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Original Article

Association between long-term exposure to air pollution and incidence of peripheral artery disease: Evidence from a longitudinal study

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ABSTRACT

Introduction: The association between air pollution and cardiovascular diseases is well established. However, fewer studies focused on the relationship between air pollution and peripheral artery disease (PAD), notwithstanding that not only it is a predictor of CVD mortality but also that incidence is globally rising, particularly in low-middle income countries.

Objectives: The aim of this study is to estimate the association between long-term exposure to air pollutants and the incidence of PAD in the Rome Longitudinal Study (RLS) during 2011–2019.

Methods: Using the Health Information Systems, we identified the first episodes of hospitalizations with discharge diagnosis for PAD (ICD-9 codes: 440.20-24; 444.0; 444.21; 444.22; 444.81; 447.1), lower limb vascular surgery (ICD-9 codes: 38.18; 39.29; 39.50; 39.90; 84.11; 84.12; 84.15; 84.17) or drug prescription (ATC code: B01AC23) in the period 2011–2019. In order to focus on incidence, we excluded from the population at risk prevalent cases based on hospital discharges in the 10 years before enrolment (October 9th, 2011). We assigned to the participants one-year average exposure to $PM_{2.5}$, NO_2 and black carbon (BC) from the ELAPSE Europe-wide hybrid land-use regression (LUR) models at 100 m^2 spatial resolution on the basis of their baseline geocoded addresses. We also applied Cox regression models adjusted for individual and area-level covariates. The estimates were expressed as hazard ratios (HR) and 95 % confidence intervals (95 % CI) per pollutant-specific interquartile range (IQR) increase. We also analyzed any effect modification by socio-demographic and comorbidity variables and explored concentration-response curves using natural splines with 3 degrees of freedom.

Results: Starting from a population at risk of 1,719,475 subjects aged 30 years or above, a total of 14,629 incident cases were identified. An IQR (1.13 μg/m^3) increase in $PM_{2.5}$ was positively associated with a HR of 1.011 (95 % CI: 0.988, 1.034). Positive associations were also obtained for NO_2 ([IQR 7.86 μg/m^3] HR: 1.022 (95 % CI: 0.998, 1.048)) and black carbon ([IQR 0.39 x10^{-5}/m] HR: 1.020 (95 % CI: 0.994, 1.047)). Effect modification analysis showed stronger associations when considering males and individuals in the 55–69 age class. Concentration-response curve for NO_2 showed a linear shape, with increases of risk already at low concentrations.

Conclusions: Long-term exposure to $PM_{2.5}$, NO_2 and BC is associated with an increased incidence of PAD, and male subjects and individuals aged between 55–69 years were at greater risk.

1. Introduction

Cardiovascular disease (CVD) is one the most frequent cause of death and disability globally, including Europe. CVD causes 3.9 million annual deaths in the European Union and the loss of 26 million disability-adjusted life years (DALYs) [1]. Among CVD, peripheral artery disease (PAD) is the third most frequent clinical manifestation of atherothrombosis after coronary artery disease and stroke. It affects more than 200 million people globally (236 million in 2015) and its prevalence is increasing not only in high-income but also in low-middle-income countries [2].

PAD is one of the major risk factors of cardiovascular morbidity and

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mortality, even in the asymptomatic phase, owing to the fact that patients have a more severe pattern of coronary artery disease manifested by a higher burden of multivessel disease [3]. This notwithstanding, PAD received relatively less attention than the other main atherothrombosis diseases, such as coronary artery disease and stroke. For instance, it is well-established that the major risk factors for PAD are, beside age, cigarette smoking, hypertension, diabetes and hypercholesterolemia, but there is a paucity of reports on the role of exposure to such ubiquitous environmental risk factors as ambient air pollution and its main components [4–6].

Air pollution has emerged as a pressing global health concern, with particulate matter (PM), nitrogen dioxide (NO_2), and black carbon (BC) identified as contributors to adverse health outcomes. Among the various pollutants, fine particulate matter with a diameter of 2.5 micron or less ($PM_{2.5}$) has garnered significant attention due to its ability to penetrate deep into the respiratory system and enter the bloodstream, exerting systemic effects on human health [7]. Concurrently, NO_2, primarily emitted from vehicle exhaust and industrial processes, and BC, a by-product of incomplete combustion of fossil fuels and biomass, have been linked to respiratory ailments and cardiovascular diseases [8,9].

Recent evidence has highlighted the role of long-term exposure to even low levels of air pollution for many health outcomes [10–12]. A multicohort study called ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) involved several European well characterized cohorts in order to investigate the effects of low-level air pollution on health [10] and found a significant increase in the risk of natural-cause, cardiovascular, respiratory, and lung cancer mortality. These findings suggest the need to implement and report studies aimed at providing evidence on the chronic effects of air pollution on health outcomes.

With this background and gaps of knowledge, the aim of this study was to investigate longitudinally the association between the incidence of PAD and long-term exposure to such ambient air pollutants as $PM_{2.5}$, NO_2 and BC. This study was carried out in a population-based cohort from the Italian metropolitan area of Rome, the Rome Longitudinal Study (RLS), in the 9-year period 2011–2019.

2. Material and methods

2.1. Study design and population

The study cohort was defined from the linkage between the 2011 Italian census and the Rome Municipal Register's data [13–15] providing socio-demographic information on all citizens of the city of Rome aged more than 30 years at the start of the follow-up. To each subject of the cohort, we linked health data provided by the Health Information Systems. Individuals were observed from the 9th of October 2011 (baseline) until the occurrence of events such as emigration, death, the PAD outcome of interest or the end of the 9-year follow-up period (31st of December 2019), whichever came first.

2.2. Outcome

Incident cases of PAD were defined as those subjects who had a first hospital discharge diagnosis (International Classification of Diseases, 9th revision – ICD-9 codes: 440.20-24; 444.0; 444.21; 444.22; 444.81; 447.1), underwent a first lower limb vascular surgery (ICD-9 codes: 38.18; 39.29; 39.50; 39.90; 84.11; 84.12; 84.15; 84.17), or received a first prescription of cilostazol, a drug that in Italy is dispensed only for patients with PAD (ATC code: B01AC23), during the period between the enrolment date and the end of the follow-up (details in the supplementary material). We considered the hospital discharge diagnoses and surgeries that occurred both as primary or secondary diagnoses or interventions.

To ensure the identification of newly diagnosed cases of PAD during the study period, we defined the population at risk as subjects free from the disease at baseline. Therefore, we excluded prevalent cases in whom the outcome of interest had occurred in the 10 years before enrolment for hospital diagnosis or surgery, or in the 5 years before enrolment for drug prescriptions.

2.3. Exposures

We considered one-year (2010) average estimates of $PM_{2.5}$, NO_2 and BC from the ELAPSE Europe-wide hybrid land-use (LUR) models at 100 m^2 [16] as exposures to air pollution. Briefly, in these models, concentration levels were obtained by the combination of AirBase routine monitoring data of the European Environmental Agency (EEA) and ad hoc ESCAPE monitoring data, incorporating satellite observations, dispersion model estimates, land use and traffic data as spatial predictors. We then assigned exposures for each subject at baseline residence addresses.

2.4. Covariates

From the census records we collected a number of covariates on individual information: age at the baseline, sex, marital status (single, married, separated/divorced, widowed/widow), place of birth (Rome, elsewhere), citizenship (Italian, foreign), level of education (primary or less, secondary, high school, university or higher), and employment status (employed, seeking first employment, unemployed, retired, student, house maker, others). According to the geocoded residential addresses, we also considered area-level covariates as the census block-level socioeconomic deprivation index categorized by quintiles [13], and district-level unemployment rate, percentage of graduates and house prices [17].

2.5. Statistical analysis

Continuous variables were reported as means and standard deviations, categorical covariates as frequency and relative percentages. The analysis of the association between air pollutants and the incidence of PAD was performed by using Cox proportional hazard regression models. We applied three different adjustment models: in the first one, we adjusted for age (as time-scale) and sex; in the second, we additionally adjusted for all the other individual-level variables; and in the third, we adjusted for both individual and area-level covariates (main model). Proportional hazards assumption was tested by the Schoenfield's residuals analyses (data not shown), and covariates that did not respect that assumption were inserted in the models as strata. We also explored potential effect modifications by socio-demographic variables i.e., sex, age classes (30–54; 55–69; 70+ years) as well as the deprivation index split in three classes (low; medium; high) and the prevalence of the main risk factors for PAD (hypertension [ICD-9: 401 - 405] in the 10 years before the baseline; type 2 diabetes [ICD-9: 250 or exemption: 013.25 or drug prescription ATC code: A10 (at least 2 within 6 months)] in the 5 years before; hypercholesterolemia as defined by the use of statins [ATC code: C10AA] as proxy in the 5 years before the baseline). We included an interaction term between each exposure and the putative effect modifier in the main model and performed the Wald test. Moreover, we analyzed concentration-response functions for $PM_{2.5}$, NO_2 and BC using a spline with 3 degrees of freedom. We also performed a sensitivity analysis defining incident cases for PAD as free from hypertension in the 10 years before the baseline, type 2 diabetes (in the 5 years before the baseline) and hypercholesterolemia (use of statins in the 5 years before the baseline as proxy). Results are expressed as hazard ratios (HRs) and relative 95 % confidence intervals (95 %CI) per interquartile range (IQR) increases of pollutants. Analyses were conducted by using R statistical software (version 4.2) (http://R-project.org).

3. Results

We identified 1,739,277 subjects during the study period. After exclusion of prevalent cases and subjects with missing information (respectively 0.8 % and 0.3 % of the initial cohort), a total of 1,719,475 individuals were considered in the analyses. Table 1 shows the descriptive characteristics at baseline of the subjects involved in the study. 55 % of the cohort subjects were females and the mean age at baseline was 56.3 years (SD 15.8). The majority of them were born in Rome (54 %), married (65 %) and Italian citizens (94 %). The 50 % was employed and 23 % had high educational level, i.e. a university degree or higher. In Table 2 we report descriptive statistics of the exposures. The annual averages were 16.6 (SD 0.93) μg/m^3 for $PM_{2.5}$, 32.1 (SD 6.46) μg/m^3 for NO_2 and 2.2 (SD 0.30) x10^{-5}/m for BC and the IQRs were 1.13 μg/m^3, 7.86 μg/m^3 and 0.39 x10^{-5}/m, respectively.

In Fig. 1 the results for each model and pollutant are shown. For each pollutant the association moves from negative, when considering the model adjusted for only sex and age (Mod 1) to positive, even if not statistically significant, when including both individual and area-level information (Mod 3). The strongest signals for an adverse association with PAD were for NO_2 (HR: 1.022; 95 %CI: 0.998–1.048) and black carbon (HR: 1.020; 95 %CI: 0.994–1.047) in Mod 3.

Supplementary Table 4 presents the results for Model 3 for each pollutant when excluding from the subjects at risk of PAD those with hypertension, type 2 diabetes and hypercholesterolemia, the latter defined by the use of statin at baseline. The estimates are not statistically significant and the hazard ratios very similar to those reported in Fig. 1.

Table 3 shows the estimates of the association between air pollution and PAD, considering sex, age and the deprivation index as effect modifiers of the association between air pollution and incidence of PAD.

Table 1
Descriptive characteristics of the cohort at risk (N = 1,719,475) at baseline (9th of October 2011).

		N/mean	%/SD
Individual-level variables			
Sex	Male	771,713	44.8 %
	Female	947,762	55.1 %
Age (years)		56.2	15.8
Place of birth	Elsewhere	790,007	45.9 %
	Rome	929,468	54.0 %
Marital status	Single	386,507	22.4 %
	Married	1,112,820	64.7 %
	Separated/divorced	67,325	3.9 %
	Widower/widow	152,823	8.8 %
Education level	Primary school	293,165	17.0 %
	Middle school	394,021	22.9 %
	High school	640,893	37.2 %
	University or higher	391,396	22.7 %
Employment status	Employed	866,487	50.3 %
	Seeking first employment	10,986	0.64 %
	Unemployed	52,160	3.03 %
	Retired	473,397	27.5 %
	Student	7,381	0.43 %
	Housewife	211,597	12.3 %
	Other	97,467	5.6 %
Citizenship	Foreign	102,194	5.9 %
	Italian	1,617,281	94.0 %
Area level variables			
Deprivation index	Low	359,163	20.8 %
	Medium-low	468,267	27.2 %
	Medium	313,972	18.2 %
	Medium-high	263,343	15.3 %
	High	314,730	18.3 %
Unemployment rate (%)		6.4 %	1.3 %
Percentage of graduates		39.6	20.2
House price	Low	342,578	19.9 %
	Medium-low	339,420	19.7 %
	Medium	350,057	20.3 %
	Medium-high	361,279	21.0 %
	High	326,141	18.9 %

Similar results can be seen for the three pollutants in the study. By sex and age, there are signals of stronger effects related to males (HR: 1.017; 95 %CI: 0.989–1.046 for $PM_{2.5}$, HR: 1.034; 95 %CI: 1.004–1.065 for NO_2 and HR: 1.038; 95 %CI: 1.006–1.071 for BC) and older individuals (55–69 y.o.) (HR: 1.042; 95 %CI: 1.005–1.080 for $PM_{2.5}$, HR: 1.047; 95 %CI: 1.009–1.087 for NO_2 and HR: 1.038; 95 %CI: 0.997–1.080 for BC). Considering the deprivation index as an effect modifier, the hazard ratio (HR) was lowest in the high class of deprivation.

Supplementary Table 5 shows the estimates of the association under study when considering hypertension, type 2 diabetes and hypercholesterolemia as effect modifiers. None of the results are statistically significant, and no differences are observed between the presence and absence of the risk factors examined.

In Fig. 2 concentration-response curves of $PM_{2.5}$ and BC show similar trends, with a steeper slope at medium-high concentrations and a decrease at the highest ones. Instead, the shape of hazard ratio for NO_2 is linear, with increasing risks already at the lowest concentrations.

4. Discussion

In a population at risk of 1,719,475 individuals aged 30 years or more, incident cases of PAD were as many as 14,629. Pertaining to our background hypothesis of an association between the incidence of this atherothrombotic disease with ambient air pollution and its main components, the main findings of the present retrospective longitudinal population-based study were an increased incidence of PAD in association to a greater exposure of the particulate pollutant $PM_{2.5}$. Stronger associations have been found for other pollutants such as NO_2 and black carbon, that are traffic-related pollutants. There was clear evidence of a linear shape of the concentration-response curve for NO_2, indicating a higher risk at higher levels of this gaseous pollutant, but with risks increasing already from the lowest concentrations in accordance to previous studies [6,12]. Notwithstanding fact that the functional shape of the curve for $PM_{2.5}$ has large uncertainty, it suggests effects on the incidence of PAD even at lowest concentrations. Comparisons are difficult because previous studies on PAD [4–6] considered other air pollutants or did not assess the concentration-response curves. Furthermore, results of the exposure-response function for $PM_{2.5}$ should be taken with caution, because the ELAPSE model was able to capture only a small amount of variability in $PM_{2.5}$ exposure over the Rome domain (SD=0.93 μg/m^3, Table 2).

Other main results of the effect modification analysis showed stronger associations among males and individuals with age 55–69 years and weakest associations in highly deprived individuals. The retrospectively design of the study is unable to establish causation beyond association.

These findings extend current knowledge on the noxious effects of air pollution on the most frequent atherothrombotic cardiovascular diseases that until now was more largely available and consolidated for coronary artery and cerebrovascular disease but less so for PAD. The common mechanism of the adverse effects of ambient air pollution on atherothrombotic diseases is the development of oxidative stress leading to a low-grade systemic inflammation, i.e., the main pathophysiological trigger together with hormonal disruption and autonomic dysfunction of the local and systemic effects exerted by air pollutants [18,19].

A few epidemiological studies previously tackled the relationship between long-term exposure to air pollution and incident PAD [4–6]. A retrospective cohort study based upon an administrative database of the general population of 292,091 subjects from South Korea found that for 5,243 incident PAD cases NO_2 and sulfur dioxide but not $PM_{2.5}$ and PM_{10} were independently associated with the disease in the context of a follow-up period of 4 years [6]. An earlier small study conducted in the northeastern USA found an association between PAD hospitalizations and a prediction model of acute and chronic exposure to $PM_{2.5}$ [4]. Moreover, a nationwide cohort study from Taiwan evaluating 1588 PAD incidence cases during a 10-year follow-up found that CO and $PM_{2.5}$

Table 2
Descriptive statistics of the exposure variables.

Pollutant	Mean	SD	Min	Percentiles					Max	IQR
				5th	25th	50th	75th	95th		
$PM_{2.5}$	16.64	0.93	11.58	15.00	16.14	16.62	17.28	18.14	21.44	1.13
NO_2	32.14	6.46	10.74	20.61	28.37	32.66	36.23	42.21	87.46	7.86
BC	2.18	0.30	1.39	1.68	1.97	2.20	2.36	2.65	4.87	0.39

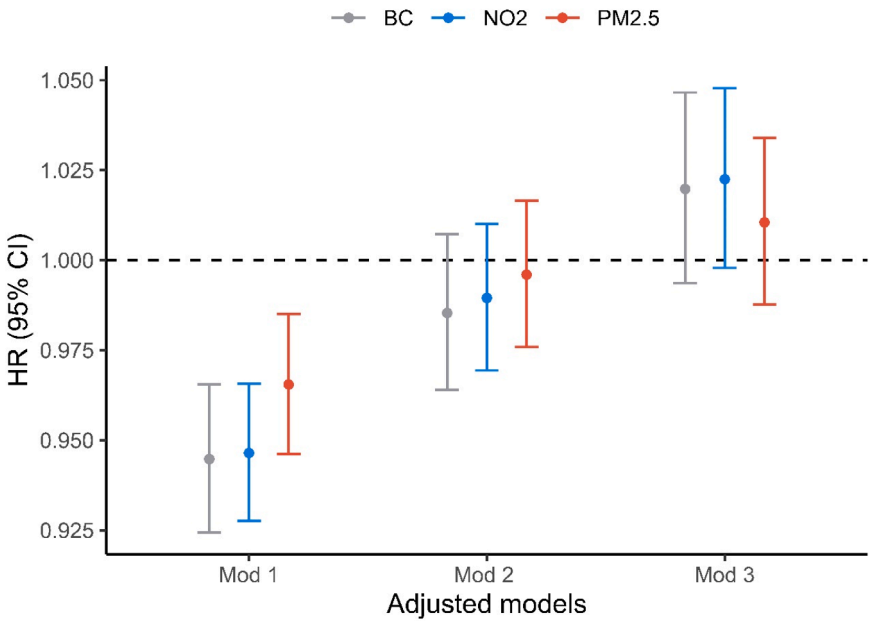

Fig. 1. Results of the association between exposure to air pollution and incidence of PAD, expressed as hazard ratios (HR) and 95 % confidence intervals (95 % CI) per pollutant-specific interquartile range (IQR) increase (IQRs: 1.13 μg/m^3 for $PM_{2.5}$, 7.86 μg/m^3 for NO_2 and 0.39 x10^{-5}/m for BC).

Table 3
Results of the association between exposure to air pollution and incidence of PAD by sex, age groups and deprivation index, expressed as hazard ratios (HR) and 95 % confidence intervals (95 % CI) per pollutant-specific interquartile range (IQR) increase (IQRs: 1.13 μg/m^3 for $PM_{2.5}$, 7.86 μg/m^3 for NO_2 and 0.39 x10^{-5}/m for BC).

		N	cases	$PM_{2.5}$				NO_2				BC			
				HR	95 % CI		p-value*	HR	95 % CI		p-value*	HR	95 % CI		p-value*
Sex	*Male*	771,713	8733	1.017	0.989	1.046	0.457	**1.034**	1.004	1.065	0.182	**1.038**	1.006	1.071	0.056
	Female	947,762	5896	1.001	0.968	1.036		1.006	0.971	1.041		0.994	0.958	1.032	
Age	*30-54*	881,379	1841	0.952	0.900	1.007	0.022	0.963	0.909	1.020	0.043	0.953	0.895	1.015	0.060
	55-69	440,560	4791	**1.042**	1.005	1.080		**1.047**	1.009	1.087		1.038	0.997	1.080	
	70+	397,536	7997	1.006	0.976	1.036		1.022	0.991	1.054		1.024	0.991	1.058	
Deprivation	*Low*	827,430	6420	1.026	0.993	1.059	0.064	**1.039**	1.005	1.075	0.030	**1.036**	1.000	1.073	0.019
Index	*Medium*	313,972	2521	1.040	0.989	1.094		**1.062**	1.011	1.115		**1.065**	1.011	1.122	
	High	578,073	5688	0.979	0.945	1.015		0.988	0.952	1.026		0.981	0.942	1.021	

* p-values calculated using the Wald test

were strongly associated with the cumulative incidence of PAD [5]. More recently in 2023, Ma et al. [20] conducted a prospective analysis in the frame of the UK Biobank in 27,827 patients with type 2 diabetes and found that their exposure to NO_2 was positively associated not only with the incidence of coronary artery disease but also with PAD [18]. Additional important findings of this study were that effect estimates were approximately 3-fold higher for PAD than for coronary artery disease, and that the noxious effect of ambient air pollution was present also when diabetics were exposed to concentrations well below the WHO guideline limits.

The main strengths of the present study are its basis on real world data, the large sample size of incident cases identified through multiple administrative archives and a prolonged observation period. Incident cases were identified employing the 9th Revision of the International Classification of Disease, that is the classification used in the Health Information Systems and is widely used after many studies established the diagnostic accuracy and validity of ICD codes [21]. The study has limitations such as lack of individual data on an important risk factor for PAD such as smoking, but such other potential confounders as diabetes, hypertension and dyslipidemia were taken into account. Moreover, the generalization of the findings is limited by the fact that practically all the population members were from Europe, where the concentration of air pollution is lower than in Asian, African and South American countries. The finding of an association of PAD and air pollution with socioeconomic inequity among the participants is not surprising, because economically disadvantaged people tend to live in areas with more intense car traffic and poor greenness.

In conclusion these findings demonstrate that exposure to air pollution is a risk factor also for the third most frequent atherothrombotic cardiovascular disease beside coronary artery and

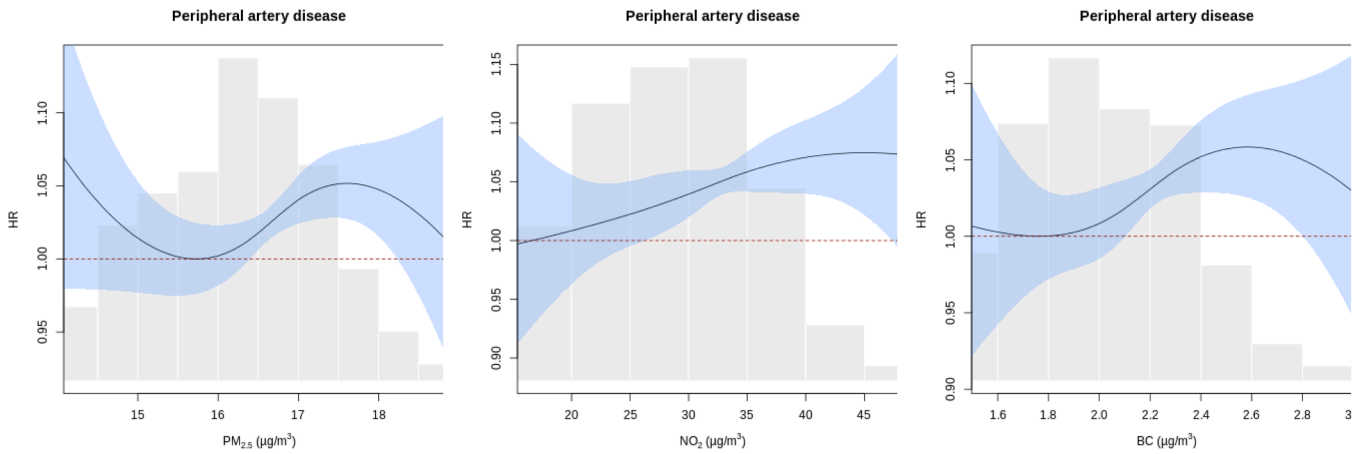

Fig. 2. Concentration-response curves of the association between air pollutants and PAD.

cerebrovascular disease. A few general recommendations are warranted. A frequent and general feeling is that exposure to air pollution is an unavoidable risk factor that can only be controlled by measures beyond the realm of the individual. Very simple measures of primary or secondary prevention are indeed feasible [22–25] and particularly cogent in people at high risk because carriers of the main risk factors for PAD such as hypertension, diabetes and dyslipidemia. Needless to say, active and passive smoking interact very strongly with air pollutants and its fight should be aggressively enforced.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.11.031.

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