Environment International 213 (2026) 110326

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Association between first ischemic major acute cardiovascular events and long-term outdoor air pollution exposure in men: exploring the interaction with cardiovascular health profiles

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ARTICLE INFO

Keywords:
Air pollution
Cardiovascular health
Lifestyles
Coronary heart disease
Ischemic stroke
Incidence
Long-term exposure

ABSTRACT

Modifiable cardiovascular health profiles might modulate the detrimental effects of long-term air pollution exposure on cardiovascular risk, but effect modification is so-far under investigated. We derived the American Heart Association Life's Simple 7 (LS7)-behavior and LS7-factor scores in a population-based cohort of 2119 men, 50–75 years old and disease-free residents in the Varese city (Northern Italy) at baseline (2013–2016). Exposures were the average concentrations of $PM_{2.5}$, NO_2 and O_3 in the 12 months before baseline (EXPANSE project models). From healthcare records, we identified first ischemic Major Acute Cardiovascular Event (iMACE) before 31/12/2022, fatal or non-fatal. We assessed the interaction between each LS7 score and pollutants on relative and absolute scales using Cox and Poisson models, respectively, adjusting for age, education, area-based deprivation, and contextual environmental factors. In 7.6 years of median follow-up, we observed n = 160 events (rate = 10.4 per 1,000 person-years). Mean ± SD $PM_{2.5}$ were 18.6 ± 1.8 μg/m^3; men with poor LS7-behavior were the most exposed. The HR for 1.93 μg/m^3-increase in $PM_{2.5}$ was 1.24 (95%CI:1.02–1.50), and 1.45 (95%CI:1.07–1.97) in men with poor LS7-behavior (interaction test p-value = 0.001); we estimated 7.7 (95%CI:2.8–12.5) additional events per 1,000 person-years due to the interaction. Physical activity and adherence to Mediterranean diet mitigated the effect of $PM_{2.5}$. Conversely, we observed no interaction between LS7-factor and $PM_{2.5}$. NO_2 showed similar interaction paths. The promotion of healthy behaviors in urban settings may contribute to reduce the harmful effect of pollutants on the cardiovascular system during the transition period to the achievement of EU air quality limits.

1. Introduction

In recent *meta*-analyses, every 10 μg/m^3 increase in long-term exposure to particulate matter of size <2.5 μm ($PM_{2.5}$) has been associated with a higher incidence of major cardiovascular events (de Bont et al., 2022), with estimated risk excesses of 8–10%, 13–23% and 18% for incident coronary heart disease (Zhu et al., 2021; Alexeeff et al., 2021); stroke (Alexeeff et al., 2021; Yuan et al., 2019), and ischemic stroke (Alexeeff et al., 2021), respectively, in men and women combined. Evidence for an independent role of nitrogen dioxide (de Bont et al., 2022) (NO_2) and ozone (Olaniyan et al., 2022) (O_3) is less conclusive for the inconsistency of the findings. Most of these *meta*-analytical estimates combine administrative healthcare cohort studies with poor availability of individual-level data on modifiable cardiovascular disease (CVD) risk factors, especially lifestyles (Zhu et al., 2021; Alexeeff et al., 2021). Neglecting behavioral and clinical risk factors might result in overestimation of the independent effects of pollutants (Vanoli et al., 2025). In addition, these might also play a role as *effect modifiers* due to shared underlying biological pathways (Lechner et al., 2020; Schraufnagel et al., 2019), potentially determining increased susceptibility to the detrimental effects of pollutants in individuals with poor cardiovascular health profiles (Schraufnagel et al., 2019). So far, cardiovascular susceptibility to pollutants has been mainly investigated in relation to un-modifiable traits including genetic risk (Li et al., 2025).

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https://doi.org/10.1016/j.envint.2026.110326
Received 5 February 2026; Received in revised form 27 April 2026; Accepted 22 May 2026
Available online 23 May 2026

With the EU air quality limits of 10 μg/m^3 in yearly average $PM_{2.5}$ exposure set to be reached by 2030, or even by 2040 upon member states' request, studies with contemporary assessment of exposure, lifestyles and a longitudinal follow-up are unique opportunities to identify what individuals can modify at a personal level to mitigate the adverse effects of air pollution exposure in the meantime.

The American Heart Association introduced in 2010 Life's Simple 7 (LS7), a guideline for cardiovascular health combining modifiable *health behaviors* – avoiding or quitting cigarette smoking, engaging in sufficient physical activity and adhering to healthy diet – and *health factors* – achieving normal body weight and maintaining low levels of cholesterol, blood pressure, and glucose also through medical treatments (Lloyd-Jones et al., 2010). In many observational studies, improvements in LS7 reduced the incidence of coronary heart disease and stroke (Radovanovic et al., 2023). In a recent cohort study of highly-exposed (average $PM_{2.5}$ annual mean: 52.6 μg/m^3), initially CVD-free Chinese adults, the detrimental effects of long-term exposure to $PM_{2.5}$ on the risk of first self-reported CVD event were the highest in individuals with poor cardiovascular health as measured at baseline by a modified LS7 score (without diet) (Hu et al., 2024). No other study examined the interplay between the comprehensive individuals' cardiovascular health profiles and environmental stressors on the incidence of major cardiovascular events, other contributions focusing on single lifestyles (Kim et al., 2020; Lim et al., 2019) and mortality (Lim et al., 2019). Hence, the findings (Hu et al., 2024) warrant confirmation in study settings representative of current European air pollution levels, using objective events' ascertainment methods, and including diet.

In a North Italian urban population-based cohort of 50–75 years old individuals, we aim to investigate the association between long-term exposure to outdoor $PM_{2.5}$, PM_{10}, NO_2 and O_3 with the incidence of ischemic Major Acute Cardiovascular Events (iMACE) in men, and specifically assessing the role of *health behaviors* and of *health factors* as effect modifiers for the associations. By looking at the two domains of LS7 separately, we better identify specific population subgroups at increased susceptibility to pollutants' effects and suggest targeted guidance for preventive interventions.

2. Methods

2.1. Study population

The RoCAV study (Gianfagna et al., 2016) is a population-based cohort of 2404 men (50–75 years old) and 1373 women, (60–75 years old) randomly selected from residents in the city of Varese (55 km^2 of surface, about 80,000 inhabitants), located in Northern Italy close to the Swiss border and the Alps. The study was designed to estimate the prevalence of cardiovascular risk factors and of abdominal aortic aneurism in the population. Study participation was 65% in men and 61% in women (Gianfagna et al., 2016); we observed no difference in the spatial distribution within the city between participants and non-participants. Here we included only men free of coronary heart disease and stroke at baseline (n = 2141), since sex-specific analyses might be more appropriate to address the association between ambient air pollution and CVD risk (Kraus et al., 2025) and we deemed the observed number of incident events amongst CVD-free women (n = 47) not well-suited to allow precise estimates of effect modification. The study received approval by the local Ethics Committee (Azienda Socio Sanitaria Territoriale Sette Laghi, ID 66/2011), and participants signed written consent forms for study participation, conservation of biological samples in the study biobank, and follow-up activities.

2.2. Baseline data collection and definition of cardiovascular health metrics

From June 2013 to May 2016, participants underwent a comprehensive baseline examination mostly using European standards (Gianfagna et al., 2016). Measurement methods for the risk factors in the LS7 metrics are documented in the Supplementary Material. From these, we defined the health metrics in LS7 on the poor (0 point), intermediate (1 point), and ideal (2 points) scale (Radovanovic et al., 2023; Lim et al., 2019) as detailed in Table S1. Points were summed-up to obtain two separate scores representing the LS7 domains of *health behaviors* (LS7-behavior; cigarette smoking, physical activity and adherence to the Mediterranean diet), as poor (0–2 points), intermediate (3–4 points) and ideal (5–6 points); and *health factors* (LS7-factor; Body Mass Index [BMI], total cholesterol, blood pressure, and blood glucose), as poor (0–3 points), intermediate (4–5 points) and ideal (6–8 points). The cut-off values were taken from the literature (Radovanovic et al., 2023). BMI was grouped into *health factors* as recommended in the most recent update of the cardiovascular health guidelines (Lloyd-Jones et al., 2022).

2.3. Air pollution exposure

We retrieved the monthly concentrations for $PM_{2.5}$, PM_{10}, NO_2 and O_3 at a spatial resolution of 25 m from the EXPANSE project models (Shen et al., 2024), as recruitment visits spanned from June 2013 to May 2016. In the EXPANSE project, monthly average concentrations over the period 2000–2019 were collected from routine monitoring stations over Europe. Input data were daily concentrations for PM_{10} and $PM_{2.5}$; hourly concentrations for NO_2; and daily maximum 8-h mean from hourly data for ozone. Land Use Regression models were then built separately per month, including both monthly-fixed and –varying spatial variables, using supervised linear regression to select predictors and geographically weighted regression to estimate spatially-varying regression coefficients for each month. The assessment of models' performance vs. the measured concentrations at the European Environment Agency monitoring stations active in the city of Varese during the study period revealed good reliability and low prediction errors, consistent with the cross-validated values in (Shen et al., 2024), especially for PM (Table S2). Individuals' residential address at baseline were geocoded to make a spatial linkage with EXPANSE data. For each pollutant, based on the literature (Yuan et al., 2019; Hu et al., 2024; Kim et al., 2020) the main individuals' exposure metric was the average concentration in the 12 months before the month of baseline visit. We also derived the average concentration in the 24 months before the month of baseline visit, and used this to evaluate the robustness of our findings with respect to the choice of the exposure metric.

2.4. Study endpoints

The study endpoint was the occurrence of first iMACE: acute coronary event (myocardial infarction, acute coronary syndrome and coronary revascularization), ischemic stroke or carotid endarterectomy, whichever occurred first, fatal or non-fatal, before Dec 31st, 2022. We excluded hemorrhagic strokes from the endpoint definition to better elucidate the mechanisms linking air pollution to major ischemic-related cardiovascular events (Schraufnagel et al., 2019). Events were ascertained through record linkage with Electronic Health Records (hospital discharge, emergency department admissions and mortality) provided by the Local Health Agency. For hospitalized events, based upon international epidemiological standards [https://www.thl.fi/publications/morgam/qa/followup/followup.htm] we selected discharge codes suggestive of myocardial infarction and unstable angina (ICD-IX codes: 410–411) or coronary revascularization; cerebrovascular infarction (ICD-IX 433 or 434) or endarterectomy with stenosis at cerebral or precerebral arteries (ICD-IX 433.1, 433.3, 434.0). Selected records were then reviewed to identify, retain and adjudicate the first index case. Fatal out-of-hospital cases were identified from underlying causes of deaths suggestive of coronary deaths (ICD-X codes: I21-I25) or ischemic stroke (I63). Censorship occurred at the date of death from other causes, emigration outside the study Region as ascertained by contacting the

municipality of residency, or Dec 31st, 2022, whichever came first.

2.5. Covariates

At individuals' level, potential confounders were age and education, categorized as high, intermediate and low from sex and year of birth-specific thirds of full-time schooling years (Karvanen et al., 2007). As area-level confounders (Vanoli et al., 2025), we considered the 2011 deprivation index developed by the National Institute of Statistics (ISTAT) and validated in Italy for epidemiological studies (Rosano et al., 2020), available at the census sections and consisting of five dimensions of social and material deprivation (low education, unemployment, renting, household crowding and living in single-parent family). The index was categorized according to sample quintiles as recommended (Rosano et al., 2020). Furthermore, ISTAT defined within the city of Varese 6 census areas (i.e., spatial aggregation of census sections), which closely correspond to well-identified urban neighborhoods (e.g. city Centre, residential districts at different population density). Census area was also included as categorical variable in the models, to capture contextual environmental exposures such as greenness, noise pollution, and other built environment features.

2.6. Statistical analyses

Sample distributions of LS7 scores and metrics, as well as of air pollutants were summarized using descriptive statistics, and correlations were estimated using Spearman coefficients. Analyses were carried out using separated models for the LS7-behavior and the LS7-factor scores, categorized as reported above; and were driven by the directed acyclic graph (DAG) to assess effect modification (Bours, 2023) reported in the Supplementary Material (Fig. S1). To assess the relationships of the LS7 scores with exposures and outcomes, we first used linear regression models with each pollutant as a dependent variable, LS7 as independent variable ("ideal" as reference) and adjusted for the identified confounders. We then estimated event rates and rate ratios for LS7 from Poisson regression models with robust standard error estimators adjusting for the identified confounders. Rates are expressed for 1,000 person-years and at the sample mean values for covariates. We estimated the Hazard Ratios (HR) and 95%CI based on robust standard error estimators for 1 interquartile range (IQR) width increase in air pollutants from single-pollutant Cox models with attained age during follow-up on the time scale, adjusting for confounders (Model1), and further for each LS7 score, for iMACE and for coronary heart disease and ischemic stroke events separately. In sensitivity analysis on Model 1, we addressed co-exposures through bi-pollutant models. Treating non-cardiovascular deaths as competing events did not modify our results, as their number (n = 125) was low compared to censorship due to end of follow-up period.

We investigated effect modification by looking at the interactions between the LS7 scores and air pollutants on risk of first iMACE. We added to Cox models two LS7*air pollutant interaction terms, formally testing the null hypothesis of homogeneity of pollutant effects on the relative scale through Wald chi-square tests (2 degrees of freedom). Models' diagnostics confirmed Cox assumption on hazards proportionality based on Schoenfeld residuals; and linearity in the pollutants' effects and interactions based on −2LogL ratio tests vs. models including cubic splines. As sensitivity analyses, we replicated these models *i.* using the 24-month pollutants' average as exposure; and *ii.* on the n = 1760 men (83% of the sample; iMACE: n = 127) who were residents for the entire follow-up period at the same residential address as at baseline. In the presence of an interaction, we *i.* reported the E-value for effect heterogeneity (Mathur et al., 2022) to measure the strength of unmeasured confounders that would have shifted the interaction estimates to the null; *ii.* further explored the specific contribution of each of the health metrics comprising the LS7 score; and *iii.* we used Poisson models to estimate the additional number of events due to interactions at the sample mean values for pollutants and confounders. Analyses were carried out using SAS software 9.4TM8 release (SAS Institute Inc., Cary, NC, USA), and R (version 4.4.3) for drawing plots.

3. Results

From the 2141 CVD-free men at baseline, we excluded 22 (no events) due to missing data on either education or one LS7 metric, leaving a final sample size of 2119. The sample mean age (±standard deviation, SD) was 63.3 ± 7.1 years. Men with ideal LS7-behavior and ideal LS7-factor were 16.5% and 26.8%, respectively (Table 1); a difference that can be attributed to the scoring, since two "intermediate" and two "ideal" metrics were sufficient to qualify for the category in LS7-factor; whereas, for LS7-behavior, two "ideal" and one "intermediate" metrics are needed.

The prevalence of the "ideal" category was 47%, 21% and 31% for cigarette smoking, physical activity and adherence to the Mediterranean diet, respectively. Amongst the metrics in the LS7-factor domain, the modal category was "intermediate" for total cholesterol and blood pressure; these individuals were likely to be under treatment (37% and 48%, respectively). The prevalence of either anti-hypertensive or lipid lowering treatments across categories of the LS7-factor score were 66%, 52% and 31% in poor, intermediate and ideal, respectively. The LS7-

Table 1
Sample characteristics and distributions of the American Heart Association Life's Simple 7 scores and metrics at baseline. Men, free of coronary heart disease and stroke at baseline (n = 2119).

LS7-behavior score, n (%)	
Poor (0–2 points)	731 (34.5%)
Intermediate (3–4 points)	1038 (49.0%)
Ideal (5–6 points)	350 (16.5%)
LS7-behavior metrics	
Cigarette Smoking, n (%)	
Poor (current smoker)	392 (18.5%)
Intermediate (former, quit ≤12 months)	737 (34.8%)
Ideal (never or quit >12 months)	990 (46.7%)
Physical Activity, n (%)	
Poor (no exercise)	1303 (61.5%)
Intermediate (<150 min of moderate exercise or <75 min of vigorous exercise/week)	372 (17.6%)
Ideal (≥150 min of moderate exercise or ≥75 min of vigorous exercise/week)	444 (20.9%)
Adherence to Mediterrean diet, n (%)	
Poor (0–2 points, Mediterranean diet score^)	259 (12.2%)
Intermediate (3–5 points, Mediterranean diet score^)	1213 (57.2%)
Ideal (6–9 points, Mediterranean diet score^)	647 (30.5%)
LS7-health score, n (%)	
Poor (0–3 points)	494 (23.3%)
Intermediate (4–5 points)	1058 (49.9%)
Ideal (6–8 points)	567 (26.8%)
LS7-health metrics	
Body weight, n (%)	
Poor (BMI ≥ 30 kg/m^2)	431 (20.3%)
Intermediate (BMI 25–29.99 kg/m^2)	1021 (48.2%)
Ideal (BMI < 25 kg/m^2)	667 (31.5%)
Total cholesterol, n (%)	
Poor (≥240 mg/dL)	447 (21.1%)
Intermediate (200–239 mg/dL or treated to goal)	1106 (52.2%)
Ideal (<200 mg/dL, untreated)	566 (26.7%)
Blood pressure, n (%)	
Poor (SBP ≥ 140 or DBP ≥ 90 mmHg)	464 (21.9%)
Intermediate (SBP 120–139 mmHg or DBP 80–89 mmHg or treated to goal)	1430 (67.5%)
Ideal (SBP/DBP < 120/80 mmHg, untreated)	225 (10.6%)
Blood glucose, n (%)	
Poor (≥126 mg/dL)	225 (10.6%)
Intermediate (100–125 mg/dL or treated to goal)	630 (29.7%)
Ideal (<100 mg/dL, untreated)	1264 (59.7%)

^: score by Trichopoulou A, et al., New Engl J Med 2003;348:2599–608. Abbreviations: LS7 = Life's Simple 7; BMI = Body Mass Index; SBP=Systolic Blood Pressure; DBP = Diastolic Blood Pressure. Full details on measurement methods and scoring are reported in the Supplementary Material.

behavior and LS7-factor scores were modestly, positively correlated (Spearman correlation coefficient: 0.087, p-value <0.0001). Men with ideal physical activity were less likely to be current smokers and more likely to have higher adherence to the Mediterranean diet. Furthermore, physical activity was negatively correlated with BMI, blood pressure and blood glucose, and positively correlated with total cholesterol (Table S3), mainly through the HDL-fraction (not shown).

Summary statistics for exposures are reported in Table S4; the sample

Table 2
Association between Life's Simple 7 scores and air pollutants. Men, free of coronary heart disease and stroke at baseline (n = 2119).

	$PM_{2.5}$		PM_{10}		NO_2		O_3	
	Mean Difference (95%CI)	p-val	Mean Difference (95%CI)	p-val	Mean Difference (95%CI)	p-val	Mean Difference(95%CI)	p-val
LS7-behavior score								
Poor	0.271 (0.070; 0.471)	0.03	0.183 (−0.049; 0.414)	0.30	0.118 (−0.211; 0.447)	0.75	−0.066 (−0.429; 0.298)	0.64
Intermediate	0.195 (0.013; 0.377)		0.125 (−0.086; 0.335)		0.040 (−0.259; 0.340)		−0.150 (−0.494; 0.194)	
Ideal	Ref		Ref		Ref		Ref	
LS7-factor score								
Poor	−0.115 (−0.307; 0.076)	0.49	−0.079 (−0.296; 0.139)	0.77	0.025 (−0.288; 0.338)	0.94	−0.270 (−0.605; 0.064)	0.12
Intermediate	−0.067 (−0.227; 0.094)		−0.026 (−0.209; 0.156)		0.047 (−0.217; 0.309)		0.037 (−0.245; 0.318)	
Ideal	Ref		Ref		Ref		Ref	

Mean difference (and 95% Confidence Intervals, CI): difference in the air pollutant annual mean (in $\mu g/m^3$) from the reference category, as the beta-coefficient from single-pollutant linear regression models, adjusting for individuals' age and education, area-based deprivation (quintiles) and census area.

Table 3
Hazard ratios for incident coronary heart disease or ischemic stroke associated with one interquartile range increase in $PM_{2.5}$, PM_{10}, NO_2 and O_3. Men, free of coronary heart disease and stroke at baseline (n = 2119).

Endpoint, pollutant	Model 1 (M1)			M1 + LS7-behavior			M1 + LS7-factor		
	HR	(95%CI)		HR	(95%CI)		HR	(95%CI)	
iMACE (n = 160)									
$PM_{2.5}$	1.24	(1.02;	1.50)	1.22	(1.01;	1.47)	1.24	(1.02;	1.51)
PM_{10}	1.22	(1.02;	1.47)	1.21	(1.01;	1.45)	1.22	(1.02;	1.47)
NO_2	1.20	(0.92;	1.56)	1.19	(0.92;	1.54)	1.19	(0.92;	1.54)
O_3	1.16	(0.89;	1.50)	1.17	(0.90;	1.52)	1.18	(0.91;	1.53)
CHD (n = 121)									
$PM_{2.5}$	1.14	(0.92;	1.41)	1.13	(0.92;	1.39)	1.15	(0.93;	1.42)
PM_{10}	1.13	(0.93;	1.39)	1.13	(0.92;	1.37)	1.14	(0.93;	1.39)
NO_2	1.14	(0.85;	1.54)	1.14	(0.85;	1.52)	1.13	(0.84;	1.52)
O_3	1.16	(0.86;	1.56)	1.16	(0.86;	1.57)	1.18	(0.88;	1.59)
Ischemic stroke (n = 43)									
$PM_{2.5}$	1.67	(1.09;	2.55)	1.60	(1.06;	2.42)	1.66	(1.09;	2.55)
PM_{10}	1.71	(1.12;	2.61)	1.66	(1.10;	2.51)	1.70	(1.11;	2.59)
NO_2	1.56	(0.90;	2.70)	1.52	(0.89;	2.59)	1.54	(0.89;	2.67)
O_3	1.30	(0.77;	2.19)	1.31	(0.78;	2.20)	1.31	(0.78;	2.21)

The sum of coronary heart disease (CHD) and ischemic stroke events is larger than the total number of iMACE events as some individual had more than one event type during follow-up. Model 1 (M1): single-pollutant Cox regression model, with attained age during follow-up on the time scale, education, deprivation index (quintiles), census area, and each air pollutant as linear predictor. Hazard Ratios (HR) and 95% Confidence Intervals (CI) are expressed for 1 IQR width increase in air pollutant, namely: $PM_{2.5} = 1.93\ \mu g/m^3$; $PM_{10} = 2.10\ \mu g/m^3$; $NO_2 = 4.27\ \mu g/m^3$; $O_3 = 4.69\ \mu g/m^3$.

Table 4
Interactive effects of air pollutants with cardiovascular health on the risk of first iMACE during follow-up. Men, free of coronary heart disease and stroke at baseline (n = 2119).

	No. of events	$PM_{2.5}$			PM_{10}			NO_2			O_3		
		HR	(95%CI)		HR	(95%CI)		HR	(95%CI)		HR	(95%CI)	
LS7-behavior													
Poor	65	1.45	(1.07;	1.97)	1.46	(1.19;	1.97)	1.50	(1.00;	2.24)	1.30	(0.91;	1.86)
Intermediate	73	1.29	(1.01;	1.66)	1.26	(0.99;	1.59)	1.17	(0.88;	1.63)	1.14	(0.79;	1.64)
Ideal	22	0.68	(0.49;	0.94)	0.73	(0.54;	0.98)	0.68	(0.40;	1.14)	0.89	(0.39;	2.02)
Wald heterogeneity test p-value			0.001			0.002			0.05			0.67	
LS7-factor													
Poor	45	1.15	(0.84;	1.55)	1.19	(0.88;	1.60)	1.13	(0.75;	1.71)	1.36	(0.91;	2.02)
Intermediate	85	1.29	(0.99;	1.68)	1.22	(0.95;	1.56)	1.13	(0.84;	1.53)	1.15	(0.81;	1.63)
Ideal	30	1.27	(0.87;	1.85)	1.30	(0.91;	1.86)	1.59	(0.87;	2.90)	0.92	(0.45;	1.90)
Wald heterogeneity test p-value			0.82			0.92			0.55			0.62	

Hazard Ratios (HR) and 95% Confidence Intervals (CI) from single-pollutant Cox regression models, with attained age during follow-up on the time scale, education, deprivation index (quintiles), census area as covariates, each air pollutant as linear predictor, the relevant LS7 score, and two air pollution*LS7 score interaction terms. HR and 95%CI are expressed for 1 IQR width increase in air pollutant, namely: $PM_{2.5} = 1.93\ \mu g/m^3$; $PM_{10} = 2.10\ \mu g/m^3$; $NO_2 = 4.27\ \mu g/m^3$; $O_3 = 4.69$.

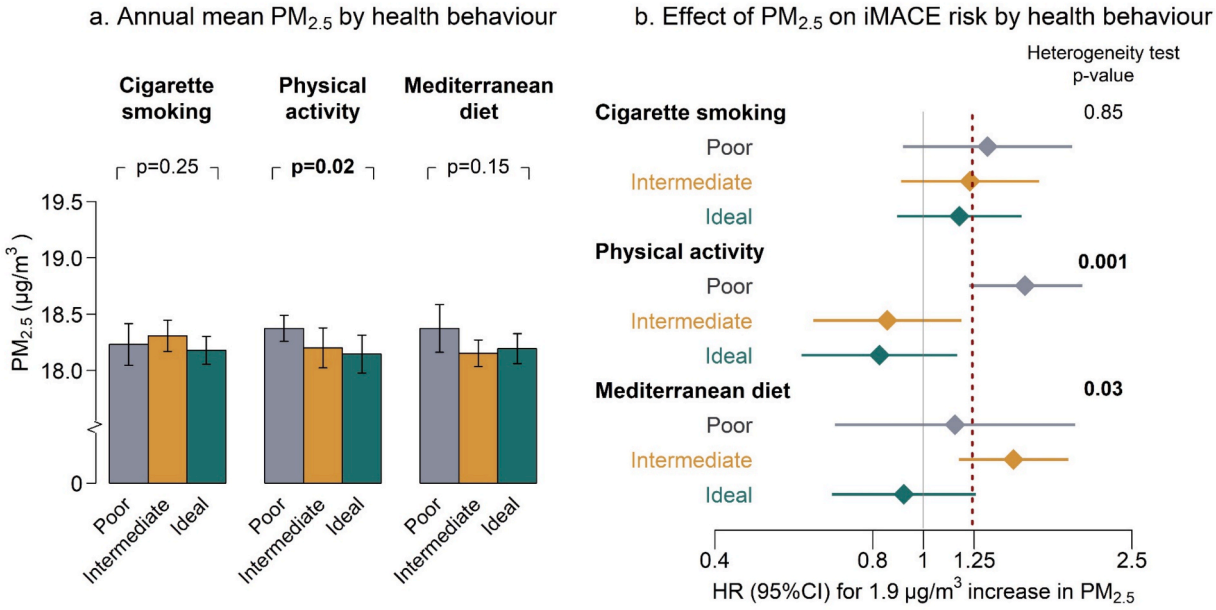

Fig. 1. Mean difference in $PM_{2.5}$ by lifestyles (panel a; ideal as reference), and interactive effects of $PM_{2.5}$ with smoking, physical activity and adherence to the Mediterranean diet on the risk of first iMACE during follow-up (panel b). Men, free of coronary heart disease and stroke at baseline (n = 2119). Bars in panel a are the confidence intervals around the means. In panel b, the red dashed line represents the overall effect of $PM_{2.5}$ on the composite endpoint (Model 1 in Table 3). The definition of "poor", "intermediate" and "ideal" for each of the three healthy behavior metrics are in Table S1 of Supplementary Material. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mean ± SD 12-month average $PM_{2.5}$, PM_{10}, NO_2 and O_3 concentrations at baseline were 18.6 ± 1.8, 25.6 ± 2.1, 32.3 ± 3.4 and 74.6 ± 3.0 µg/m^3, respectively. $PM_{2.5}$ and PM_{10} were positively correlated with NO_2 and O_3 concentrations; while O_3 was negatively correlated with NO_2, as previously observed in our urban setting (Veronesi et al., 2022; Veronesi et al., 2025) (Table S4).Yearly PM and NO_2 mean concentrations in the city of Varese remained above the EU guideline limits during the entire follow-up (Table S5). LS7-behavior was inversely associated with $PM_{2.5}$, men with poor and intermediate vs. ideal score being more exposed (p-value = 0.03; Table 2). These associations were mostly driven by physical activity (Fig. 1 panel a). Conversely, we observed no association between pollutants and the LS7-factor score.

During 7.6 years of median follow-up time (25th-75th percentiles: 6.9–8.3 years) we observed 160 first iMACE, corresponding to a crude rate of 10.4 per 1,000 person-years. Men with poor vs. ideal LS7-factor showed higher event rates, consistently across event types; while the associations between LS7-behavior with the endpoints were slightly weaker (Table S6). After the adjustment for confounders, for every IQR width increase in exposure to $PM_{2.5}$ we estimated a 24% increased risk of iMACE (95%CI: 1.02–1.50; Model 1 in Table 3). The association was consistent for PM_{10} (HR = 1.22, 95%CI: 1.02–1.47); and positive but not statistically significant for NO_2 and O_3. Of note, pollutants were more strongly associated with ischemic strokes than with coronary heart disease. Further separate adjustments for LS7-behavior or LS7-factor scores did not substantially modify these associations (Table 3). Finally, bi-pollutant models (Table S7) suggested that $PM_{2.5}$ and PM_{10} might enhance risk independently of NO_2 and O_3; while NO_2 risk excess was completely explained by PM co-exposure.

We found evidence of interaction between $PM_{2.5}$, PM_{10}, and NO_2 with the LS7-behavior score (Table 4; Wald tests p-values for heterogeneity: all < 0.05), the effects being the most detrimental (up to 50% per IQR width increase) in men displaying poor lifestyles. Conversely, men displaying ideal LS7-behavior had their risk excesses due to PM exposure mitigated ($PM_{2.5}$: HR = 0.68, 95%CI: 0.49–0.94; PM_{10}: HR = 0.73, 95%CI: 0.54–0.98; Table 4). For $PM_{2.5}$ we estimated E-values of 2.28 (point estimate) and 1.64 (lower bound of the 95% confidence interval) to "explain away" the risk excess in men with poor vs. ideal LS7 due to the interaction. Sensitivity analyses on 24-month exposures, as well as in the sub-sample of individuals with no residential mobility during follow-up, substantially confirmed these findings (Table S8-S9). On the absolute scale, the interaction between LS7-behavior and $PM_{2.5}$ yielded additional 7.7 (95%CI:2.8–12.5) events per 1,000 person-years. These interactive effects were mostly driven by physical activity and Mediterranean diet for $PM_{2.5}$ (Fig. 1 panel b) and for NO_2 (Fig. S1 panel b). Conversely, we observed no effect modification due to the LS7-factor (Table 4); nor we detected any effect modification due to anti-hypertensive or lipid lowering treatments in those with poor or intermediate LS7-factor (data not shown).

4. Discussion

In our cohort of senior men free of CVD at baseline, every 1.93 µg/m^3 increase in 12-month exposure to $PM_{2.5}$ was associated with a 24% increased risk of a first major ischemic cardiovascular event during follow-up, and with 67% increased risk of ischemic stroke, independently of individual- and area-based confounders. The strength of these associations are coherent with recent literature (de Bont et al., 2022; Zhu et al., 2021; Alexeeff et al., 2021; Yuan et al., 2019). LS7-behavior emerged as important effect modifier for the $PM_{2.5}$ to cardiovascular incidence association, with 7.7 additional events per 1,000 person-years due to the interaction. Indeed, men engaging with ideal behaviors had their risk excess due to $PM_{2.5}$ exposure mitigated, the main drivers being engaging in recommended levels of physical activity and high adherence to the Mediterranean diet. On the other hand, men adopting unhealthy behaviors were the most susceptible to the detrimental effects of $PM_{2.5}$. Findings for NO_2 and O_3 were broadly consistent with those for $PM_{2.5}$, though weaker, and the bi-pollutant models suggested a predominant role for $PM_{2.5}$ in driving CVD risk. Recent studies in the nearby metropolitan area of Milan (Magnoni et al., 2021) and in a low-exposure nation-wide setting (Olaniyan et al., 2022) reached similar conclusions. Other authors described a detrimental role of O_3 on cardiovascular and respiratory outcomes in presence of elevated ozone levels (Olaniyan et al., 2022) or elevated PM co-exposure (Liu et al., 2023; Veronesi et al., 2025). All considered, our results reinforce the role of

fine PM as prime mover of air pollutants-related CVD risk, through multiple complex biological mechanisms, including oxidative stress, endothelial dysfunction, systemic inflammation, and dysregulation of the autonomic nervous system (Schraufnagel et al., 2019; Schraufnagel et al., 2019). The impact of our findings in a highly-sensitive population for cardiovascular prevention such as middle-aged and older men is two-fold. First, the interaction between cardiovascular health and $PM_{2.5}$ calls for closer integration of pollutants – now substantially overlooked (Braunwald, 2023) – into cardiovascular risk assessment tools. Second, we sustain comprehensive lifestyle approaches, targeting physical activity and healthy diet, as personal strategies to mitigate the $PM_{2.5}$ adverse effects on cardiovascular risk (Bonanni and Newman, 2024). Local efforts to implement healthier built environments in urban settings are then advocated (Münzel et al., 2026).

Men with poor *health behaviors*, and in particular with poor physical activity, were more exposed to $PM_{2.5}$. This finding is in agreement with the idea that high-traffic urban areas might prevent people from engaging in physical activity (Tainio et al., 2021): in our sample, three of the five most frequent activities were outdoor (walking, cycling and jogging). When added to Cox models, the LS7-behavior score modestly modified the risk excesses due to $PM_{2.5}$, possibly due to the weak association with the endpoint observed in our sample. We add the notion that men with a cluster of unhealthy behaviors are more susceptible to the detrimental effects of $PM_{2.5}$. These subjects constitute nearly 35% of our sample, consistent with contemporary European reports (OECD, 2024), and could benefit the most from an early adoption of the EU air quality target limits. Smoking exerts a negative effect on cardiovascular risk, likely acting synergistically with air pollution and partly through the same mechanisms related to oxidative stress (Mallah et al., 2023). Poor sport physical activity has been shown to increase cardiovascular risk in adults (Ferrario et al., 2018; Ferrario et al., 2019); and individuals who engage in any regular physical activity while living in a highly polluted environment have lower cardiovascular risk than those living in a less polluted environment but are sedentary (Kim et al., 2020). Of note, in the same study the rate ratio for CVD incidence contrasting high vs. low $PM_{2.5}$ amongst those engaging high frequency ($\geq$5 times/week) of moderate to vigorous physical activity was 0.84, coherent with the HRs below 1 reported in our study for the effect of $PM_{2.5}$ in men with ideal physical activity and ideal LS7-behavior. Finally, one large cohort study in the US found an interactive effect between $PM_{2.5}$ and adherence to the Mediterranean diet on CVD mortality (Lim et al., 2019). Questionnaires assessing lifestyles in our study were intended to capture long-lasting and habitual behaviors, including time since start/quit smoking, habitual physical activity and dietary intake over the past year (Ferrario et al., 2018; Lasalvia et al., 2021). These may mark oxidative stress and systemic inflammation (Lechner et al., 2020), two putative biological pathways also for the link between $PM_{2.5}$ and CVD (de Bont et al., 2022; Schraufnagel et al., 2019). However, epidemiological evidence so far linking long-term exposure to $PM_{2.5}$ to inflammatory markers is scanty and inconsistent (Tang et al., 2020). Our findings suggest that chronic exposure to $PM_{2.5}$ may trigger ischemic cardiovascular events in individuals with heightened systemic inflammation and a reduced ability to modulate endogenous antioxidant defenses related to their unhealthy behaviors. Triggering may occur through $PM_{2.5}$'s capacity to promote coagulation and impair fibrinolysis, leading to an hypercoagulability state that increases the risk of thrombotic events in susceptible individuals (Robertson and Miller, 2018). The following points are in support with our interpretation. First, it aligns well with $PM_{2.5}$ conferring greater excess risk for ischemic stroke than coronary heart disease, both in our study and in the literature (Alexeeff et al., 2021). Second, exposure windows closer in time to incident CVD events contribute the most to $PM_{2.5}$ excess risk (Kriit et al., 2022), as also observed in our sensitivity analyses on cumulative 24-month exposure, again suggesting a triggering mechanism. Finally, the clustering of at least two "ideal" healthy behaviors – rather than adopting a single one – is needed to offset the harmful effects of $PM_{2.5}$. Of note, physical activity and high adherence to the Mediterranean diet played a role in mitigation, possibly due to their beneficial effects on plaque vulnerability, other than for their anti-inflammatory (Lechner et al., 2020; Wu et al., 2026) and anti-atherogenic actions (Lechner et al., 2020). In addition, people who adopt ideal behaviors may be more aware of their residency pollutants' levels, and take actions to reduce their outdoor exposures.

We did not find evidence of interaction between the LS7-factor score and $PM_{2.5}$. It is worth mentioning that the health metrics included in the LS7-factor score define *control* of blood pressure, total cholesterol and glucose, as the "poor" and the "intermediate" categories comprise both untreated and treated-at-target individuals. Literature suggests that treatments such as beta-blockers and statins might mitigate the adverse effects of $PM_{2.5}$ through their anti-inflammatory and antioxidant properties, as well as through their effects on the autonomic system and heart rate variability (Grifoni et al., 2025). These effects may have contributed to the observed result, although we did not find indication of treatment-related mitigation in our sample. Furthermore, LS7-factor lacked of a consistent association with $PM_{2.5}$. With respect to long-term $PM_{2.5}$ exposure, the literature conveys on increased blood pressure and risk of hypertension (de Bont et al., 2022) and with higher risk of diabetes (Rajagopalan et al., 2024). Conversely, there is no convincing evidence on increasing total cholesterol levels (Gaio et al., 2019), and the link with obesity in European adults is weak (Huang et al., 2020). Future studies might better elucidate these relationships and estimate the presence of independent effects of $PM_{2.5}$ on plaque accumulation and atherosclerosis through metabolic dysfunction (de Bont et al., 2022).

We acknowledge some study limitations. First, we did not include women due to event number considerations, hence generalization is needed. Our main definition of long-term exposure is based on the average in the year before recruitment, as common in the literature (Yuan et al., 2019; Hu et al., 2024; Kim et al., 2020). Pollutants' concentrations in Varese were consistently above the EU limits also during the COVID-19 pandemic years, in line with the literature suggesting an impact of lockdown on pollutants in urban settings limited to short-period changes in NO_2 (Gualtieri et al., 2020). In addition, sensitivity analyses using 24-month average as exposures, and restricted to the subsample with no residential mobility during follow-up, substantially confirmed effect modification. Taken together, these strengthen the confidence on our metrics being representative of chronic exposures. Although we were able to adjust for individuals' education, area-based deprivation and census area capturing shared neighborhood characteristics, the relatively limited within-city exposure contrast may increase susceptibility to residual confounding due to spatially correlated factors such as built environment, traffic, noise, and greenness. As guidance, we reported the E-value for effect heterogeneity (Mathur et al., 2022), whose value is much larger than the hazard ratios for myocardial infarction risk recently estimated for noise and lack of greenness (Poulsen et al., 2023). Then, we cannot completely rule out unmeasured confounding but the entire analytical plan suggests that our findings might be reasonably robust to it. The recent update of the cardiovascular health guidelines added sleep duration to the behavioral domain (Lloyd-Jones et al., 2022). We collected self-reported sleep duration in a subset of individuals; due to sample size considerations, we did not include the metric in our analysis. Study strengths include the high participation rate (65% in men) and the low attrition during follow-up (4 individuals lost). We did not find geographic patterns within the city related to participation, suggesting that it might have been independent of air pollution levels. We were able to fully characterize cardiovascular health profiles, and in particular the behavioral domains, with very low prevalence of missing data. All these factors might have limited selection bias. Furthermore, the exclusion of individuals with cardiovascular disease at baseline might have limited residual confounding by health status in the interplay between pollutants and lifestyles. Modelled pollutants' concentrations showed reasonably robustness compared to local measurements, which may have limited measurement error. Finally,

although the effect modification of LS7-behavior we observed grounds on solid biological pathways, and its pattern was consistent across pollutants and sensitivity analyses, our findings deserve confirmation with larger sample sizes. To increase external validity and facilitate replication, our cardiovascular health scores rely on a well-established, multidimensional framework and on published thresholds to define categories (Lloyd-Jones et al., 2010; Radovanovic et al., 2023; Lim et al., 2019).

To conclude, in our cohort representative of contemporary urban outdoor $PM_{2.5}$ levels, long-term exposure to $PM_{2.5}$ was associated with an increased risk of a first coronary heart disease or ischemic stroke event in middle aged and older men. Interpreted in light of existing knowledge, our findings suggest that chronic exposure to $PM_{2.5}$ may trigger acute events in individuals with elevated systemic inflammation due to a clustering of unhealthy behaviors. These form a large percentage of the population in Europe, and can benefit the most from an early implementation of the EU air quality limits. In the transition period, the promotion of healthy lifestyles mitigating the harmful effects of long-term exposure to $PM_{2.5}$ on the cardiovascular system should be prioritized, in particular in susceptible individuals, to reduce the overall burden of disease.

CRediT authorship contribution statement

Giovanni Veronesi: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Marco Campana:** Writing – original draft. **Emanuele Maria Giusti:** Writing – review & editing, Methodology. **Francesco Gianfagna:** Writing – review & editing, Funding acquisition, Conceptualization. **Sara De Matteis:** Writing – review & editing. **Marco Mario Ferrario:** Writing – review & editing, Funding acquisition, Conceptualization.

Funding

This paper was developed within the project funded by Next Generation EU – "Age-It – Ageing well in an ageing society" project (PE0000015), National Recovery and Resilience Plan (NRRP) – PE8 – Mission 4, C2, Intervention 1.3". The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. The baseline visit of the RoCAV cohort study was supported by the Health Administration of Lombardy Region (Decr. RL 13465, December 22, 2010). The funders had no role in study design, data collection, analysis, interpretation, and writing of the manuscript.

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.

Acknowledgments

The authors are grateful to all the RoCAV study participants. The RoCAV cohort study follow-up activities were made possible with the contribution of dr. Zucchi Nicoletta, Head of the Demographic Services, Municipality of Varese, as well as of dr. Sarah Grossi and dr. Mattia Sersale, for active vital status ascertainment of study participants; and of the management of the Local Health Agency (ATS) Insubria for record linkage activities with hospital records and death certificates. The authors also acknowledge the contribution of dr. Ilaria Mato, for data quality assessment of physical activity data; and of dr. Daniele Loffredo, for the adjudication of coronary heart disease and stroke events during follow-up. We also acknowledge dr. Hannah Forrest Ferrario for her careful revision of the English language of this paper. Exposome surfaces were made available through the following projects: EXPANSE (EC H2020, grant agreement No 874627) and EXPOSOME-NL. EXPOSOME-NL is funded through the Gravitation program of the Dutch Ministry of Education, Culture, and Science and the Netherlands Organization for Scientific Research (NWO grant number 024.004.017).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2026.110326.

Data availability

The datasets generated and analyzed during the current study cannot be made available to third parties due to obligations with the EXPANSE project data.

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