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RESEARCH ARTICLE

The role of leukocytes in cognitive impairment due to long-term exposure to fine particulate matter: A large population-based mediation analysis

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Abstract

INTRODUCTION: Our understanding of how fine particulate matter ($PM_{2.5}$) impacts cognitive functioning is limited. Systemic inflammation processes may play a role in mediating this effect.

METHODS: This prospective cohort study used data from 66,254 participants aged 18+ between 2006 and 2015 from the Dutch Lifelines Cohort Study and Biobank. Causal mediation analysis was conducted to examine the impact of ambient $PM_{2.5}$ exposure on cognitive processing time (CPT), using the change in white blood cell (WBC) count and its subtypes as potential mediators.

RESULTS: Heightened $PM_{2.5}$ exposure was associated with slower CPT (total effect = 81.76×10^{-3}, 95% confidence interval [CI] 59.51×10^{-3}–105.31×10^{-3}). The effect was partially mediated via increased WBC count (indirect effect [IE] = 0.42×10^{-3}, 95% CI 0.07×10^{-3}–0.90×10^{-3}), particularly driven by an increase in monocytes (IE = 0.73×10^{-3}, 95% CI 0.24×10^{-3}–1.31×10^{-3}).

DISCUSSION: Systemic inflammation processes may partially explain the harmful effects of $PM_{2.5}$ on cognitive functioning, why lower levels of systemic inflammation may help contain its neurotoxic effects.

KEYWORDS
causal mediation analysis, cognitive functioning, fine particulate matter, leukocytes, systemic inflammation, white blood cell count

Highlights

- The pathways leading to the neurotoxic effects of fine particulate matter ($PM_{2.5}$) are poorly understood.
- We analyzed data from over 66,000 participants using causal pathway analysis.
- Increased white blood cell (WBC) count mediates the effect of $PM_{2.5}$ on cognitive functioning.

- Monocyte count played a crucial role in this low-pollution setting.
- Systemic inflammation may contribute to the neurotoxic effects of $PM_{2.5}$.

1 | BACKGROUND

Cognitive decline and neurodegenerative disorders represent a substantial and pressing global public health challenge. The prevalence of these diseases is projected to increase in the coming years[1] due to the aging population worldwide.[2] In 2017, neurological disorders were the third leading cause of both disability and premature mortality within the European Union.[3] Consequently, there is an urgent need to delve into the potential risks and preventive strategies associated with cognitive functioning to facilitate healthy aging and enable timely interventions.

Ambient fine particulate matter with diameters of 2.5 μm and smaller ($PM_{2.5}$) is among the world's leading environmental health risk factors[4] and contributes to the development of mild cognitive impairment[5] and neurodegenerative diseases, for example, dementia,[6,7] Alzheimer's disease (AD),[8] and Parkinson's disease.[9] An observational and longitudinal study conducted among older adults in Sweden revealed an inverted U-shaped relationship between $PM_{2.5}$ and cognitive decline.[10] The study identified an 81% increased risk of rapid cognitive decline per interquartile range difference, up to a mean $PM_{2.5}$ level of 8.6 $\mu g/m^3$, for individuals 80 years of age or older. A study in the United States combined observational data with experimental mouse models and found that exposure to the highest quartile of $PM_{2.5}$ (14.34–22.55 $\mu g/m^3$) was associated with an 81% increased risk of accelerated global cognitive decline and a 92% increased risk of incident dementia.[11] In vitro experiments conducted in the that study demonstrated that exposure to nanoparticles (nPMs), which are also components of $PM_{2.5}$, increased the pro-amyloidogenic processing of the amyloid precursor protein in neuroblastoma cells (N2a-APP/swe).[11]

However, comprehending the underlying mechanisms is crucial for the development of appropriate interventions to address cognitive impairment caused by $PM_{2.5}$, particularly about the future global aging population. Despite recent reductions in global $PM_{2.5}$ exposure, these improvements in $PM_{2.5}$ concentrations may not sufficiently alleviate the emergence of $PM_{2.5}$-related diseases, given the ongoing trends of population growth, aging,[12] and urbanization.[13]

Previous research has already explored some mediating pathways of $PM_{2.5}$ on cognitive functioning. These studies showed a significant mediating role of lung function,[14–16] depressive symptoms and hippocampal cytokine expression,[17] sleep quality,[18] alpha event-related desynchronization,[19] and deoxyribonucleic acid (DNA) methylation.[20]

Theory suggests that the pathway over inflammatory processes plays also a crucial role in the adverse effects of fine particles on people's brains.[21,22] A first hypothesis of this scholar is that $PM_{2.5}$ may take a direct route via the bloodstream (systemic route) or the olfactory nerve (olfactory route), crossing the blood–brain barrier and causing local inflammatory effects in the brain. A second hypothesis proposes that $PM_{2.5}$ may induce (chronic) systemic inflammation processes, which subsequently lead to impairments in the brain (peripheral inflammatory effects) in the medium- or longer run. (Figure 1)

In line with the second hypothesis, this prospective cohort study investigated the mediating role of changes in white blood cell (WBC) count as a systemic inflammatory marker—in the association between $PM_{2.5}$ and cognitive functioning. This was tested within a large general population cohort located in a low-pollution setting in the Northern Netherlands.

2 | METHODS

2.1 | Study population and design

We used longitudinal observational data (2006–2015) from the Dutch Lifelines Cohort Study and Biobank (from now on "Lifelines"). Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The study encompasses a diverse adult population 18 years of age or older. Approximately 10% of the population in the three provinces of the Northern Netherlands—a low-pollution setting—participated in the study, resulting in a cohort of 110,908 adults who underwent both baseline (2006–2012) and follow-up assessments (2014–2015). The data set includes information obtained through surveys, as well as data collected from blood samples and anthropometric measurements.[23] The Lifelines Cohort Study adheres to the principles outlined in the Declaration of Helsinki and has received approval from the medical ethical committee of the University Medical Center Groningen (UMCG), the Netherlands.

To enrich the Lifelines data, we integrated the participants' current and previous residential addresses, which were acquired from municipal administration records. The Lifelines data management team has already completed this task: The residential addresses were linked to ambient air pollution exposure data obtained from the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (further details provided below).

We included all participants 18 years of age or older who had available data on residential addresses at baseline, valid air pollution

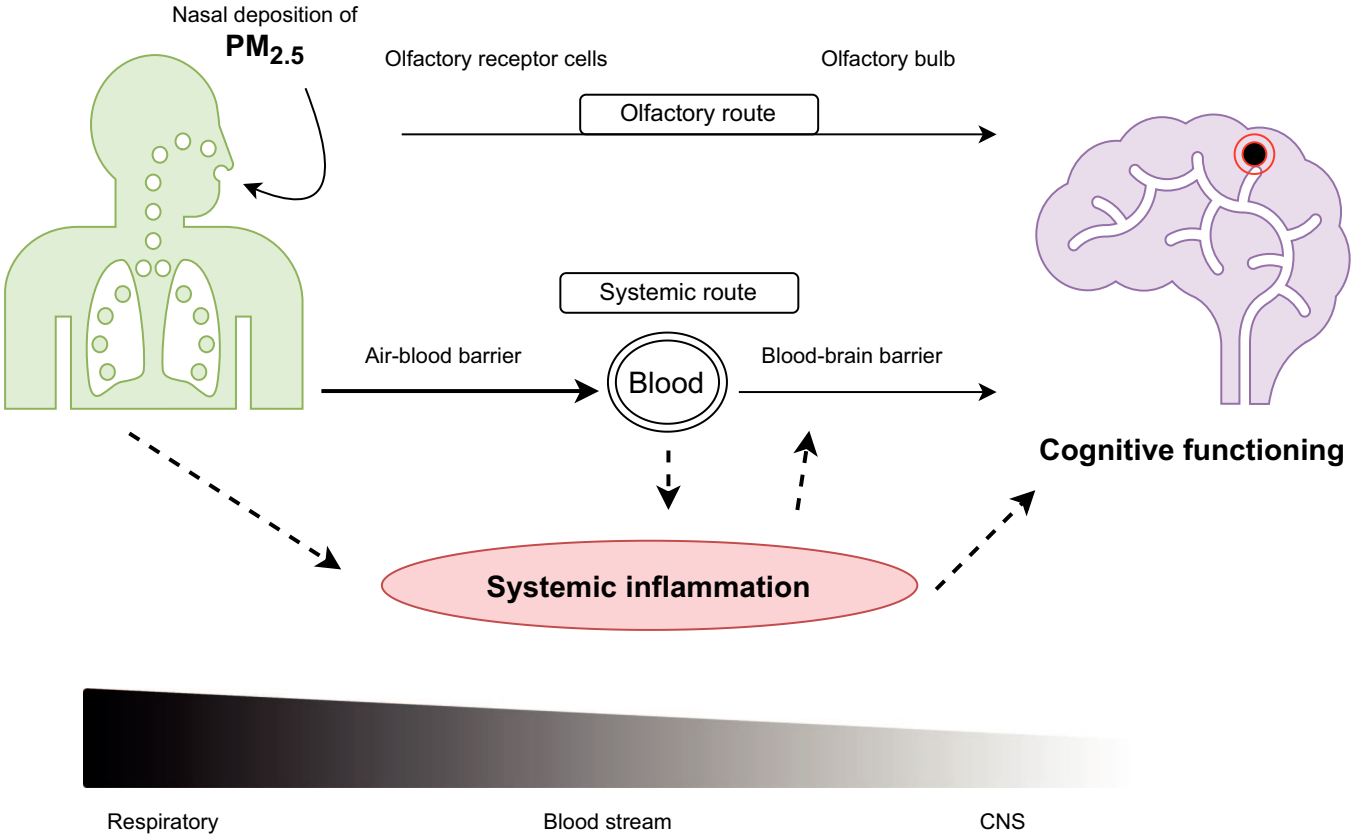

FIGURE 1 Hypothesized pathogenic pathways taken by fine particulate matter ($PM_{2.5}$) to cause cognitive impairment. $PM_{2.5}$, particulate matter with a diameter of 2.5 μm and smaller. Two main hypotheses exist regarding the underlying mechanisms of how inflammatory processes are involved in the pathogenic effects of $PM_{2.5}$ on the development of neurodegenerative diseases: The first hypothesis suggests that $PM_{2.5}$ may take a direct route via the bloodstream (systemic route) or the olfactory nerve (olfactory route), crossing the blood–brain barrier and causing local inflammatory effects in the brain. The second hypothesis proposes that $PM_{2.5}$ may induce (chronic) systemic inflammation, which subsequently leads to impairments in the brain (peripheral inflammatory effects).

exposure data, valid WBC measurements at baseline (2006–2012) and follow-up (2014–2015), and a valid cognitive functioning measurement at follow-up (2014–2015). The construction of the analysis population ($n = 66{,}254$) was illustrated in Figure S1.

In our study design, we addressed the issue of establishing a correct causal time order among the factors involved, namely the exposure to $PM_{2.5}$ (the assumed cause), the change in WBC count (the assumed mediator), and cognitive functioning (the assumed outcome). To accomplish this, we distinguished between three time periods. The first period encompassed the baseline phase (2006–2012), during which participants were recruited for the Lifelines cohort study, and measurements of $PM_{2.5}$ exposure at their residential addresses as well as WBC count (including their subtypes), were recorded. The second period comprised the follow-up phase (2014–2015), during which participants' WBC count and cognitive functioning were assessed once again. We utilized the change in WBC count between the baseline and follow-up assessments as the mediator of interest.

2.2 | Outcome assessment: Cognitive functioning measured by cognitive processing time (CPT)

The Cogstate Brief Battery (CBB), a validated and standardized computerized tool, was used to assess cognitive functioning during the follow-up period (2014–2015). CBB measures cognitive functioning in four domains: psychomotor speed (primary outcome measured by reaction time), visual attention (primary outcome measured by reaction time), visual learning (primary outcomes measured by reaction time and accuracy), and working memory (primary outcome measured by accuracy).[24] CBB has demonstrated good test–retest reliability[25] and validity.[26] In addition, it has been effective in detecting mild cognitive impairment[27] and dementia.[28,29] Previous research has shown that composite scores of the CBB have greater sensitivity in identifying cognitive impairment compared to individual CBB measures.[28,29]

In more detail, the CBB consists of four card tasks completed within an 11-minutes timeframe, each task focusing on one of the cognitive

RESEARCH IN CONTEXT

1. **Systematic review**: We conducted a thorough literature review using traditional sources, for example, PubMed and Web of Science, and meeting abstracts as well as presentations. Although the neurotoxic effects of fine particulate matter have not been studied extensively, experimental rodent research involving engineered nanoparticles suggests that the translocation of (ultra)fine particles into the bloodstream may be a critical mechanism.
2. **Interpretation**: Our study, based on a large cohort in the Netherlands with relatively low pollution levels, supports the hypothesis derived from experimental studies. Specifically, we found that leukocytes, serving as markers for systemic inflammation, particularly the monocyte count, are involved in the neurotoxic effects of fine particulate matter.
3. **Future directions**: This study provides novel insights into the neurotoxic effects of fine particulate matter within the general population, enhancing the external validity of previous experimental findings. Future research should explore additional systemic inflammation markers to further elucidate the mechanisms underlying these effects.

domains: detection (2 min), identification (2 min), visual learning and memory (5 min), and working memory (2 min). The tasks are accompanied by textual instructions, and participants are required to solve various exercises related to speed or accuracy by selecting the "Yes" or "No" buttons on the screen.[24] To participate, individuals should have the ability to operate a computer keyboard or mouse with one hand and have clear visibility of the computer screen.

In Lifelines, the CBB was administered systematically, with participants completing the battery under supervision during their visit to the Lifelines location. Participants were required to use a computer keyboard or mouse with one hand and to have normal vision to see the computer screen. The speed measures in each domain represent the mean time taken to provide correct responses and were log (10)-transformed to improve normality. Subsequently, we z-standardized each speed measure using age-specific normative data, which were already validated previously for the CBB.

The normative data were obtained from Cogstate Limited, which is the organization responsible for developing the CBB, and covers age groups ranging from 18–34, 35–49, 50–59, 60–69, 70–79, 80–89, and 90–99.[30] The normative sample used for standardization represents data from a healthy adult population enrolled in clinical trials and research studies across various regions, including North and South America, Europe, Asia, and Australia. Some studies incorporated single assessments, whereas others employed longitudinal research designs involving practice, baseline, and follow-up assessments. Age bins for the 18- to 34 and 35- to 49-year groups were larger as Cogstate data revealed no age effect within this range, which is consistent with large internal and external normative data sets.[30] Gender differences on the Cogstate battery are minimal,[31] and cross-cultural equivalence has been demonstrated elsewhere.[26,32]

After standardization, we calculated a composite score representing overall CPT by summing the speed scores from the three tasks. Positive scores indicate higher CPT (i.e., longer reaction time and thus slower speed) and poorer cognitive functioning compared to the norms, whereas negative scores indicate lower CPT (i.e., faster reaction time and thus quicker speed) and better cognitive functioning. To account for response accuracy, we adjusted for the total response accuracy, which was measured by the total number of trials per participant in all of the three included CBB domains.

Previous clinical practice has shown that cognitive processing speed, defined as the ability to rapidly process information, is closely associated with solving complex cognitive tasks,[33] making it one of the crucial domains of cognitive functioning.[34] Based on previous research and in consultation with the Cogstate Research Team, we created a speed composite score using the speed measures from the detection, identification, and working memory tasks as primary outcomes.

2.3 | Exposure assessment: Long-term exposure to $PM_{2.5}$

We used data on ambient long-term exposure to particulate matter with diameters of 2.5 μm and smaller ($PM_{2.5}$) in a spatial resolution of 100 × 100 meters, and it was representative of the year 2010. The data were obtained from the project "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) (see Ref. 35 for a detailed description).

For ELAPSE, air pollution monitoring data were obtained from the study "European Study of Cohorts for Air Pollution Effects" (ESCAPE) and the AirBase database by the European Environmental Agency. The ESCAPE study provided annual mean concentrations for 2009 see Ref. 35 2010, covering 436 sites for $PM_{2.5}$ across 20 study areas. Designed to explore the link between long-term air pollution exposure and health, the ESCAPE campaign used land use regression (LUR) and conducted measurements in cohort study areas. Over 1 year (2009 or 2010), three 2-week measurement campaigns per study area were conducted for $PM_{2.5}$ using Harvard Impactors and Ogawa badges. Seasonal variations were accounted for with monitoring periods in winter, summer, and autumn or spring. Reference monitors operated year-round to adjust annual mean concentrations. AirBase v8 provided additional 2010 annual mean data from 549 $PM_{2.5}$ sites and 2400 NO_2 sites.

ELAPSE developed then Europe-wide hybrid LUR models, which regarded satellite observations, dispersion model estimates, land use, traffic variables, industrial point sources, and the ESCAPE air pollution monitoring data for the year 2010. For that purpose, two algorithms were applied: Supervised linear regression (SLR) and random forests. Pollution surfaces (100 m × 100 m grids) from both algorithms were assigned to the baseline residential address of each of the Lifelines

participants. The models predicted a substantial portion of the observed concentration fluctuation across different components at the European level, with the range spanning from 41% to 91%.[35] For $PM_{2.5}$ concentrations, the model accounted for 62% of the variance across all included sites. In addition, spatiotemporal stability tests yielded favorable results. At the country level, the agreement between $PM_{2.5}$ levels estimated using the 2010 model and those estimated using the 2013 model was 70.1% for the Netherlands. Furthermore, the comparison of measured average concentrations from the AirBase stations demonstrated a 68.3% agreement over the period from 2010 to 2013 for the Netherlands.

Lifelines has allocated the estimated $PM_{2.5}$ concentrations to the participants' home addresses to the baseline (2006–2012) assessment.

2.4 | Mediator assessment: Change in WBC (subtype) count

The indirect route proposed in our study suggests that higher exposure to $PM_{2.5}$ is associated with an increase in systemic inflammation markers resulting subsequently in impaired cognitive functioning. We used the WBC count as an inflammation marker representing the indirect systemic inflammation route. Previous research has consistently demonstrated that elevated or increased WBC count serves as one important indicator of systemic inflammation.[37–40] We used the individual change in WBC between baseline and follow-up as a systemic inflammation marker because WBC levels can vary significantly between individuals.

In Lifelines, trained medical staff collected blood samples from the participants. These blood samples were then analyzed in the laboratory medicine department of the UMCG using Sysmex analytic systems. The assessments took place at the UMCG laboratory center, which is certified by NEN-EN-ISO 9001:2008 and NEN-EN-ISO 15189:2012 standards. WBC (subtype) counts, including basophilic granulocytes, lymphocytes, monocytes, and neutrophilic granulocytes, in ethylenediaminetetraacetic acid (EDTA) blood samples were determined in cells/microliter of blood at both baseline (2006–2012) and follow-up (2014–2015) and used in this study. We calculated the change in WBC count by subtracting the follow-up assessment from the baseline assessment per participant. Higher values denote an increase in WBC (subtype) count, whereas lower values show a decrease. We included only participants with a normal WBC count, ranging from 4,000 to 10,000 cells/μL, to exclude potential confounding by undiagnosed chronic or acute conditions that could result in abnormally low (e.g., rheumatoid arthritis) or high (e.g., leukemia) WBC counts.

2.5 | Assessment of confounding variables

We adjusted both the mediator and outcome for socio-demographic, lifestyle, and morbidity variables at baseline and follow-up. Education level was categorized based on the highest completed level of education, ranging from none to university level. Vigorous physical activity was assessed using the validated Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) and classified into low, moderate, and high categories. Pack-years of cigarette smoking were calculated from participants' smoking history and categorized as never smokers (0 pack-years), lower 50th percentile of smokers (up to 8.95 pack-years), and upper 50th percentile of smokers (more than 8.95 pack-years). We controlled for the use of medications that could affect WBC count, specifically glucocorticoids or chemotherapeutics, based on baseline Anatomical Therapeutic Chemical (ATC) codes (see Supplementary Information for more details).

The following confounding variables were controlled for as time-varying characteristics: body mass index (BMI) was computed as an individual's weight divided by the square of their height and categorized as underweight (BMI less than 18.5), normal weight (BMI 18.5 to <25), overweight (BMI equal or greater than 25 and less than 30), and obese (BMI equal to or higher than 30). Hypertension was defined as a systolic pressure higher than 139 mmHg or a diastolic pressure higher than 89 mmHg, both measured by medical professionals. The prevalence of diabetes (type 1 or 2) and stroke was determined based on self-reported doctor diagnoses.

2.6 | Statistical analysis

This study examined the mediating role of WBC in the effects of long-term ambient exposure to $PM_{2.5}$ on cognitive functioning. For that purpose, a causal mediation analysis was conducted, which is a newer approach to mediation analysis simulating an experimental design by applying a counterfactual framework.[41]

In short, this mediation analysis relies on the potential outcomes framework (or counterfactual framework). The framework defines causal effects by comparing the potential outcomes that would occur under different treatment conditions. For mediation analysis, it involves assessing potential outcomes for both the mediator and the outcome variable under varying treatment levels. To obtain confidence intervals (CIs) and *p*-values for the estimated effects, bootstrapping was employed.

Causal effects are defined as the disparity between counterfactual outcomes. A counterfactual outcome refers to the hypothetical outcome value of an individual under a specific exposure condition.[42]

We adopted the annotation from Imai et al.[43] in the following. $M_i(t)$ denotes the potential value of a mediator for a unit i under the treatment status $T_i = t$ ($t = 1, 2, 3, 4, \ldots, n$). $Y_i(t, m)$ denotes the potential outcome resulting if the treatment and mediating variables are equal to t and m. The observed outcome, Y_i, can be written as $Y_i(T_i, M_i(T_i))$, where $M_i(T_i)$ is the observed value of the mediator $M_i = m$ ($m = 1, 2, 3, 4, \ldots, k$). Accordingly, the total effect can be written as

$$\tau_i \equiv Y_i\left(n_{\max}, M_i\left(k_{\max}\right)\right) - Y_i\left(n_{\min}, M_i\left(k_{\min}\right)\right). \quad (1)$$

This total effect (TE) can be then decomposed into the average causal mediation effects, which are the indirect effects (IEs), and the

average direct effects (DEs). The IEs can be expressed as

$$\delta_i(t) \equiv Y_i(t,\ M_i(k_{\max})) - Y_i(t,\ M_i(k_{\min}))\,. \quad (2)$$

All other (unobserved) causal mechanisms, either direct or indirect, are summarized in the average DEs of the treatment

$$\zeta_i(t) \equiv Y_i(n_{\max},\ M_i(t)) - Y_i(n_{\min},\ M_i(t))\,. \quad (3)$$

To apply causal mediation analysis, we used the *mediation* package in R incorporating the statistical approach described above.[44] The significance threshold was set at 0.05, and all tests were conducted using a two-sided approach. The mediator and outcome variables were checked for normal distribution (Figure S2). The analyses were conducted on R 4.1.1.[45]

3 | RESULTS

3.1 | Characteristics of the study participants

Of the 66,254 participants, 37,561 (56.69%) exhibited faster CPT, whereas 28,693 (43.31%) demonstrated slower CPT compared to the mean at the follow-up in 2014–2015 (Table 1). The average exposure to $PM_{2.5}$ was 14.84 μg/m^3, ranging from a minimum of 7.95 to a maximum of 21.83 μg/m^3 (Figure 2). As for the WBC count, the mean number of cells per microliter of blood was 6016.68 at baseline and 6109.87 at follow-up, representing an overall increase of 1.55% in the study population (Table 1, Figure 2).

In terms of the WBC subtypes, the average number of monocytes increased by 4.34%, neutrophils by 1.12%, and basophils by 51.32%, whereas the number of lymphocytes experienced a slight decrease of 0.59%. 30,777 (46.45%) of the participants reported no pack-years of cigarettes smoked, indicating that they were non-smokers, whereas the smokers had an average of 11.19 pack-years. At baseline, the BMI indicated that 445 individuals (0.67%) were underweight (BMI <18.5), 26,366 (39.80%) were overweight (25 < BMI < 30), and 9650 (14.57%) were obese (BMI ≥30). The majority of participants (39,879, 60.19%) reported engaging in low or moderate levels of vigorous physical activity. In addition, 17.34% of the participants had been diagnosed with prevalent hypertension by a doctor at baseline, 1.93% had diabetes, and 0.54% had experienced a stroke before the baseline assessment. The age of the participants at baseline ranged from 19 to 91 years, with an average age of 48.66 years.

3.2 | Association between $PM_{2.5}$ exposure and cognitive functioning

First, we calculated the TE, demonstrating the overall association between long-term exposure to $PM_{2.5}$ at baseline (2006–2012) and cognitive functioning at follow-up (2014–2015). Our analysis revealed that heightened exposure to $PM_{2.5}$ was significantly linked to a slower CPT and consequently poorer cognitive functioning (TE = 81.76×10^{-3}, 95% CI: 59.51×10^{-3}, 105.31×10^{-3}) (Figure 3). An increase in $PM_{2.5}$ exposure of one μg/m^3 is accordingly related to an increase in CPT of 3.81 ms (recalculation as follows: $10^{0.08176} \times 3.15$ [SD)] = 3.81).

3.3 | The mediating role of leukocytes and their subtypes

Second, we proceeded with a decomposition of the TEs into DEs and IEs. The DEs pertain to the direct pathways of $PM_{2.5}$, either through the olfactory nerve or the bloodstream, but also cover unobserved and uncontrolled other mediators, for example, lung function [14]. Notably, the DEs of $PM_{2.5}$ on cognitive functioning remained significant even after accounting for the indirect pathway via changes in WBC count (DE = 81.34×10^{-3}, 95% CI: 59.05×10^{-3}, 104.71×10^{-3}) (Figure 3).

The IEs signify the indirect systemic pathway of $PM_{2.5}$, which could result in heightened systemic inflammation, ultimately contributing to poorer cognitive functioning. Interestingly, we observed substantial mediation through changes in WBC count (IE = 0.42×10^{-3}, 95% CI: 0.07×10^{-3}, 0.90×10^{-3}) (Figure 3). More specifically, elevated $PM_{2.5}$ exposure was linked to an increase in WBC count, subsequently associated with a decline in CPT, indicating poorer cognitive functioning. We estimated a sensitivity model by excluding extreme values in CPT to check the robustness of our results. For this purpose, the highest and lowest 5% of CPT values were removed. This model confirmed the findings of our main model (Table S1). In addition, we checked the robustness of the mediation analysis by performing a sensitivity model using structural equation modeling (SEM). This model also confirmed the results from the main model (Table S2). To identify vulnerable subpopulations, we performed a set of models stratified by gender and age groups. These models revealed that men and participants 40 years of age or older were particularly vulnerable to the mediating effect of $PM_{2.5}$ on cognitive functioning via WBC count (Table S3).

Furthermore, the analysis of WBC subtypes revealed that an increase in monocytes significantly mediated the effect of $PM_{2.5}$ on CPT (Figure 4). However, the other WBC subtypes (basophils, lymphocytes, neutrophils) did not exhibit any significant mediation effects.

3.4 | The influence of the confounders on cognitive functioning and change in WBC count

As expected, higher age at follow-up was correlated with worse cognitive functioning (19.05×10^{-3}, 95% CI: 16.69×10^{-3} to 21.40×10^{-3}), and higher educated people with a degree from a university had better cognitive functioning (-1982.82×10^{-3}, 95% CI: -2193.40×10^{-3} to -1772.24×10^{-3}) than participants without any educational level (Table S4). Prevalent (baseline) hypertension (72.84×10^{-3}, 95% CI: 4.57×10^{-3} to 141.10×10^{-3}), diabetes (206.83×10^{-3}, 95% CI: 26.67×10^{-3} to 387.00×10^{-3}), as well as a stroke up to follow-up

TABLE 1 Descriptive statistics of the study participants ($n = 66,254$) at baseline (2006–2012) and at follow-up (2014–2015) based on the Dutch Lifelines Cohort Study and Biobank.

Characteristic	Baseline (2006–2012)	Follow-up (2014–2015)
Sex, no. (%)		
Women	38,734 (58.46)	
Men	27,520 (41.54)	
Age, mean (SD)	48.66 (12.00)	
Educational level, no. (%)		
No/primary education	966 (1.46)	
Lower or preparatory vocation	7225 (10.91)	
Junior general secondary education	8737 (13.19)	
Secondary vocational education	20,249 (30.56)	
Senior general secondary education	6052 (9.13)	
Higher vocational education	16,972 (25.62)	
University education	4305 (6.50)	
Other	1141 (1.72)	
Missing information	607 (0.92)	
Migration status		
Native Dutch (birthplace Netherlands)	64,224 (96.93)	
Migrants (birthplace abroad)	1549 (2.34)	
Missing information	481 (0.73)	
Pack-years of cigarettes smoked, no. (%)		
Never smokers	30,777 (46.45)	
Lower/equal to the 50th percentile of ever smokers	17,039 (25.72)	
Higher than the 50th percentile of ever smokers	15,429 (23.29)	
Missing information	3009 (4.54)	
Doing vigorous physical activity		
Lower level of vigorous activity	34,123 (51.50)	
Moderate level of vigorous activity	5756 (8.69)	
Higher level of vigorous activity	20,899 (31.54)	
Missing information	5476 (8.27)	
BMI, no. (%)		
Lower than 18.5	445 (0.67)	441 (0.67)
18.5 to lower than 25	39,793 (44.97)	28,876 (43.58)
25 to lower than 30	26,366 (39.80)	26,515 (40.02)
Higher/equal to 30	9650 (14.57)	10,422 (15.73)
Hypertension, no. (%)		
Yes	11,489 (17.34)	15,303 (23.10)
No	54,709 (82.57)	50,951 (76.90)
Missing information	56 (0.08)	0 (0.00)
Diabetes, no. (%)		
Yes	1282 (1.93)	2323 (3.51)
No	63,856 (96.38)	62,916 (94.96)
Missing information	1116 (1.68)	15 (0.02)

(Continues)

TABLE 1 (Continued)

Characteristic	Baseline (2006–2012)	Follow-up (2014–2015)
Stroke, no. (%)		
Yes	356 (0.54)	343 (0.52)
No	64,564 (97.99)	65,583 (98.99)
Missing information	1334 (2.01)	328 (0.50)
Medication intake		
Glucocorticoids		
No	34,078 (51.43)	
Yes	254 (0.38)	
Missing information	31,922 (60.26)	
Chemotherapeutics		
No	34,229 (51.66)	
Yes	103 (0.16)	
Missing information	39,922 (60.26)	
Long-term exposure to ambient $PM_{2.5}$ (in $\mu g/m^3$), year 2010	14.84 (0.99)	
Number of leukocytes (SD)	6016.68 (1,263.23)	6109.87 (1275.32)
Number of lymphocytes (SD)	2025.00 (541.36)	2012.96 (556.11)
Number of monocytes (SD)	481,07 (137.06)	501.97 (136.21)
Number of neutrophils (SD)	3277.82 (966.76)	3314.37 (970.51)
Number of basophils (SD)	31.55 (18.71)	47.74 (21.03)
Number of total CBB trials, mean (SD)		140.26 (24.65)
CPT, standardized with normative data, log10-transformed milliseconds, mean (SD)		1.17 (3.15)
Faster CPT (lower values) than the mean, no. (%)		37,561 (56.69)
Slower CPT (higher values) than the mean, no. (%)		28,693 (43.31)

Note: Pack-years of cigarettes smoked were calculated from the baseline questionnaire (1 pack-year = 20 cigarettes per day in 1 year). Hypertension was defined when systolic pressure was higher than 139 mmHg or diastolic pressure was higher than 89 mmHg (blood pressure was measured by medical staff). The prevalence of diseases at baseline was assessed by questions, whether a specific disease was diagnosed by a doctor or not. Long-term air pollution concentrations were assessed as 1-year annual mean concentrations at participants' baseline addresses and were estimated for the year 2010 by the ELAPSE models/project. The 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. 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.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CBB, Cogstate Brief Battery; CPT, cognitive processing time; $PM_{2.5}$, (fine) particulates with diameters of 2.5 µm and smaller.

(595.00×10^{-3}, 95% CI: 237.50 to 952.50), was related to poor cognition. Men (-267.13×10^{-3}, 95% CI: -316.64×10^{-3} to -217.63×10^{-3})] fared better than women and migrants worse (1248.84×10^{-3}, 95% CI: 1098.06×10^{-3} to 1399.63×10^{-3}) than native Dutch. A moderate (-154.89×10^{-3}, 95% CI: -238.86×10^{-3} to -70.93×10^{-3}) or high (-231.47×10^{-3}, 95% CI: -284.82×10^{-3} to -178.11×10^{-3}) level of vigorous activity was related to better cognitive functioning when compared to participants doing low levels of vigorous activity.

Higher long-term exposure to $PM_{2.5}$ was associated with an increase in WBC count between baseline and follow-up (9.49, 95% CI: 1.73 to 17.24) (Table S5). Participants with prevalent hypertension (25.11, 95% CI: 2.06 to 48.16) and diabetes (71.79, 95% CI: 10.95 to 132.62) at baseline showed an increase in WBC count. Furthermore, detrimental lifestyle factors were relevant: Smoking more than average (109.41, 95% CI: 88.78 to 130.03) and being overweight (211.34, 95% CI: 99.77 to 322.91) or obese (435.77, 95% CI: 320.35 to 551.20) at follow-up was associated with an increase in WBC count. A moderate (−42.04, 95% CI: −70.39 to −13.69) or higher (−58.73, −76.74 to −40.72) level of vigorous activity and higher age were associated with a decrease in WBC count (−4.03, 95% CI: −4.81 to −3.26). WBC counts of participants with higher (−68.46, 95% CI: −134.27 to −2.64) or university (−78.28, 95% CI: −149.31 to −7.25) education decreased compared to those without a degree. Higher WBC count at baseline was related to a decrease in WBC count between baseline and follow-up (−0.41, 95% CI: −0.42 to −0.40).

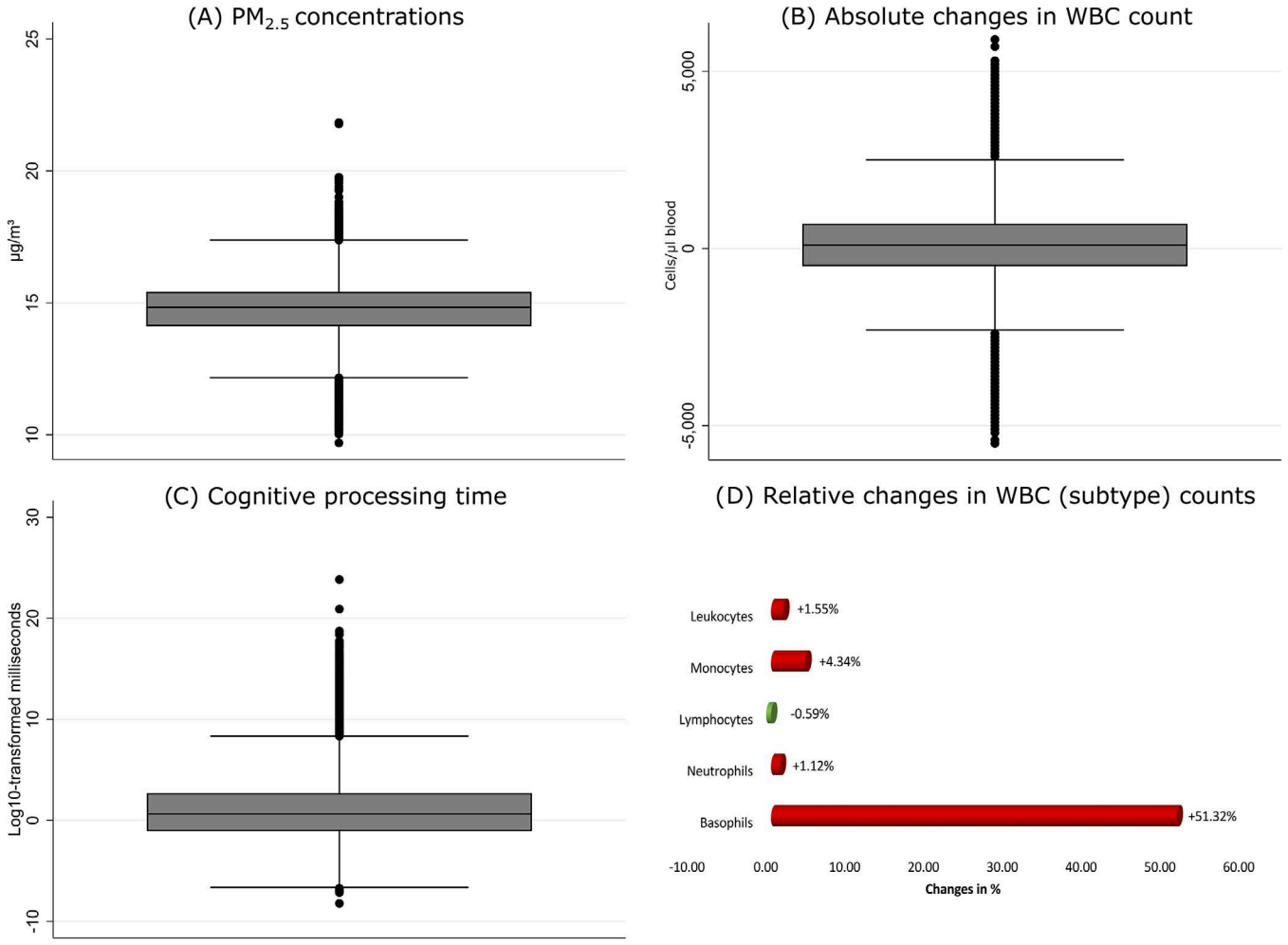

FIGURE 2 Distribution of long-term exposure to $PM_{2.5}$ at baseline (2006–2012), changes in WBC count between baseline and follow-up, and CPT at follow-up (2014–2015) in the Lifelines Cohort and Biobank. CPT, cognitive processing time; $PM_{2.5}$, particulate matter with a diameter of 2.5 µm and smaller; WBC, white blood cell (count). The table shows the decompositions of the total effects of the associations between long-term exposure to fine PM (in $\mu g/m^3$) and CPT, which is the log10-transformed total reaction time, measured by the Cogstate Brief Battery. The DE and the IE routes over the change in WBC count (= potential mediator) were modeled simultaneously by performing causal pathway analysis. Illustrated were the point estimators and confidence intervals. The models were controlled for sex, age, educational level, migration status, pack-years of cigarettes smoked, physical activity, BMI, hypertension, diabetes, stroke, medication intake, baseline number of leukocytes, and the number of total CBB trials. BMI, body mass index; CBB, Cogstate Brief Battery; CPT, cognitive processing time; DE, direct effect; IE, indirect effect; PM, particulate matter; WBC, white blood cell.

4 | DISCUSSION

4.1 | Key findings

This prospective cohort study identified a significant association between higher $PM_{2.5}$ exposure and a slower CPT, signaling diminished cognitive functioning in the Lifelines Cohort and Biobank — a low-pollution setting in the Netherlands. In addition, the study revealed a substantial mediation effect through changes in the WBC count, and the WBC subtype analysis showed that this was driven specifically by an increase in monocytes. In contrast, the other WBC subtypes did not demonstrate significant mediation effects. The findings suggest that an indirect pathway of $PM_{2.5}$ via systemic inflammation processes partially explains the detrimental cognition effects of $PM_{2.5}$. However, a direct association between $PM_{2.5}$ and cognitive functioning persisted even after accounting for WBC count — this remaining direct effect may involve other uncontrolled mediators as well.

4.2 | Discussion of the findings

The observed DEs or IEs of $PM_{2.5}$ suggest that several mechanisms may account for cognitive impairment. First, $PM_{2.5}$ may reach the brain either through a nasal-olfactory or hematological route and negatively affect neuronal processes being important for cognitive functioning in a cell-autonomous manner.[46] Likewise, non-cell autonomous effects of

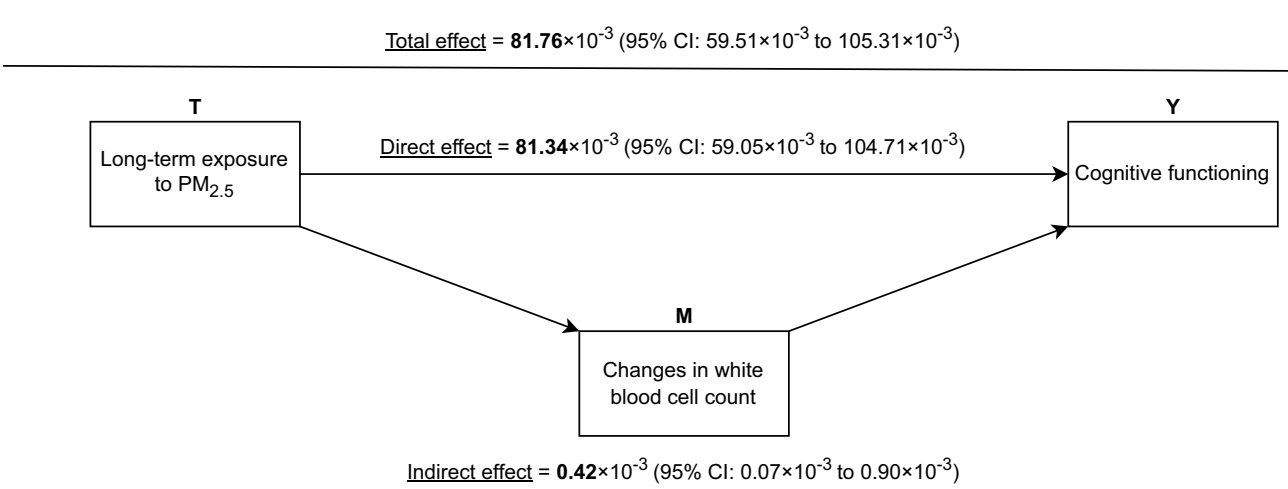

FIGURE 3 Mediation analysis and decomposition of the total effect: Long-term exposure to ambient $PM_{2.5}$, changes in the number of leukocytes, and cognitive functioning. PM2.5, particulate matter with a diameter of 2.5 µm and smaller. The figure shows the total effect and the decomposition of the total effect. The direct (DE) and the indirect (IE) routes over the change in WBC count (= potential mediator) were modeled by performing causal pathway analysis. Illustrated were the point estimators and confidence intervals. The model was controlled for sex, age, educational level, migration status, pack-years of cigarettes smoked, physical activity, BMI, hypertension, diabetes, stroke, medication intake, baseline number of leukocytes, and the number of total CBB trials. BMI, body mass index; CBB, Cogstate Brief Battery; DE, direct effect; IE, indirect effect; WBC, white blood cell.

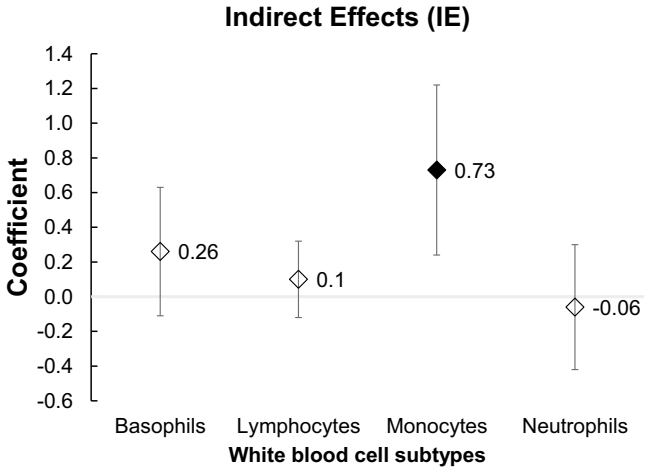

FIGURE 4 The mediating role of WBC subtypes in the association between long-term exposure to $PM_{2.5}$ and cognitive functioning. $PM_{2.5}$, particulate matter with a diameter of 2.5 µm and smaller. The figure shows the total effect and the decomposition of the total effect. The DE and the IE routes over the change in the WBC (subtype) count (= potential mediator) were modeled by performing causal pathway analysis. Illustrated were the point estimators and confidence intervals. The model was controlled for sex, age, educational level, migration status, pack-years of cigarettes smoked, physical activity, BMI, hypertension, diabetes, stroke, medication intake, baseline number of leukocytes, and the number of total CBB trials. BMI, body mass index; CBB, Cogstate Brief Battery; DE, direct effect; IE, indirect effect; WBC, white blood cell.

$PM_{2.5}$ compromising physiological functions of micro- and astroglial cells, which safeguard neuronal homeostasis and integrity, may contribute to the detrimental effect of $PM_{2.5}$. In such cases, the elevated WBC count could arise from immune stimulation in the periphery and represent a bystander effect without direct influence on cognition. In the periphery, however, any chronic inflammatory event, that causes monocyte counts to rise in the blood, could affect peripheral organ function including but not restricted to cardiac output, pulmonary blood oxygenation, or clearance mechanisms of the liver and the kidney, all of which alone or in concert can affect cognition, depending on the degree of impairment.[47]

Second, the mediation effect through changes in the WBC count found in this study could also indicate that peripheral inflammatory mechanisms affect brain function and thereby cognition. Exposure to $PM_{2.5}$ can cause low-grade systemic inflammation and an increase in WBC counts. Chronic inflammation, over time, may compromise the integrity of the blood-brain barrier (BBB), allowing brain-derived substances, including mediators that arise in response to cellular senescence or an innate immune reaction due to ongoing neurodegeneration, to be released. These mediators, generated by microglia or border macrophages and including but not limited to cytokines and chemokines, can further stimulate WBC counts. However, in the absence of additional clinical, biomarker, and imaging data, this remains hypothetical. Without degenerative changes in the brain or other factors impairing BBB function from either the luminal or parenchymal side, the elevated WBC count may solely reflect the immune response to $PM_{2.5}$. Systemic inflammation arising from non-sterile or sterile activation of immune processes and mediated through immune mediator release have been shown to affect neurocognitive functions in a variety of conditions including sepsis, burns, trauma, and autoimmune disease.[47–49] Although the precise mechanisms underlying such effects remain unclear to date, spillover of peripherally generated immune factors including cytokines, chemokines, complement factors, as well and free radical oxygens have been described, even more so as systemic inflammation can compromise the BBB. Spillover of immune

mediators or infiltration of the brain by monocytes may exert detrimental effects on neurons directly, for example, through negative regulation of synaptic plasticity or axonal transport. In addition, in both scenarios, either spilled-over immune mediators or infiltrating immune cells can stimulate local immune cells such as border macrophages, microglia, or astrocytes directly and thereby sustain a damaging inflammatory environment.[50,51] Although this is highly speculative and the current study does not allow for further mechanistic conclusions, the above-described pathophysiological machinery has been largely proven in experimental models of systemic inflammation and thus can be used for generating further mechanistic hypotheses that may be tested in future studies. Our additional analyses of long-term exposure to nitrogen dioxide (NO_2) and ozone (O_3) suggest that the pathways proposed for the impact of $PM_{2.5}$ on cognitive functioning do not apply to these other air pollutants (Table S6).

Previous research has shown that higher levels of systemic inflammatory markers in midlife are independently linked to lower regional brain volumes and reduced episodic memory 24 years later in older adults without dementia. Individuals with more elevated inflammatory markers during midlife also exhibited similar declines in brain volume and memory in a dose–response manner. The impact of increased midlife inflammation on several brain regions, including the hippocampus, was comparable to the effect of having one apolipoprotein E (*APOE*) ε4 allele in later life.[52] Our subgroup analysis conducted for stratified age groups supports the hypothesis that systemic inflammation by long-term exposure to $PM_{2.5}$ plays a more significant role in the second half of life than in the first (Table S3).

Our findings have significant implications for research in Alzheimer's disease (AD) and dementia.

First, lower CPT with respect to dementia or AD generally refers to the slowing of mental functions, that are often observed in individuals with various types of dementia.[53,54] This slowing is a hallmark of cognitive decline and is particularly relevant in the diagnosis and progression of dementia, including AD, vascular dementia, and other related disorders.[55] In AD, as the brain's neurons degenerate due to the accumulation of amyloid plaques and neurofibrillary tangles, cognitive processes slow down, leading to noticeable changes in behavior and cognitive abilities.[56]

Second, although high WBC counts could be indicative of systemic inflammation, which is a risk factor for AD, and increased CPT could suggest early cognitive decline, these factors do not directly imply that an individual is near an AD diagnosis. Instead, they may warrant closer monitoring and additional testing, especially if other symptoms or risk factors are present, for example, age, genetic predisposition (e.g., *APOE* ε4 allele), and additional cognitive symptoms.[57–59]

Third, this study was conducted in a low-pollution area in the Netherlands, which suggests that the associations may be even more relevant in regions with higher pollution levels in Europe. A previous study conducted in the United States found a strong linear relationship between annual mean $PM_{2.5}$ concentrations below 16 μg/m^3 and the risk of both Parkinson's disease and AD, followed by a plateau in the association. For $PM_{2.5}$ concentrations exceeding 25 μg/m^3, the data showed a trend of increased risk for these diseases.[60] This was confirmed by an experimental study on short-term $PM_{2.5}$ exposure and cognitive functioning. Elevated short-term exposure to $PM_{2.5}$ in the 3-day-lagged window was associated significantly with worse executive functioning. The exposure–response curves were almost linear and attenuated at high concentrations and demonstrated no sign of threshold.[19]

4.3 | Strengths and limitations

The study presents several notable strengths. First, it employs a novel approach, utilizing causal mediation analysis to dissect the pathways through which air pollutants impact cognitive function. Second, it introduces a comprehensive measure, CPT, standardized with normative data and developed in collaboration with the Cogstate Research Team, offering a nuanced evaluation of cognitive performance. Third, the study employs nonparametric modeling techniques to extract realistic dose–response relationships and delves into the role of different leukocyte subtypes, providing fresh insights into inflammation dynamics. Fourth, the robustness of the findings is verified through a series of sensitivity analyses (excluding extreme values in CPT, performing an SEM model, and subgroup analyses), confirming the reliability of the results (Tables S1–S3). We checked additionally if the characteristics of the entire Lifelines population was different from the used study population. However, there were only subtle differences in the age and education structure as well as the WBC count between both populations (Table S7). Finally, the research highlights the specific relevance of the systemic inflammation pathway among midlife participants, adding significant context to the findings.

However, the study has acknowledged limitations. The reliance on 2010 data for exposure assessments raises concerns about representing long-term exposure accurately. The study's focus on cognitive functioning levels without considering changes over time is also noted, although the established causal time order mitigates this limitation to some extent. Furthermore, the study did not account for genetic factors, like the *APOE* ε4 allele, which may influence the association between air pollution and cognitive impairment.

Finally, the study's observational nature restricts it from establishing causality conclusively, emphasizing the need for further experimental research incorporating additional inflammatory markers and air pollutants to expand the understanding of the inflammatory pathway in this context.

5 | CONCLUSION

The study emphasizes the role of systemic inflammation as a pathogenic pathway that links exposure to $PM_{2.5}$ with brain health in the general population, even in a low-pollution setting. The increase in WBC count, particularly in monocytes, triggered by $PM_{2.5}$, may contribute to the development of cognitive impairment and the development of neurodegenerative diseases. Public health surveillance and physicians should regard systemic inflammatory markers as an

important intermediate predictor for cognitive impairment, especially in regions exposed to higher concentrations of $PM_{2.5}$.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no current or potential competing financial interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All Lifelines participants have signed an informed consent (IC) form.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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