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Particulate matter exposure from motorized traffic and risk of conversion from mild cognitive impairment to dementia: An Italian prospective cohort study

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ABSTRACT

Background: Based on epidemiologic and laboratory studies, exposure to air pollutants has been linked to many adverse health effects including a higher risk of dementia. In this study, we aimed to evaluate the effect of long-term exposure to outdoor air pollution on risk of conversion to dementia in a cohort of subjects with mild cognitive impairment (MCI).

Methods: We recruited 53 Italian subjects newly-diagnosed with MCI. Within a geographical information system, we assessed recent outdoor air pollutant exposure, by modeling air levels of particulate matter with equivalent aerodynamic diameter ≤10 μm (PM_{10}) from motorized traffic at participants' residence. We investigated the relation of PM_{10} concentrations to subsequent conversion from MCI to any type of dementia. Using a Cox-proportional hazards model combined with a restricted cubic spline model, we computed the hazard ratio (HR) of dementia with its 95% confidence interval (CI) according to increasing PM_{10} exposure, adjusting for sex, age, and educational attainment.

Results: During a median follow up of 47.3 months, 34 participants developed dementia, in 26 cases diagnosed as Alzheimer's dementia. In non-linear restricted spline regression analysis, mean and maximum annual PM_{10} levels positively correlated with cerebrospinal fluid total and phosphorylated tau proteins concentrations, while they were inversely associated with β-amyloid. Concerning the risk of dementia, we found a positive association starting from above 10 $\mu g/m^3$ for mean PM_{10} levels and above 35 $\mu g/m^3$ for maximum PM_{10} levels. Specific estimates for Alzheimer's dementia were substantially similar. Adding other potential confounders to the multivariable model or removing early cases of dementia onset during the follow-up had little effect on the estimates.

Conclusions: Our findings suggest that exposure to outdoor air pollutants, PM_{10} in particular, may non-linearly increase conversion from MCI to dementia above a certain ambient air concentration.

1. Introduction

Dementia is a neurological syndrome mainly caused by neurodegenerative diseases whose incidence has increased in recent decades and is forecasted to triple by 2050, largely due to population ageing (GBD Collaborators, 2021). Epidemiologic evidence produced so far supports the hypothesis that onset of dementia, particularly Alzheimer's dementia (AD) and its neuropathological counterpart named Alzheimer's disease, is driven by a complex interplay between genetic and

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List of abbreviations

Aβ1-42	Amyloid beta 1-42
AD	Alzheimer's dementia
CI	confidence interval
CNS	central nervous system
CSF	cerebrospinal fluid
FTD	frontotemporal dementia
HR	hazard ratio
IQR	interquartile range
LBD	Lewy body dementia
MCI	mild cognitive impairment
p-tau181	phosphorylated tau
PM_{10}	<10 μm particulate matter
t-tau	total tau

environmental risk factors (Scheltens et al., 2021). The key pathogenetic process in the brain of subjects affected by AD is reflected by altered cerebrospinal fluid (CSF) levels of tau and β-amyloid proteins, respectively increased and decreased (Skillback et al., 2015; Vanmechelen et al., 2001).

Among the non-modifiable risk factors, age and female sex have largely been studied with respect to their involvement in dementia onset, by favoring it. At the same time, several environmental risk factors such as lower educational attainment in particular, hypertension, obesity, traumatic brain injury have been associated with a greater risk for dementia (Bloomberg et al., 2021; Bosi et al., 2022; Livingston et al., 2020). Outdoor air pollution has also been linked to cognitive decline and dementia (Balboni et al., 2022; Castellani et al., 2022; Livingston et al., 2020; Tang et al., 2022; Weuve et al., 2021). However, epidemiologic studies on this topic were frequently affected by methodological issues such as exposure and outcome misclassification, and to date only one seems to have examined the association between a major air contaminant such as particulate matter (PM) and dementia onset in highly susceptible individuals, those affected by mild cognitive impairment (Wu et al., 2022). PM pollution is considered to have multiple adverse health effects in the human (WHO, 2022), with major effects of air pollution mainly concerning populations (such as that of China, India, the Middle East, and Central America) exposed to exceeding high levels of PM for prolonged periods. In Europe, the Po Valley located in Northern Italy is among the most severely polluted places in Europe (Arvani et al., 2016; Bigi et al., 2012). PM may have different sizes, i.e., equivalent aerodynamic diameter, coarse, 10 μm–2.5 μm (PM_{10}); fine, <2.5 μm ($PM_{2.5}$); ultrafine, <0.1 μm.

Based on the follow up of an Italian cohort of patients newly diagnosed with MCI (Vinceti et al., 2017), we tested the hypothesis that air pollution and specifically PM_{10} exposure could be associated with a higher risk of conversion to dementia, either as AD or in other forms.

2. Methods

2.1. Study population

The flow-chart reported in Fig. 1 shows the design of the cohort study we carried out in the province of Modena, Northern Italy. After approval from the Modena Ethics Committee, we included in the study the 56 individuals receiving a diagnosis of MCI, amnestic MCI (single domain or multiple domain) or non-amnestic MCI (Limongi et al., 2019; Winblad et al., 2004) at the Cognitive Neurology Clinic of Modena University Hospital from 2008 to 2014 that had a CSF sample still available when the cohort study was designed, and were residing in the Modena and Reggio Emilia provinces (Po Valley, Emilia-Romagna region) (Vinceti et al., 2017). During the diagnostic process, each patient underwent neurological assessment, including neuropsychological examination and brain magnetic resonance imaging (MRI). Lumbar punctures were

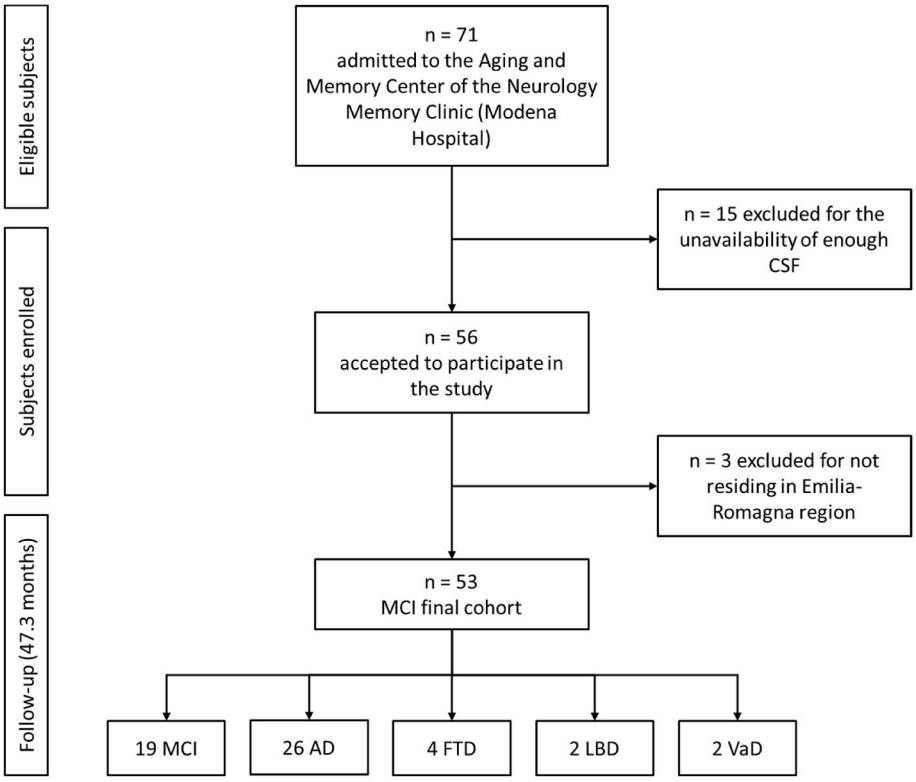

Fig. 1. Flowchart of the study population. AD, Alzheimer's dementia; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; LBD, Lewy body dementia; MCI, mild cognitive impairment; VaD, Vascular dementia.

performed in order to obtain a CSF-biomarker-based diagnosis of MCI due to Alzheimer's disease. Information on sociodemographic characteristics was also collected, including sex, date and place of birth, educational attainment and recent residential history. Data on smoking history, diabetes as well as on chronic obstructive pulmonary disease (COPD) were collected from all participants. Information on novel Coronavirus 19 infection was also retrieved during the follow-up, although all the study participants have been diagnosed with MCI or dementia before the onset of Coronavirus disease 19 outbreak and some of the participants died before the outbreak. Only patients that provided written informed consent for the use of CSF samples and personal data for both diagnostic and research purposes were included in the studies.

Cohort members were followed-up at the Neurology Clinic every six months until August 2021, a longer follow-up period compared with our previous study on the same population (Vinceti et al., 2017). We used Peterson's criteria revisions proposed by Winblad et al. for the definition of MCI amnestic form (single domain or multiple domain) or the MCI non-amnestic form of non-vascular origin to assign a MCI diagnosis (Limongi et al., 2019; Winblad et al., 2004). During each follow up visit each patient was classified as stable (i.e. confirmed MCI), or as a converter to dementia (any form, i.e. AD, frontotemporal dementia (FTD), Lewy-body dementia (LBD) or vascular dementia) (Dubois et al., 2007; Gorno-Tempini et al., 2011; McKeith et al., 2005; Rascovsky et al., 2011). Each diagnosis was also systematically *a posteriori* re-assessed and harmonized during the follow-up according to the most up-to-date diagnostic criteria (Dubois et al., 2021), without leading to any reclassification of the already performed diagnoses.

2.2. CSF biomarker measurement

CSF samples were collected through lumbar puncture in the morning in fasting patients according to Standard International Procedures for CSF Biobanking (Willemse and Teunissen, 2015), as previously described in detail (Urbano et al., 2022). After the lumbar puncture was performed, CSF samples were transferred to the Neuro-Immunology Laboratory and processed within 30 min. Each sample was then anonymized with an alphanumeric code and immediately centrifuged at 2500×*g* for 10 min at controlled room temperature. If analytical determination was not available immediately after centrifugation, samples were aliquoted into polypropylene sterile vials and kept frozen at −80 °C until testing. A manual sandwich Enzyme-Linked Immuno-Sorbent Assay (ELISA) method (INNOTEST® β-amyloid(1–42), hTau Ag and phospho-Tau(181P), Innogenetics, Ghent, Belgium) was used for the quantification of amyloid β 1–42 (Aβ1-42), total (t-tau), and phosphorylated tau (p-tau181) proteins. Laboratory specific cut-off for normal values were as follows: Aβ1-42 > 557 pg/mL, t-tau <350 pg/mL, p-tau181 < 62 pg/mL. These were established according to laboratory data and previous studies (Tondelli et al., 2015, 2022). All measurements were performed keeping laboratory personnel blinded to personal and clinical information.

2.3. Exposure assessment

Participants' exposure was estimated to medium and maximum annual concentrations of PM_{10} (as μg/m^3) by performing a spatial proximity analysis within the geographical information system (GIS) environment, as previously described in detail (Filippini et al., 2016; Vinceti et al., 2012, 2016). Briefly, each participant's current residence was geocoded and ambient air concentrations of PM_{10} were modeled at these locations in 2006 using an air dispersion model. In particular, concentrations at ground level and the deposition flux of PM_{10} were estimated using the CAlifornia LINE version 4 (CALINE4) (Department of Transportation, Division of New Technology and Research, Sacramento, CA, USA) air quality dispersion model for roads and other linear sources. The CALINE4 is a stationary plume dispersion model for roads and other linear sources used to assess the dispersion and deposition of pollutants (e.g., carbon monoxide, particulate matter, nitrogen dioxide, benzene) and other contaminants at selected spatial receptors. Corresponding PM_{10} levels at these locations were computed also taking into account a matrix of demographic and occupational information for residents in the province, along with mobility information collected from the 2001 national census and validated using *ad hoc* surveys as well as road vehicle counters (Vinceti et al., 2012). The model was finally validated through the PM_{10} levels measured at four air quality monitoring stations in Modena (Vinceti et al., 2012). While average yearly PM_{10} concentration was defined as the average of all hourly concentrations in the entire year, the maximum PM_{10} levels was the highest hourly concentrations over the modeled year.

2.4. Sensitivity analysis

Magnetic fields from electrical power lines and electrical transformers have been suggested to be involved in dementia etiology, and therefore could be a potential confounder in epidemiologic studies assessing the role of other environmental risk factors (Khan et al., 2020). Distance from high-voltage overhead electrical power lines of study participants' residences was assessed as previously described (Andreuccetti and Zoppetti, 2004; Malagoli et al., 2010) and together with distance from transformer stations identified from the database of the Emilia-Romagna Environmental Protection Agency, was added to our multivariable analysis for risk ratio calculation. We also added to the multivariable model CSF levels of an inorganic selenium compound, selenate, based on results obtained from a previous study on the same cohort (Vinceti et al., 2017).

We also performed sensitivity analyses by excluding subjects converting to dementia within 12 months from the first visit, or by restricting the outcome to AD. Such sensitivity analyses could not be performed for the other dementia forms, given their very limited number of cases.

Additional analyses were performed by adding in the model CSF levels of the biomarkers of neurodegeneration (tau protein) and amyloidosis. Concerning potential confounding by concomitant disease, we carried out additional analyses by excluding the two cohort members with antecedent diabetes and the two affected by COPD. The last two subjects were also classified as smokers, and together with five other participants were excluded from a sensitivity analysis to assess the effect of smoking status.

2.5. Data analysis

We assessed yearly mean levels and maximum hourly concentrations of PM_{10} according to participants' characteristics, i.e., sex, age category (<65 and ≥ 65 years at recruitment), and educational attainment (<8, 8–12, and ≥13 years). We performed spline regression analyses to assess the correlation between PM_{10} concentrations and baseline CSF levels of the biomarkers of amyloidosis (Aβ1-42) and neurodegeneration (t-tau and p-tau181), by using a restricted cubic spline regression model with knots fixed at three percentiles (10th, 50th, and 90th).

We also computed hazard ratios (HRs) with a 95% confidence interval (CI) of MCI conversion to dementia, by using a Cox proportional hazards model adjusting for potential confounders. For this purpose, person-time at risk was defined as the time range between initial MCI diagnosis and August 2021, or the date at which a dementia diagnosis was made, whichever occurred first. Moreover, the event was defined as the incidence of dementia. The multivariable Cox model was initially fitted by adjusting for age at entry as a continuous variable, with sex and educational attainment as a categorical one. We also ran an analysis restricted to AD as an outcome, by excluding *ab initio* the occurrence of other dementia cases. In computing the HR of MCI conversion to dementia, we used the mean and maximum annual values of PM_{10} defined as cutoff concentrations by European and international bodies (20 and 50 μg/m^3, respectively) (EEA, 2022; WHO, 2021). We also calculated

rate risk for mean PM_{10} levels of 5–10 μg/m^3, 10–20 μg/m^3 and >20 μg/m^3 by using the category ≤5 μg/m^3 as a reference, and for maximum PM_{10} levels of 20–50 μg/m^3 and >50 μg/m^3 (reference: ≤20 μg/m^3). We finally implemented a restricted cubic spline regression analysis within the Cox regression analysis, in order to assess the existence of a non-linear association between PM_{10} levels and dementia risk by using the same knots (10th, 50th, and 90th percentile) used in the regression analysis.

3. Results

We recruited 53 subjects with MCI (28 males and 25 females) with median age of 66.3 years at recruitment. The baseline characteristics of the study population are reported in Table 1. Mean and maximum annual PM_{10} levels were available for all participants. Table 2 reports median and IQR for annual mean and maximum annual PM_{10} concentrations in the overall study population, and according to age, sex and educational attainment of the study participants. Both mean and maximum annual PM_{10} levels were found to be higher in females compared to males, in subjects aged ≥65 years and in participants with the lowest educational attainment (<8 years).

During an average 47.3-month follow up, 19 of the 53 cohort members did not convert to dementia, while 26 converted to AD, 4 to FTD, 2 to LBD, and 2 to vascular dementia. The results of the Cox linear regression analysis are reported in Table 3. Mean and maximum annual PM_{10} levels were positively associated with the risk of overall dementia and AD, with a stronger HR estimate for the former indicator of exposure. Older age, female sex and lower educational attainment were also associated with higher hazard rates of conversion to both overall dementia and AD. For this reason, age, sex and educational attainment were added as covariates to the Cox and spline regression analyses. A slightly positive association emerged for 10-unit increased levels of t-tau, while for p-tau181 the hazard ratio corresponded to 1.12 and 1.19 for overall dementia and AD, respectively. Conversely, the association between 10-unit increased levels of the biomarker of amyloidosis (Aβ1-42) and AD and overall dementia risk was inverse.

In the restricted cubic spline regression analysis model, mean and maximum annual PM_{10} levels were positively and almost linearly correlated with p-tau181 concentrations, though only above 62 pg/mL of the latter. A positive but not entirely linear association was also found with t-tau concentrations. When considering Aβ1-42 as a dependent variable, conversely, mean annual PM_{10} levels were negatively and linearly correlated with this amyloidosis biomarker. For maximum PM_{10} levels, a negative association was found with Aβ1-42 concentrations, although the curve flattened at PM_{10} levels above 30 μg/m^3 (Fig. 2).

Using exposure categories predefined according to fixed cutpoints (5, 10, and 20 μg/m^3), we found an increased risk of conversion from MCI to any cause of dementia in all categories, with the highest HR found in the highest one (≥20 μg/m^3) (HR = 2.77, 95% CI 0.61–12.47). These results were somewhat different when the analysis was restricted to AD cases,

Table 2
Mean and maximum annual particulate matter ≤10 μm (PM_{10}) with interquartile range concentrations according to participants' characteristics.

Study population	Mean PM_{10} (μg/m^3)	Maximum PM_{10} (μg/m^3)
All subjects (n = 53)	8.17 (5.13–13.10)	23.64 (14.73–34.52)
Sex		
Males (n = 28)	5.86 (4.49–13.04)	15.94 (13.31–34.14)
Females (n = 25)	10.82 (7.72–15.96)	26.12 (19.03–40.60)
Age		
<65 (n = 22)	7.95 (4.14–12.76)	20.62 (13.18–34.84)
≥65 (n = 31)	10.79 (5.51–13.42)	26.72 (15.37–34.52)
Education		
<8 (n = 18)	10.96 (6.13–14.17)	28.41 (16.19–37.12)
8–12 (n = 15)	5.71 (2.55–12.48)	16.97 (6.57–28.83)
≥12 (n = 20)	8.73 (4.50–15.62)	21.34 (13.66–40.51)
APOE ϵ4 carriership		
Non-carriers (n = 21)	9.28 (5.98–12.97)	24.27 (16.25–34.52)
Carriers (n = 17)	8.01 (5.01–13.4)	25.65 (13.89–37.12)
Missing (n = 15)	5.51 (3.38–12.76)	14.73 (9.23–28.83)

Table 3
Bivariate analysis of risk of any dementia and Alzheimer's dementia according to sex, age, educational attainment, cerebrospinal fluid biomarkers of neurodegeneration and amyloidosis, and mean and maximum annual particulate matter levels with diameter below 10 μm (PM_{10}). HR: hazard ratio, CI: confidence interval.

	Any dementia		Alzheimer's dementia	
	HR	**95% CI**	**HR**	**95% CI**
Age (years)	1.02	0.97–1.06	1.02	0.97–1.08
Sex (females)	1.26	0.65–2.43	1.28	0.60–2.70
Educational attainment (years)	1.03	0.96–1.11	1.03	0.96–1.11
beta 1–42 (Aβ1-42)[a] (pg/mL)	0.98	0.96–0.99	0.96	0.94–0.98
Total tau (t-tau)[a] (pg/mL)	1.02	1.01–1.03	1.03	1.02–1.04
Phosphorylated tau (p-tau181)[a] (pg/mL)	1.12	1.03–1.22	1.19	1.08–1.30
PM_{10} (mean μg/m^3)	1.35	0.78–2.33	1.33	0.73–2.41
PM_{10} (max μg/m^3)	1.13	0.90–1.42	1.12	0.87–1.44

[a] Risk calculated over 10-unit increase of the cerebrospinal fluid biomarkers.

Table 1
Baseline characteristics of study participants according to diagnosis at the end of follow up.

	MCI		AD		FTD		LBD		VaD	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
All subjects (n = 53)	19	100	26	100	4	100	2	100	2	100
Sex										
Males (n = 28)	11	57.9	12	46.1	2	50.0	1	50.0	2	100.0
Females (n = 25)	8	42.1	14	53.9	2	50.0	1	50.0	0	0.0
Age at first diagnosis (years)										
65 (n = 22)	10	52.6	8	30.8	4	100.0	0	0.0	0	0.0
≥65 (n = 31)	9	47.4	18	69.2	0	0.0	2	100.0	2	100.0
Educational attainment category (years)										
<8 (n = 18)	9	47.4	7	26.9	0	0.0	2	100.0	0	0.0
8–12 (n = 15)	3	15.8	10	38.5	0	0.0	0	0.0	2	100.0
≥12 (n = 20)	7	36.8	9	34.6	4	100.0	0	0.0	0	0.0
APOE ϵ4 carriership										
Non-carriers (n = 21)	10	52.6	6	23.1	3	75.0	1	50.0	1	50.0
Carriers (n = 17)	3	15.8	12	46.1	0	0.0	1	50.0	1	50.0
Missing (n = 15)	6	31.6	8	30.8	1	25.0	0	0.0	0	0.0
Follow up (months)[a]	48	35–54	43	28–60	38	30–44	39	30–48	64	24–104

[a] Values are median and interquartile range. Abbreviations: AD Alzheimer's dementia, APOE apolipoprotein E, FTD frontotemporal dementia, IQR interquartile range, LBD Lewy body dementia, MCI mild cognitive impairment, VaD vascular dementia.

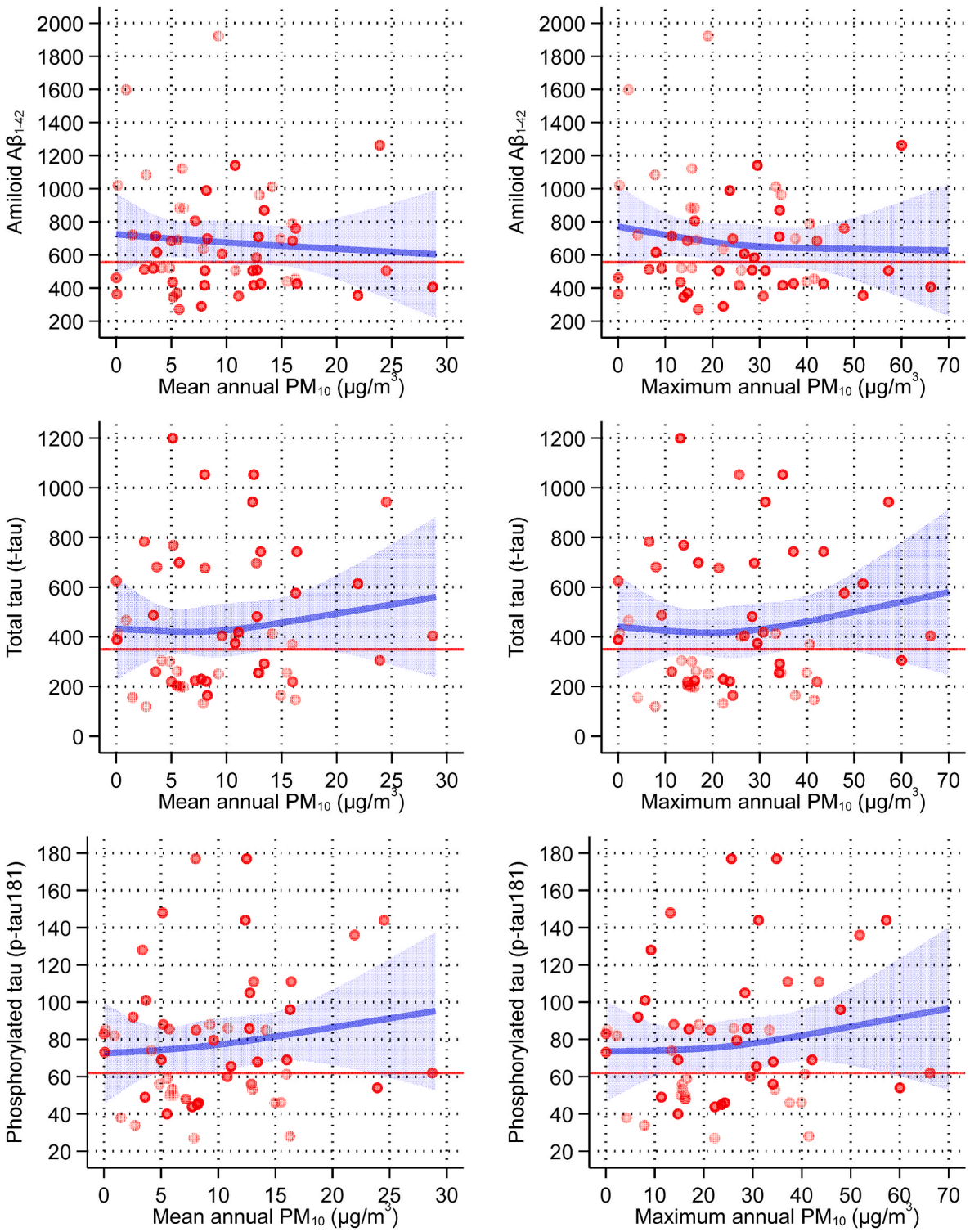

Fig. 2. Correlation between cerebrospinal biomarkers (beta-amyloid, total tau protein, phosphorylated tau-protein) and traffic-related mean and maximum annual particulate matter levels (PM_{10}). Light and dark red dots indicate subjects who remained MCI and converted to dementia, respectively. The blue line represents spline regression analysis with 95% confidence interval (light blue area). The red continuous line represents the biomarker cut-off values used at the Modena Neuroimmunology laboratory (Aβ1-42: 557 pg/mL; t-tau: 350 pg/mL; p-tau181: 62 pg/mL).

where an excess risk was only found at PM_{10} levels above 20 μg/m^3 (HR = 3.10, 95% CI 0.64–14.93). For maximum PM_{10} levels and with the use of 20 and 50 μg/m^3 cut-points, an increased risk ratio for any cause of dementia was found in the intermediate and highest exposure categories. For AD cases, on the other hand, an excess risk was only found ≥50 μg/m^3 (HR = 3.34, 95% CI 0.74–15.02) (Table 4). In the most fully adjusted model also including selenate, summary risk estimates were similar for both overall dementia and AD (Table S1), as it was when adjusting for CSF biomarkers of amyloidosis and neurodegeneration (Table S2).

In spline regression analysis adjusted for sex, age and educational attainment category, we found an increased risk of overall dementia for

Table 4
Risk of any dementia and Alzheimer's dementia according to increasing exposure to average and maximum annual particulate matter levels with diameter below 10 μm (PM_{10}), in a multivariable analysis adjusting for age, sex, and years of education. HR: hazard ratio, CI: confidence interval.

Any dementia				Alzheimer's dementia			
	N	HR	95% CI		N	HR	95% CI
PM_{10} (mean) (μg/m^3)				**PM_{10} (mean) (μg/m^3)**			
≤5	12	1.00	–	≤5	5	1.00	–
>5-≤10	18	1.39	0.50–3.86	>5-≤10	9	0.66	0.21–2.06
>10-≤20	19	1.19	0.43–3.31	>10-≤20	8	0.75	0.20–2.73
>20	4	2.77	0.61–12.47	>20	4	3.10	0.64–14.93
PM_{10} (max) (μg/m^3)				**PM_{10} (max) (μg/m^3)**			
≤20	23	1.00	–	≤20	9	1.00	–
>20-≤50	26	1.37	0.63–2.99	>20-≤50	13	0.73	0.28–1.92
>50	4	2.96	0.70–12.47	>50	4	3.34	0.74–15.02

mean PM_{10} levels above 10 μg/m^3 and for maximum PM_{10} levels above 35 μg/m^3 (Fig. 3). When using AD as specific outcome, we found a non-linearly increased risk above 15 μg/m^3 of mean PM_{10} levels. For maximum PM_{10} levels, a trend emerged towards a U-shaped association with AD risk, with a turning point at around 25 μg/m^3. At 70 μg/m^3 of PM_{10}, risk of overall dementia increased by 50%. We also performed an additional analysis in order to assess the risk of dementia and AD after the exclusion of subjects converting within 12 months (Fig. 4). The shape of the associations became more linear, but estimates were not substantially different from the overall analysis.

Adding to the multivariable model a potential confounder such as magnetic field exposure, assessed through distance from either power lines or electric transformers, had negligible effects on the estimates (Figs. S1–S2). In an additional multivariable model, we adjusted for CSF biomarkers of amyloidosis and neurodegeneration (Figs. S3–S4). We found that adding Aβ1-42 concentrations attenuated the risk of overall dementia and AD associated with PM_{10} exposure, which became almost null, except at the highest levels of exposure. On the contrary, when adding t-tau and p-tau181 as adjustment factors, the risk of overall dementia and AD in relation to mean and maximum PM_{10} was enhanced, though showing a U-shaped association especially for AD risk. In that case, the turning points were observed at around 10 μg/m^3 for mean PM_{10} levels and at 25 μg/m^3 for maximum PM_{10} levels (Figs. S5–S8). Sensitivity analyses performed by excluding subjects affected by diabetes or COPD had no substantial effect on the risk estimates (Figs. S9–S10), as did exclusion of smokers (Fig. S11), though in this case the shape of the curve indicated a stronger and more linear association compared to the main analysis. Similarly, higher risk estimates were observed by adding in the multivariate model mini-mental state examination score assessed at baseline, to take into account potential differences in MCI diagnosis timeless, possibly related to socioeconomic status and therefore with air pollution exposure (Fig. S12).

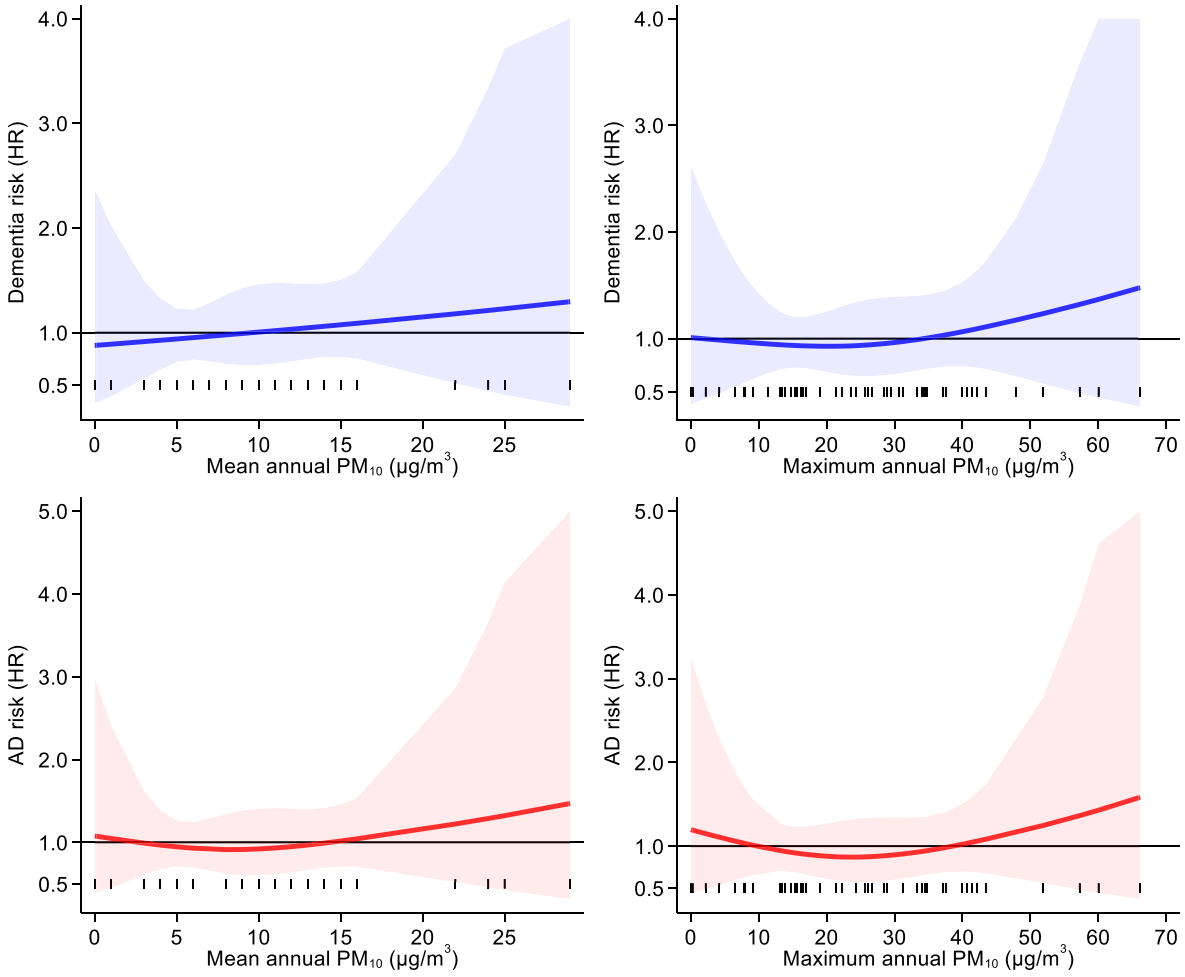

Fig. 3. Spline regression analysis for the association between mean and maximum annual particulate matter levels (PM_{10}) and risk of developing any type of dementia and Alzheimer's dementia (AD). The solid line indicates hazard ratio (HR) and the shaded areas the 95% confidence intervals. Analysis adjusted for sex, age at entry, and education.

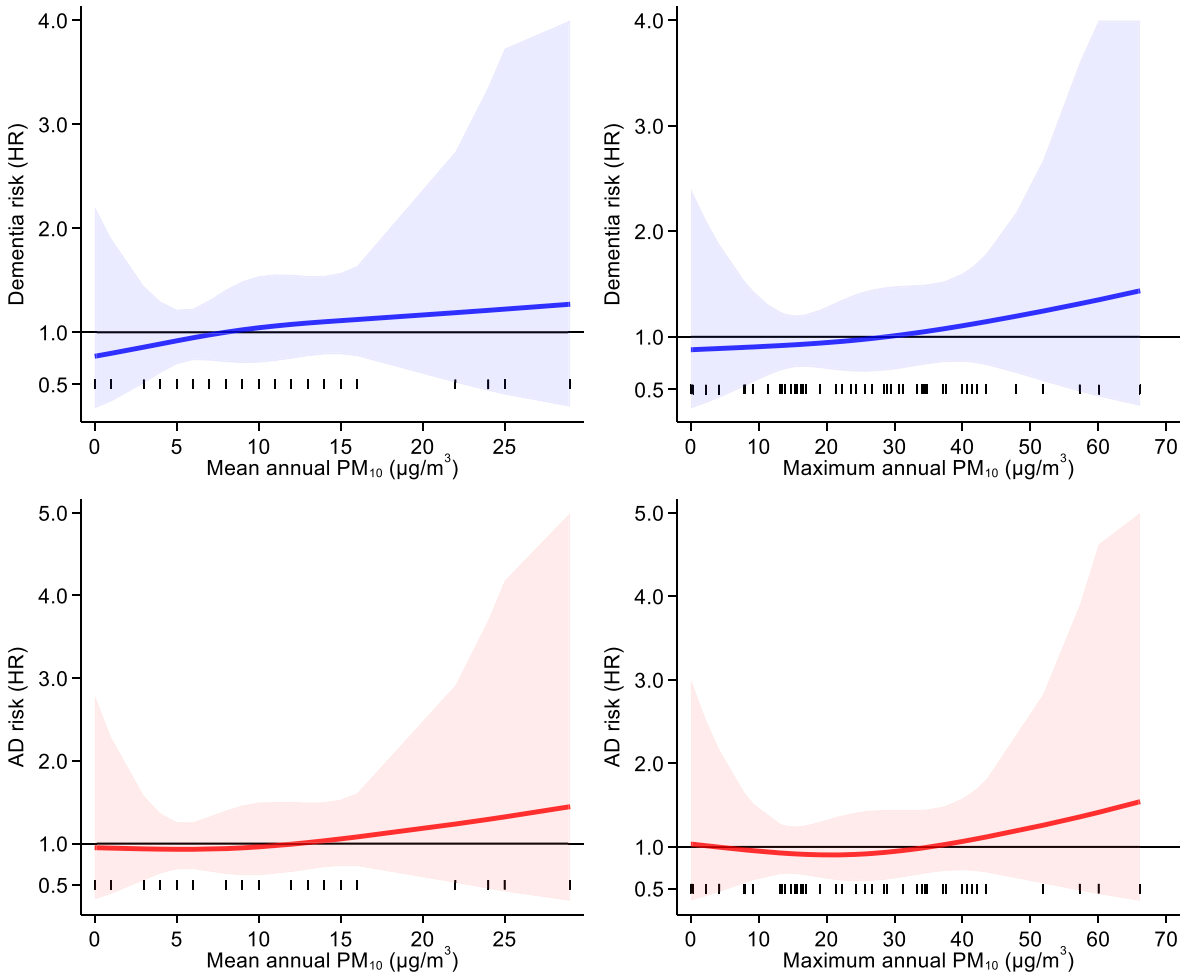

Fig. 4. Spline regression analysis for the association between mean and maximum annual particulate matter levels (PM_{10}) and risk of developing any type of dementia and Alzheimer's dementia (AD) by excluding *ab initio* subjects converting within 12 months (n = 2). The solid line indicates hazard ratio (HR) and the shaded areas the 95% confidence intervals. Analysis adjusted for sex, age at entry, and education.

4. Discussion

The results from this prospective cohort study of an Italian population indicate that relatively but not exceedingly high levels of traffic-related outdoor air pollution, as assessed through PM_{10} levels, were associated with increased risk of MCI conversion to dementia. Such association was non-linear, occurred above a certain threshold of exposure, and was robust enough to resist to inclusion of several potential confounders in the multivariable model, to the restriction of analysis to dementia cases occurring after the first period of follow-up, or to the AD form only. The existence of such a relation was further supported by the association between PM_{10} exposure and baselines biomarkers of amyloidosis and neurodegeneration. These findings were of particular interest considering the location of the study area in the Po Valley, which is one of the most severely polluted areas in Europe due to topographic and meteorological conditions inhibiting pollutant dispersion (Bigi et al., 2012), with maximum PM_{10} concentrations frequently exceeding in many locations the EU daily limit value of 50 µg/m^3 and generally higher pollution levels compared to the other Italian regions (EEA, 2022).

In this study, the increased risk of dementia was observed at PM_{10} levels below the EU daily limit value, since mean annual PM_{10} levels above 10 µg/m^3 and maximum PM_{10} levels above 35 µg/m^3 were already associated with increased risk of dementia. Nonetheless, the highest risk was found in subjects exposed to maximum annual PM_{10} levels exceeding ≥50 µg/m^3, given the steeper increase in risk above that cut-point. Our results are in keeping with the growing evidence suggesting that air pollution increases the risk of dementia (Cho et al., 2023; Mork et al., 2023; Peters, 2023; Shi et al., 2023; Tang et al., 2022), despite some inconsistent finding (de Crom et al., 2023).

There is some biological plausibility for a PM_{10}-dementia causal association, since PM exposure may exacerbate accumulation of amyloid-beta oligomers in the brain and phosphorylation of tau protein (Cacciottolo et al., 2017; Park et al., 2021). Long-term exposure to air pollutants tend to increase levels of selected neuroinflammatory and pro-inflammatory markers in the brain, leading to neuroinflammation, neurodegeneration, oxidative stress enhancement, and blood-brain barrier dysfunction (Block and Calderon-Garciduenas, 2009; Costa et al., 2019; Shou et al., 2019). Recent evidence has also suggested an involvement of the gut microbiome in the pathophysiology of dementia (Kohler et al., 2016). Since PM can enter the gastrointestinal tract, another mechanism by which PM_{10} may increase AD risk is by causing higher permeability of the gut barrier (Mutlu et al., 2018).

The consistency of our findings and their potential etiologic relevance are supported by the observation that higher PM_{10} exposure was positively associated not only to dementia risk, but also to the baseline levels of CSF neurodegeneration biomarkers, namely t-tau and p-tau181, as well as (inversely) with CSF amyloid levels, another hallmark of AD. Our results are also consistent with a recent study that evaluated the association of NO_2, $PM_{2.5}$ and PM_{10} with biomarkers of AD pathology in a population of cognitively unimpaired adults at increased risk of AD (Alemany et al., 2021; Crous-Bou et al., 2020). Interestingly, in our

analysis adjusted also for Aβ levels, the risk was considerably attenuated. Thus, we speculate that the relation between PM_{10} and dementia risk may depend upon the triggering of the process of amyloid deposition in the brain.

A key limitation of the present study is its sample size, which limits the precision of our estimates, as reflected by their wide confidence intervals. In addition, though we took into account potential key confounders such as sex, age and education, comorbidities, and magnetic fields exposure from power lines and electric transformers, we could not assess vicinity to green spaces, a factor possibly associated with dementia with an U-shaped pattern (Zagnoli et al., 2022). Moreover, as usual in observational studies, we cannot entirely rule out the occurrence of residual confounding due to other factors.

Concerning exposure assessment, we used a validated and carefully constructed air pollution model based on multiple sources of data and validated at the air monitoring stations of the study area (Vinceti et al., 2012). Industrial sources were not included in the model as they were considered to be of limited relevance, neither were domestic heating boilers, which in the study area were almost entirely based on the use of natural gas and not of Diesel fuel or firewood, and therefore were not a source of PM. We focused on PM_{10} and not on the fine particulate matter ($PM_{2.5}$), whose association with dementia risk may be stronger under both an epidemiologic (Balboni et al., 2022; Fu and Yung, 2020; Mortamais et al., 2020; Power et al., 2016; Sullivan et al., 2021) and biological (Chen et al., 2021; Shou et al., 2019) perspective. However, $PM_{2.5}$ is generally around 70% of total PM_{10} (Zapponi and Marconi, 2003), thus allowing to approximately estimate the exposure levels for the former pollutant in our study setting. We also acknowledge that our pollutant dispersion model was built upon data collected in 2006, i.e., before the start of the follow-up but possibly not covering the entire window of exposure of etiologic relevance for dementia onset. However, such relevant period of exposure that is really meaningful for dementia etiology is not precisely known, and in addition the exposure levels in the study area tended to smoothly decrease in the last decades, thus suggesting that our exposure assessment could have underestimated the real levels of air pollution etiologically meaningful for dementia onset. However, our study specifically aimed at assessing the risk of conversion to dementia of individuals with mild cognitive impairment, therefore suggesting that the relevant window of exposure for such a conversion was likely close to the period of diagnosis of MCI, and therefore captured by our approach.

Credit author statement

Tommaso Filippini, Carlotta Malagoli and Marco Vinceti conceived and designed the original study. Annalisa Chiari recruited study participants. Teresa Urbano performed the statistical analysis with Tommaso Filippini and Marco Vinceti. Roberta Bedin performed analytical determinations with the help of Teresa Urbano. Andrea Cherubini and Giuseppe Maffeis performed the exposure assessment with the help of Sofia Costanzini, Sergio Teggi, Carlotta Malagoli and Tommaso Filippini. Teresa Urbano, Tommaso Filippini, Marco Vinceti interpreted the data and drafter the original manuscript, and all other authors provided revisions. All authors read and approved the final manuscript.

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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.

Data availability

The data that has been used is confidential.

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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.2023.115425.

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