790 (47.86)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); $PM_{2.5}$, (fine) particulates with diameters of 2.5 μm and smaller; BC, black carbon proportion in the fine particulate matter.

[a] Pack-years of cigarettes smoked were calculated from the baseline questionnaire (1 pack-year = 20 cigarettes per day in 1 year).

[b] Hypertension was defined when systolic pressure was higher than 139 mmHg or diastolic pressure higher than 89 mmHg (blood pressure was measured by medical staff).

[c] Prevalence of diseases at baseline was assessed by questions, whether a specific disease was diagnosed by a doctor or not.

[d] Long-term air pollution concentrations were assessed as one-year annual mean concentrations at participants' baseline address and were estimated for the year 2010 by the ELAPSE models/project.

[e] Lung function was measured by spirometry by trained medical staff.

[f] Number of CBB trials represents the total number of responses given by the participants during the three subtests (detection, identification, working-memory) of the Cogstate Brief Battery.

[g] Accuracy was measured by the proportion of correct responses. For each domain (detection, identification, working-memory), the accuracy of each response to each trial was recorded. The three already arcsine-transformed measures from the Cogstate Brief Battery were summed to measure the total accuracy.

[h] Cognitive Processing Time was measured by using three single (detection, identification, working-memory) log10-transformed speed measures from the Cogstate Brief Battery. The three measures were summed up to measure the total average reaction time.

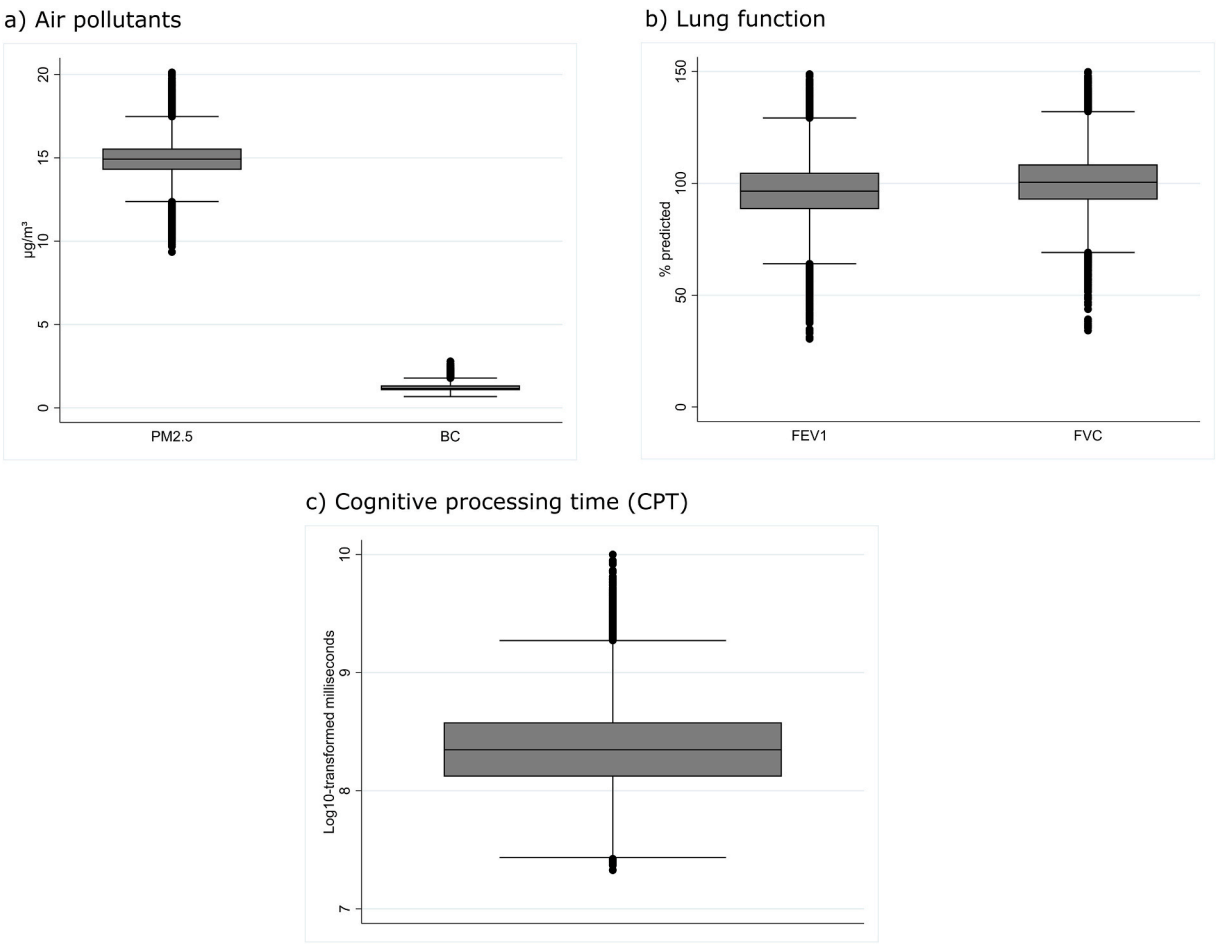

Fig. 2. Distribution of long-term exposure to $PM_{2.5}$ and BC at baseline (2006–2012), lung function at baseline and cognitive processing time at follow-up (2014–2015). Abbreviations: PM2.5, (fine) particulates with diameters of 2.5 µm and smaller; BC, black carbon proportion in the fine particulate matter; FEV1, Forced Expiratory Volume in 1 s; FVC, Forced Volume Capacity. Description: Boxplots included a) long-term exposure to fine particulate matter at the study participants' baseline address, b) lung function measures at baseline (2006–2012), and c) cognitive processing time (CPT), the outcome of interest, at follow-up (2014–2015). The boxes indicate the interquartile range (IQR) and the line in the center indicates the median concentration. Outlier observations are shown as circles.

reference values for FEV_1 and FVC as provided by the Global Lung Initiative (GLI) (Quanjer et al., 2012). Subsequently, the predicted proportion of the empirical lung function scores compared to the predicted reference scores were calculated for all both lung function measures. Scores beyond 100% mean that people had better lung parameters compared to the reference values, whereas scores lower than 100% mean that they had worse.

2.5. Assessment of potential confounders

We controlled for age, sex, socio-demographic and lifestyle confounders, and respiratory and cognition-related diseases either at baseline (2006–2012) only, or as time-dependent variables for both baseline and follow-up (2014–2015). In detail, age, province of residence (Drenthe, Groningen, Friesland, other), education, BMI, hypertension, and age were included as time-dependent confounders by controlling lung function for the baseline information and CPT for the follow-up information.

Education level was defined as the highest education level completed (none, primary, lower secondary vocational, secondary vocational, senior general secondary, higher vocational, university, other). Income was measured by an individual's net income per month (less than 1500 Euro, between 1500 and 2500 Euro, higher than 2500 Euro, unknown/unexpressed). Body mass index (BMI) was calculated as the individual's measured weight divided by measured height square and categorised in one of three groups: less than 25, between 25 and less than 30, and equal to or higher than 30. Hypertension was operationalised by a systolic pressure higher than 139 mmHg or a diastolic pressure higher than 89 mmHg. Systolic and diastolic blood pressure was measured by medical staff. Prevalence of respiratory diseases, namely asthma and COPD, as well as cognition-related diseases, namely multiple sclerosis, depression, diabetes (type I or II), and stroke, was derived by a question whether a doctor has ever diagnosed that specific disease in participants before (yes/no). Pack-years of cigarettes smoked (1 pack-year = 20 cigarettes per day/1 year) were calculated from the baseline questionnaire collecting data on a person's smoking history.

In the sensitivity models using the time-weighted average exposure assessment (TWA-model), we controlled additionally for the total time period in days (continuous variable) to which the long-term exposure to air pollution applied.

2.6. Statistical analysis

We used mediation analysis to explore whether the association between air pollution (X) and CPT (Y) followed a direct route to the brain or was mediated by lung function (*M*). We performed linear structural equation models (SEM) without feedback loops and with robust standard errors by Huber/White (Breusch-Pagan-Test, $p < 0.001$). Exposure

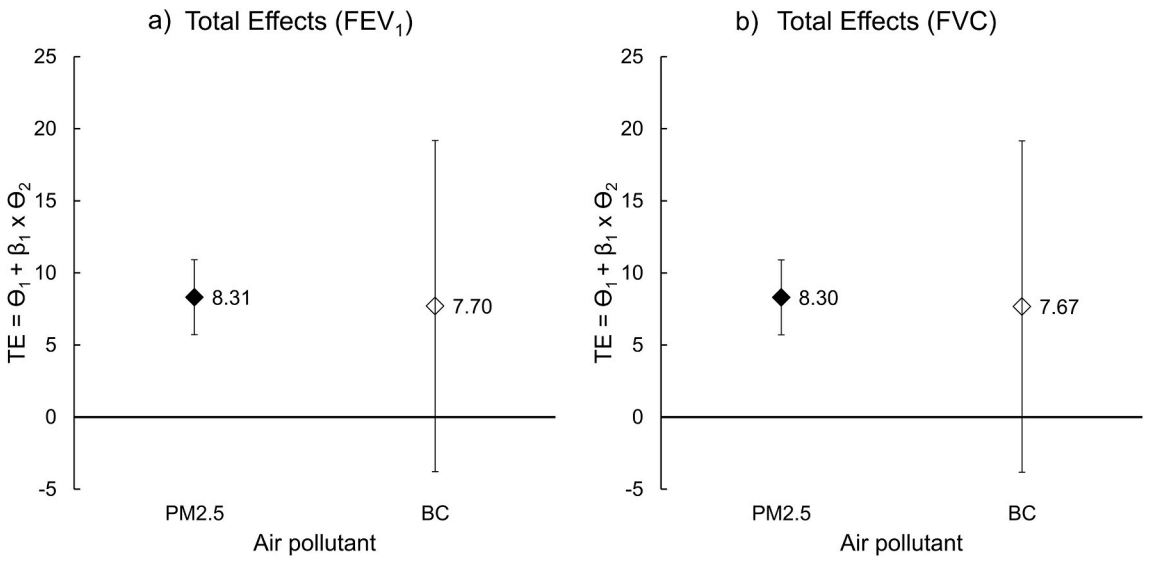

Fig. 3. Total Effects: Associations between long-term exposure to $PM_{2.5}$ and BC, and cognitive processing time (CPT). Abbreviations: PM2.5, (fine) particulates with diameters of 2.5 μm and smaller; BC, black carbon proportion in the fine particulate matter; FEV1, Forced Expiratory Volume in 1 s; FVC, Forced Volume Capacity. Description: Interval plots show the Total Effects (a, b) of the associations between long-term exposure to fine particulate matter (in μg/m^3) and Cognitive Processing Time (CPT), which is the log10-transformed total reaction time, measured by the Cogstate Brief Battery. The models related to each unit increase of long-term exposure to $PM_{2.5}$ or BC. Shown values for point estimators, lower and upper confidence intervals were multiplied by 10^3.

and confounders were treated as exogenous variables, and lung function as well as CPT were seen as endogenous variables. We introduced an outcome equation (equation (1)) and a mediator equation (equation (2)), whereby C_n denote the specific confounding variables, and θ_0 to θ_n, and β_0 to β_n are the unobserved parameters (see also Supplementary Figure S2 for the model approach):

$$Y = \theta_0 + \theta_1 X + \theta_2 M + \theta_3 C_1 + \theta_4 C_2 \ldots + \theta_n C_n + \varepsilon_2 \quad (1)$$

$$M = \beta_0 + \beta_1 X + \beta_2 C_1 + \beta_3 C_2 + \ldots + \beta_n C_n + \varepsilon_1 \quad (2)$$

We estimated the two equations simultaneously and performed subsequently a decomposition of the total effect (the following usage of the words total, indirect or total effect does not imply causality; terms represent standard technical terms) $TE = \theta_1 + \beta_1 \times \theta_2$ into a direct effect $DE = \theta_1$ and the two separate indirect paths (β_1, θ_2). The both indirect path coefficients can be combined into one indirect effect $IE = \beta_1 \times \theta_2$ (Gunzler et al., 2013). To test the significance of the indirect effect (*IE*) we used the delta method/Sobel Test (Sobel, 1982). We calculated direct effect proportions ($DEP = \frac{(\theta_1)}{(\theta_1+\beta_1\times\theta_2)} \times 100$) and indirect effect proportions ($IEP = \frac{(\beta_1\times\theta_2)}{(\theta_1+\beta_1\times\theta_2)} \times 100$) to quantify the importance of the significant direct effect and indirect effect compared to the total effect. The significance threshold was 0.05 and all tests were 2-sided. The calculations were performed using Stata MP 13.1.

We performed three kinds of sensitivity analyses. First, we checked the robustness of our SEM approach to ensure that our results were valid. We applied causal mediation analysis using a potential outcome approach with bootstrapping (1000 iterations) for inference evaluation. Causal mediation analysis was performed by using the "mediation" package in Stata, which is based on the "mediation" package for causal mediation analysis in R (Tingley et al., 2014).

Second, we estimated SEMs for study participants aged 45 because the air pollution effects on cognitive performance are assumed especially evident for those ages when cognitive decline has generally started (Singh-Manoux et al., 2012).

Third, we calculated time-weighted average concentrations over a minimum of ten years up to baseline based on participants' residential history (TWA-model) to investigate if the results change when we take exposure history into account.

3. Results

3.1. Characteristics of the study participants

Of the 49,705 participants 25,915 (52.14%) had faster Cognitive Processing Time (CPT) and 23,790 (47.86%) slower CPT than the mean at follow-up (2014–2015) (Table 1). The average exposure to $PM_{2.5}$ was 14.92 [min = 9.35, max = 20.12] μg/m^3, and 1.22 [min = 0.68, max = 2.79] μg/m^3 to BC (Fig. 2). For lung function, the average FEV_1 was 3.50 L (96.54% predicted) and FVC 4.56 L (100.78% predicted) (Table 1).

There were 23,773 (47.83%) people who had zero pack-years of cigarettes smoked, suggesting that they were never-smokers, and the smokers had an average of 11.25 pack-years. The body mass index of 19,892 (40.02%) participants indicated they were overweight (30 > BMI ≥ 25), and 7063 (14.21%) were obese (BMI ≥ 30) at baseline. The proportion of obese people increased to 15.32% at follow-up. 7.65% of the participants had prevalent asthma at baseline diagnosed by a doctor, 4.69% COPD, 7.10% diabetes, 9.79% depression, and 0.53% had ever a stroke before baseline. Age at baseline ranged from 18 to 88 and the average age was 44.77 years, whereas the average age was 48.94 years (min = 20, max = 92) at follow-up.

3.2. Associations between air pollution exposure and cognitive processing time (CPT)

First, we estimated the total effect showing the overall associations between long-term air pollution exposure at baseline and CPT at follow-up (2014–2015). We found that higher exposure to $PM_{2.5}$ was significantly related to slower CPT and so worse cognitive performance even when we controlled for both lung function mediators, namely FEV_1 [$PM_{2.5}$: 8.31×10^{-3} (95% CI: 5.71×10^{-3}, 10.91×10^{-3})] and FVC [$PM_{2.5}$: 8.30×10^{-3} (95% CI: 5.69×10^{-3}, 10.90×10^{-3})] (Fig. 3, Supplementary Table S1). An increase in $PM_{2.5}$ exposure of one μg/m^3 is accordingly related to an increase in cognitive processing time of 2% (recalculation, e.g. for FEV_1, as follows: $(10^{0.00831} - 1) \times 100 = 1.93$). We additionally estimated adjusted CPT predictions for the values of $PM_{2.5}$ from the minimum integer value (9) to the maximum (20) value under our model assumptions (Supplementary Figure S3). This showed that in our linear model people exposed to an average value of 16μg/m^3 or

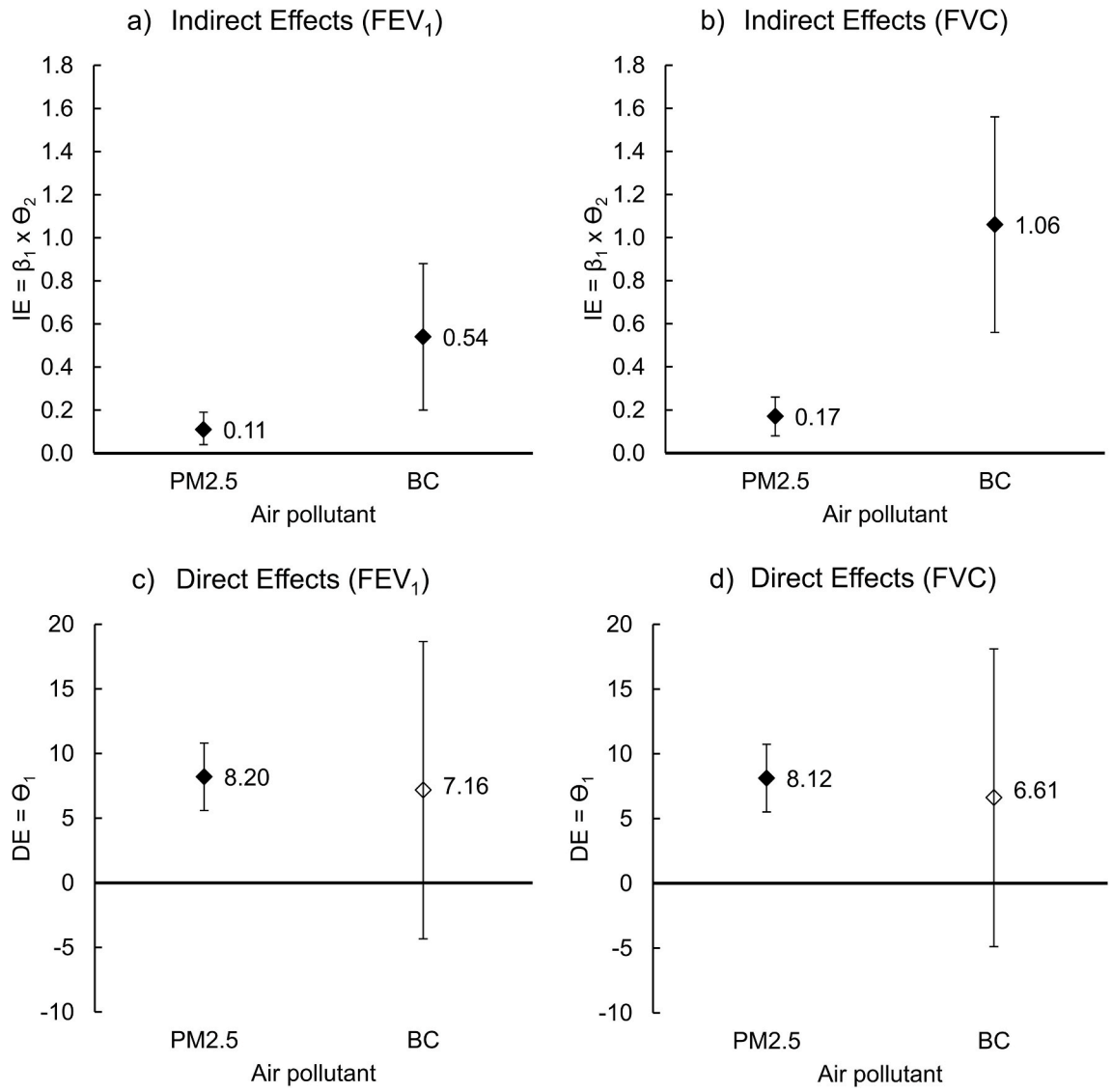

Fig. 4. Decomposition of the associations between long-term exposure to $PM_{2.5}$ and BC, and cognitive processing time (CPT). Abbreviations: PM2.5, (fine) particulates with diameters of 2.5 μm and smaller; BC, black carbon proportion in the fine particulate matter; FEV1, Forced Expiratory Volume in 1 s; FVC, Forced Volume Capacity. Description: Interval plots show the decompositions of the Total Effects into direct and indirect effects. The models related long-term exposure to fine particulate matter (in $\mu g/m^3$) to Cognitive Processing Time (CPT), which is the log10-transformed total reaction time, measured by the Cogstate Brief Battery. The Indirect Effects a), b) represent the indirect routes over the lung function measures FEV1 and FVC (potential mediators) and the Direct Effects c), d) the direct routes over the olfactory nerve/blood stream. The models related to each unit increase of long-term exposure to $PM_{2.5}$ or BC. Shown values for point estimators, lower and upper confidence intervals were multiplied by 10^3.

higher had worse cognitive performance than the mean in our study population (CPT = 8.37 log10-transformed milliseconds, red line in Figure S3) had. For BC, however, no significant total associations existed.

3.3. Mediation analysis and decomposition of the total effect into the direct and indirect effect

Second, we conducted a decomposition of the total effects into a direct and an indirect effect. The direct effect represents the direct route of air pollutants through the olfactory nerve or the lung, with subsequent entry into the blood stream, providing access to the brain. The direct effects for $PM_{2.5}$ on CPT were seen even when we controlled for lung function measures at baseline (2006–2012), so the indirect routes, namely for FEV_1 [$PM_{2.5}$: 8.20×10^{-3} (95% CI: 5.59×10^{-3}, 10.80×10^{-3})] and FVC [$PM_{2.5}$: 8.12×10^{-3} (95% CI: 5.52, 10.73)]. No significant direct effects were found for BC (Fig. 4).

The indirect effect represents the indirect route of air pollutants, which first impair the lung, which in turn leads to worse cognitive performance. For $PM_{2.5}$, we observed mediation by both lung function measures, namely for FEV_1 [$PM_{2.5}$: 0.11×10^{-3} (95% CI: 0.04×10^{-3}, 0.19×10^{-3})] and FVC [$PM_{2.5}$: 0.17×10^{-3} (95% CI: 0.08×10^{-3}, 0.26×10^{-3})] (Fig. 4 and see Supplementary Table S1 for the estimation parameters of β_1, θ_1 and θ_2). We also found indirect effects for BC, namely for both lung function measures (BC, FEV_1: [0.54×10^{-3} (95% CI: 0.20×10^{-3}, 0.88×10^{-3}); BC, FVC: [1.06×10^{-3} (95% CI: 0.56×10^{-3}, 1.56×10^{-3})].

Our first sensitivity analysis using g-formula supported our results and showed that our model approach came to nearly the same estimations (Supplementary Table S2). The second sensitivity analysis including participants aged 45 and older only (see Supplementary Table S4 for descriptive statistics) showed also same results than the all-participant model in line with our hypothesis (Table 2). Our third sensitivity analysis (TWA-model) used the estimated time-weighted

Table 2
Outcomes of our decomposition analysis for our main analysis, and the two sensitivity analyses: one using participants aged 45+ only, and one using time-weighted average exposure concentrations (TWA-model).

Air pollutant	Lung function measure	One-year annual mean concentrations from 2010 at baseline address (n = 49,705)			Participants aged 45+ only (n = 25,812)			TWA-model (n = 31,232)		
		Total Effect	Indirect Effect	Direct Effect	Total Effect	Indirect Effect	Direct Effect	Total Effect	Indirect Effect	Direct Effect
$PM_{2.5}$	FEV_1	**8.31** (5.71, 10.91)	**0.11** (0.04, 0.19)	**8.20** (5.59, 10.80)	**7.50** (3.75, 11.25)	**0.12** (0.01, 0.23)	**7.39** (3.64, 11.14)	**8.30** (4.86, 11.73)	**0.14** (0.03, 0.24)	**8.16** (4.73, 11.60)
	FVC	**8.30** (5.69, 10.90)	**0.17** (0.08, 0.26)	**8.12** (5.52, 10.73)	**7.49** (3.74, 11.24)	**0.19** (0.06, 0.33)	**7.30** (3.55, 11.05)	**8.29** (4.85, 11.73)	**0.22** (0.08, 0.36)	**8.07** (4.63, 11.51)
BC	FEV_1	7.70 (−3.78, 19.19)	**0.54** (0.20, 0.88)	7.16 (−4.33, 18.65)	7.82 (−10.30, 25.94)	**1.04** (0.34, 1.74)	6.78 (−11.34, 24.90)	−2.65 (−18.13, 12.84)	0.71 (0.21, 1.21)	−3.35 (−18.84, 12.13)
	FVC	7.67 (−3.82, 19.16)	**1.06** (0.56, 1.56)	6.61 (−4.88, 18.10)	7.78 (−10.34, 25.90)	**1.85** (0.87, 2.82)	5.93 (−12.21, 24.07)	−2.66 (−18.15, 12.83)	**1.28** (0.53, 2.03)	−3.94 (−19.44, 11.56)

Abbreviations: CI, confidence interval; $PM_{2.5}$, (fine) particulates with diameters of 2.5 μm and smaller; BC, black carbon proportion in the fine particulate matter; FEV_1, Forced Expiratory Volume in 1 s; FVC, Forced Volume Capacity.
Description: Table shows the decompositions of the Total Effects (estimates and confidence intervals in brackets) of the associations between long-term exposure to fine particulate matter (in $\mu g/m^3$) and Cognitive Processing Time (CPT), which is the log10-transformed total reaction time, measured by the Cogstate Brief Battery. The direct (Direct Effect) and the indirect (Indirect Effect) routes over the lung function measures FEV_1 and FVC (potential mediators) were modelled simultaneously by performing linear structural equation models with robust standard errors by Huber/White. Illustrated were the point estimators and confidence intervals coming from single models for each air pollutant, controlled for sex, age, province of residence, educational level, income, pack-years of cigarettes smoked, hypertension, asthma, COPD, diabetes, depression, stroke, multiple sclerosis, BMI, the CBB accuracy, and the total number of CBB trials. Shown values for point estimators, lower and upper confidence intervals were not transformed after estimation. Bold values mark significant coefficients.

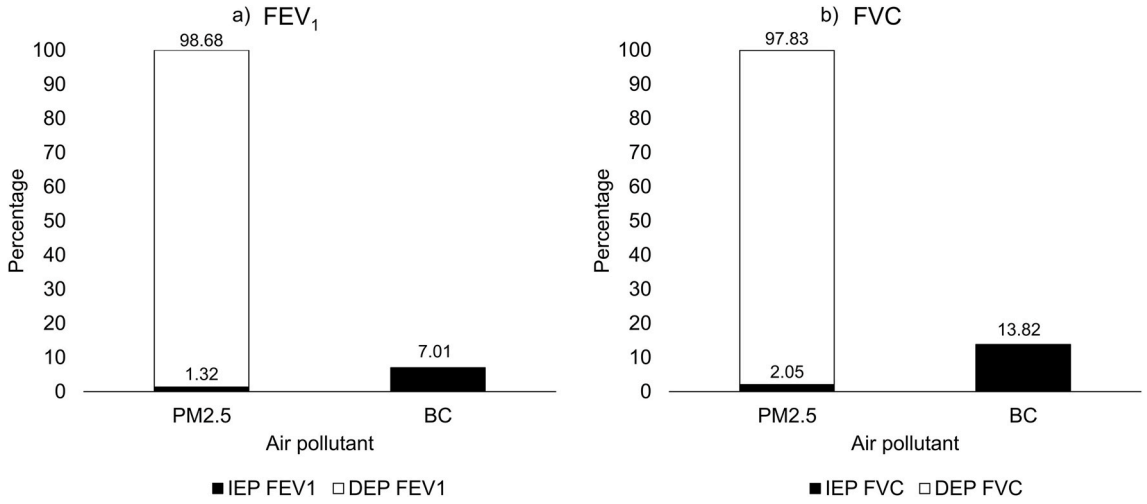

Fig. 5. The importance of the found Indirect (IEP) and Direct Effects (DEP) of long-term exposure to $PM_{2.5}$ and BC on cognitive processing time (CPT) calculated as proportions in percentage of the Total Effects. Abbreviations: PM2.5, (fine) particulates with diameters of 2.5 μm and smaller; BC, black carbon proportion in the fine particulate matter; FEV1, Forced Expiratory Volume in 1 s; FVC, Forced Volume Capacity; IEP, indirect effect proportion; DEP, direct effect proportion. Description: Bars show the found significant indirect effects (IEP) and the direct effect proportions (DEP) found in the decomposition of the total effects for both lung function measures FEV1 a) and FVC b) acting as potential mediators. Indirect effect proportions were calculated by dividing the size of the indirect effects by their total effects. The direct effect proportions were calculated by dividing the size of the direct effects by their total effects.

average concentrations of $PM_{2.5}$ and BC based on the participants' address history of the last 10 years at least, excluding all those with less than ten years of address history (see Supplementary Table S4 for descriptive statistics). Results did not change as compared to our main model (Table 2), which indicates that the exposure concentrations at baseline address used in our study may be considered as a valid proxy for chronic long-term exposure.

By calculating the importance of direct and indirect effects, we found that 98.68% (FEV_1) or 97.83% (FVC) of the total effect of $PM_{2.5}$ was directly associated with cognitive performance. The highest indirect effect proportions were seen for BC (FVC, 13.82%) and the lowest indirect effect proportion was seen for $PM_{2.5}$ by FEV_1 (1.32%) (Fig. 5).

3.4. The influence of confounders on the associations between fine particulate matter and cognitive performance

As expected, higher age at follow-up was correlated with worse cognitive performance [9.16×10^{-3} (95% CI: 8.89×10^{-3}, 9.43×10^{-3})], and higher educated people had better cognitive performance [-104.61×10^{-3} (95% CI: −161.23, −48.00)] than participants without any educational level. Prevalent diabetes [38.41×10^{-3} (95% CI: 27.36×10^{-3}, 49.46×10^{-3})] as well as a stroke in the past [57.33×10^{-3}

(95% CI: 13.29 × 10^{-3}, 101.36 × 10^{-3})] were related to poor cognition, all other morbidities did not show significant effects on cognitive performance. Men [men: −26.75 × 10^{-3} (95% CI: −32.08 × 10^{-3}, −21.41 × 10^{-3})] fared better than women.

Participants with prevalent COPD [FEV_1: −6.35% predicted (95% CI: −7.00, −5.69); FVC: −2.78% predicted (95% CI: −3.32, −2.25)] and asthma [FEV_1: −4.19% predicted (95% CI: −4.64, −3.73); FVC: −1.09% predicted (95% CI: −1.49, −0.69)] had worse lung function. But also diseases, which were not directly related to respiratory health, were associated with worse lung function, namely stroke [FEV_1: −3.49% predicted (95% CI: −5.19, −1.80); FVC: −2.62% predicted (95% CI: −4.15, −1.09)], diabetes [FEV_1: −0.79% predicted (95% CI: −1.24, −0.35); FVC: −1.08% predicted (95% CI: −1.50, −0.65)], and hypertension [FEV_1: −1.18% predicted (95% CI: −1.50, −0.87); FVC: −1.19% predicted (95% CI: −1.49, −0.89)].

Lower income, a higher number of packyears and obesity, but not a lower educational level, were associated with lower FEV_1 and FVC. Higher age at baseline was related to both higher FEV_1 and FVC indicating that the age-standardisation by the GLI reference values was not fully successful for our cohort and an additional inclusion of age in our models was important to avoid confounding by age. For sex, we found an association with FVC only confirming that the sex-standardisation was successful for FEV_1, but not for FVC.

4. Discussion

4.1. Summary of the findings

To the best of our knowledge, our cohort study is one of the first to demonstrate the importance of the direct and the indirect route over the lung taken by inhaled fine particulate matter in general and Black Carbon in particular in cognitive impairments for both genders.

In the low pollution setting of the Netherlands, higher exposure to $PM_{2.5}$ was associated with slower cognitive processing time at follow-up (2014–2015) among participants aged 18+, and associations were also evident in a sensitivity model including participants aged 45 and older. Further analyses showed that, based on our model assumptions, an average $PM_{2.5}$ exposure level of 16–20 μg/m^3 was related to worse cognitive performance compared to the mean in our study population, whereas people experiencing only 9–14 μg/m^3 on average had better cognitive performance. By decomposing the total effects into a direct and an indirect effect respectively, we showed that $PM_{2.5}$ was directly related to slower cognitive processing time and, thus to worse cognitive performance. This direct effect constituted more than 97% of the total effect of $PM_{2.5}$ on cognitive performance when we included mediation by lung function at baseline (2006–2012) in our model. In addition to the direct effect, there was also small significant indirect effects for both lung function measures FEV_1 and FVC contributing just about 1%–2% to the total effect.

For BC, the associations were solely mediated via lung function. We found significant indirect effects, which contributed about 7.01% (FEV_1) to 13.82% (FVC) to the total effects. Both mediations however, were too small to translate significance to the total effect since there were insignificant direct effects which contribute (partially) to the total effect as well.

As most important covariates/confounders, we identified age, educational level and diabetes prevalence for cognitive performance, and prevalence of COPD, asthma, stroke, diabetes, and hypertension as well as income and packyears for lung function.

The main aim of this study was to test the two hypothesised routes taken by fine particulate matter in general ($PM_{2.5}$) and Black Carbon (BC) as one of the main components of the fine particulate matter. Our results indicate that the direct route may be more important for $PM_{2.5}$ and the indirect route for BC.

4.2. Interpretation and comparison of the findings

Our finding that BC may not be able to cross the direct route to reach the brain is contrary to earlier findings for people 60 and older (Colicino et al., 2017; Wurth et al., 2018). Explanations for this could be that we applied a low pollution setting or that we explored participants in the age of 18 or older, who are less fragile than older people. Previous research accordingly found that older people (≥ 65 years old) are more prone to the negative effects of air pollution (Shumake et al., 2013; Simoni et al., 2015) than younger people. If PM2.5 can reach the human's brain through the direct route according to the results of our study, then BC may follow this route as well since BC is a part of PM2.5 and is of very small size.

We found that $PM_{2.5}$, however, may affect cognition directly. It is known that fine particles, e.g. $PM_{2.5}$ and especially ultrafine particles (diameter < 0.01 μm), a component of $PM_{2.5}$ as well, are potentially able to penetrate the central nervous system, resulting in subsequent neuroinflammation (Maher et al., 2016). We further know that microglia may be activated by the direct route, but also upon occurrence of systemic neuroinflammation (Widmann and Heneka, 2014). In vivo and in vitro studies also provide insights into the neurotoxic effect of PM exposure; i.e., higher levels of PM are linked to significantly higher levels of pro-inflammatory cytokines such as interleukin, as well as tumor necrosis factor and glial responses indicating the presence of inflammation (Kilian and Kitazawa, 2018). In turn, neuroinflammation is an important risk factor for neurodegenerative diseases, e.g. Alzheimer's and Parkinson's disease (Glass et al., 2010; Heneka et al., 2015; Sarlus and Heneka, 2017). Another possibility is that the pollutants inhaled reach the brain via the lung, which provides the initial entry to the body, and then pass from the alveoli into the bloodstream, using circulation to reach the central nervous system (CNS) (Lee and Shah, 2018). We further know that exposure to $PM_{2.5}$ is associated with DNA methylation, which may in turn affect lung function or/and brain health negatively (Shi et al., 2019).

Additionally, we found evidence for the relevance of the indirect route over the lung in cognitive impairments by fine particulate matter. That is, $PM_{2.5}$ to a small extent and BC to a greater extent affect cognitive performance by first impairing the lung function and subsequently leading to cognitive impairment. For BC, this seemed to be the main route in our study to unfold adverse cognition effects, since we found that the effect of BC on cognitive performance was solely mediated by FEV_1 and FVC with a mediated proportion of about 7%–14% and we found no evidence that BC is able follow the direct route. Previous studies have also found that higher exposure to BC and $PM_{2.5}$ are associated with lower FEV_1 and FVC (Guo et al., 2018; Lepeule et al., 2014), and inflammatory processes in the lung, oxidative stress and activation of microglia cells resulting in subsequent neuroinflammation have been suggested as causal pathways (Guarnieri and Balmes, 2014). However, the fact that the found mediated proportion is only 7.01%–13.82% for BC suggests that there are potential additional routes missed in our study, e.g. cardiovascular health/diseases, which could be relevant in impairing cognition by BC. We know accordingly from previous research that higher exposure to BC was related to adverse cardiovascular outcomes (Gan et al., 2011). In turn, another study has found that better cardiovascular health was related to better cognitive health (Kulshreshtha et al., 2019).

Our study was conducted in the low-pollution setting of adults aged 18+ in the Netherlands. For $PM_{2.5}$ (14.92 μg/m^3), the exposure level was clearly lower compared to the relatively restrictive EU-wide limit values (25 μg/m^3 for $PM_{2.5}$) (Guerreiro et al., 2018), and also lower compared to previous epidemiological cohort studies (ECRHS, 16 μg/m^3; EGEA, 15 μg/m^3; E3N, 15 μg/m^3; SALIA, 18 μg/m^3; SAPALDIA, 17 μg/m^3) (Jacquemin et al., 2015). This was also true for BC, which was 1.22 μg/m^3 in our study, but 1.5 μg/m^3 or higher in other cohorts (ECRHS, 2.0 μg/m^3; EGEA, 2.1 μg/m^3; E3N, 1.8 μg/m^3; SALIA, 1.5 μg/m^3; SAPALDIA, 1.9 μg/m^3) (Jacquemin et al., 2015). Higher

exposure levels in other spatial units or countries may result in even stronger associations between air pollution and cognition than what is demonstrated in this study's population, under the assumption of a non-linear, e. g exponential, dose-response relationship. To the best of our knowledge, there is no previous study which evaluated the dose-response relation between fine particulate matter and cognitive performance among adults, so that more research is needed here.

4.3. Strengths and limitations

Our study has several strengths. First, we did not only explore the overall relationship (total effect) between fine particulate matter and cognitive performance as done by previous research (Power et al., 2011; Wurth et al., 2018; Zhang et al., 2018), but additionally performed a decomposition of the total effects in order to disentangle the potential routes taken by the air pollutants, which are closely related to causal mechanisms/pathways. For this purpose, we applied a causal mediation approach by using SEM. To the best of our knowledge, the only previous cohort study that explored the mediating role of lung function was not able to find any significant indirect effects (Hüls et al., 2018), potentially because they observed only a small female cohort in Germany. The adverse total effect of $PM_{2.5}$ they observed, however, supports our results.

Second, in a sensitivity model (TWA-model) we calculated time-weighted average concentrations over a minimum of ten years up to baseline to check if the results change when we took exposure history into account. We found same results in this TWA-model why we assumed that the used one-year average concentrations were good proxies for long-term exposure. Using one-year mean concentrations only, as done in previous studies (Colicino et al., 2017; Nuβbaum et al., 2020; Wang et al., 2020; Wurth et al., 2018), may confound the results by unobserved positive health selection into living environments with low exposure levels (Oakes, 2014), even when our third sensitivity model showed that this is not true in our study.

Third, we used a standardised and multidimensional (composite) outcome variable, cognitive processing time (CPT), which was computed in close contact with the Cogstate research team, to measure the participants' cognitive performance. The speed measures coming from the CBB may be summarised into a composite, also used to determine the overall cognitive performance and not only to detect clinical abnormalities (in single cognition domains). Previous studies mostly used the MMSE as an outcome to measure mild cognitive impairment, e. g. when MMSE scores were ≤ 25 (Colicino et al., 2017; Shehab and Pope, 2019; Wang et al., 2020). This, however, has a relative lack of sensitivity when detecting subtle cognitive impairments (Proust-Lima et al., 2007) and detailed differences in cognitive performance within a specific population.

Fourth, a series of sensitivity analyses confirmed our results. (1) A replication analyses using a counterfactual approach and bootstrapping for testing the causal routes (Supplementary Table S2), yielded similar results to our SEM approach, also when we stratified by age (age < 45, age ≥ 45. (2) This was also true when we used our model strategy (SEM) for the analysis of individuals aged 45 and older only, which gives even more plausibility to our results, because previous research suggested that cognitive decline starts from the mid-40s (Singh-Manoux et al., 2012). (3) Using time-weighted average concentrations over a minimum of ten years up to baseline (historical addresses of the participants' residence linked to concentrations estimated for 2010) did not change our results.

Despite the strengths of our study, there are some limitations. First, ambient air pollution concentrations at the residential address, especially those estimated by land use regression models, do not reflect the overall air pollution people are indeed exposed to in their living environments. People are also exposed to (potentially different) air pollution levels, which are relevant for brain health, during daily road travel or when they are indoor (Saenz et al., 2018). Second, we used the air pollution exposure data from the ELAPSE project, which seems to have better quality than previous data (de Hoogh, 2018). But, the data were only available for the year 2010 and these data from 2010 were linked to the participants' baseline address or address history, so that it is possible that these concentrations for 2010 are poor proxies for long-term/chronic exposure concentrations at home. We feel however, that our sensitivity model including a time-weighted average exposure assessment of at least ten years, supports the assumption that the 2010-exposure concentrations also reflect long-term chronic exposure. Third, we analysed only the levels of health and not the changes in health over time, which suggests generally more causal explanatory power. We, however, minimised the effect of this limitation by ensuring correct causal time order between cause (in the TWA sensitivity model), mediator and outcome. Furthermore, in the TWA sensitivity model we included only those participants for whom exposure data was available for at least ten years, and verified our results by performing causal mediation analyses with a potential outcome approach (see our first sensitivity analysis). Fourth, we were not able to account for genetic factors, e.g. the apolipoprotein-ε4 allele (APOE-ε4), which are known to be the most prevalent genetic risk factors for Alzheimer's disease (Miyata and Smith, 1996), and whose variants modify the association between air pollution and cognitive impairment resulting in a stronger air pollution effect for APOE risk variant carriers (Schikowski et al., 2015). Fifth, our models assumed a linear dose-response relationship between air pollution exposure and cognitive performance. In doing so, we followed previous studies in the field, which explored e.g. the dose-response relationship between $PM_{2.5}$ and daily deaths (Schwartz et al., 2002), $PM_{2.5}$ and daily respiratory deaths (Ren et al., 2017), prenatal exposure to $PM_{2.5}$ and development of brain white matter and cognition in later childhood (Peterson et al., 2015), which all identified a linear relationship. However, there is also evidence for the existence of non-linear relations between $PM_{2.5}$ and mortality due to respiratory disease (COPD, lung cancer, lower respiratory infection), especially for lower concentrations below 25 $\mu g/m^3$ (Cohen et al., 2017).

5. Conclusion

Our study provides new insights in the association between ambient exposure to fine particulate matter and brain health by disentangling underlying direct and indirect pathways over lung function. Our results emphasise the importance of the lung acting as a mediator in this relationship. Especially BC seems to impair the lung or activate inflammatory responses of immune cells residing in the lung, causing subsequent cognitive impairments. Thus, brain health seems to depend on, among others, a good lung function, and lung function in turn may benefit from low air pollution exposure. Fine particles as $PM_{2.5}$ seem to mainly follow the direct route, which calls for a special attention to fine particles due to their ability to reach vital organs directly. Future research is needed that explores, beside of the indirect lung function route found in our study, further pathways taken by inhaled air pollution to subsequently affect cognition.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111533.

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