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Global burden of peripheral arterial disease (1990–2021), global burden trends and the impact of blood lead on peripheral arterial disease: a multidimensional analysis based on NHANES, GBD, and Mendelian randomization

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Abstract

Objective Peripheral arterial disease (PAD) is a common cardiovascular disease that it is an important reason for the decline of patients' quality of life and the increase of family economic burden. To systematically evaluate the association between environmental lead exposure and peripheral arterial disease (PAD) and to characterize the global distribution of PAD disease burden, while exploring differences among regions with varying socioeconomic development.

Methods Using data from the National Health and Nutrition Examination Survey (NHANES), the Global Burden of Disease (GBD) database, and genome-wide association studies (GWAS), we employed multivariable logistic regression to examine the link between lead exposure and PAD. Mendelian randomization (MR) was used to infer causality, and we analyzed PAD disease burden trends across countries of differing income levels.

Results The burden on PAD patients worldwide shows a downward trend. In high SDI and high middle SDI countries, the burden of PAD gradually decreases, while in low middle SDI and low SDI countries, the burden of PAD gradually decreases. After adjusting for potential confounders, a significant dose-response relationship was observed between blood lead levels and PAD risk (OR = 1.04, 95% CI: 1.00-1.09). This association was more pronounced among males (OR = 1.07, 95% CI: 1.05–1.09), individuals with higher education (OR = 1.24, 95% CI: 1.16–1.32), and patients with hypertension (OR = 1.07, 95% CI: 1.05–1.09). MR analysis supported a causal link between lead exposure and PAD.

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Global trend analysis indicated that PAD burden is declining in high-income countries but rising in low-income regions, highlighting significant health inequities.

Conclusion Environmental lead exposure is significantly associated with increased PAD risk, with notable differences in population susceptibility. These findings underscore the necessity of environmental exposure control and tailored prevention strategies to enhance cardiovascular health worldwide.

Keywords Environmental lead exposure, Peripheral arterial disease, Mendelian randomization, Global disease burden, Health inequity

Introduction

Peripheral arterial disease (PAD) of the lower limbs is a progressive atherosclerotic vascular condition that represents a major cause of global disability and mortality [1, 2]. PAD severely diminishes quality of life and raises the risk of cardiovascular events and mortality; studies have shown that the 5-year cardiovascular mortality rate among PAD patients can reach as high as 15–20% [3, 4]. With the accelerating pace of global population aging and the widespread adoption of unhealthy lifestyles, the burden of PAD continues to increase [5, 6]. According to the Global Burden of Disease (GBD) study, the number of PAD cases worldwide exceeded 236 million in 2019, nearly doubling since 1990 [7]. More alarmingly, the disease burden differs markedly between countries, growing faster in low- and middle-income countries compared to high-income ones [8, 9]. A systematic review of 68 countries indicated an annual increase in age-standardized PAD prevalence of 3.2% in low-income regions compared to 1.8% in high-income areas [10].Traditional risk factors for PAD have centered on smoking, diabetes, and hypertension [11]. However, recent attention has been drawn to environmental influences, particularly heavy metal exposure, and their connection to cardiovascular diseases [12, 13]. Lead, a persistent environmental pollutant, enters the human body through various routes and accumulates in tissues over time [14]. Epidemiological studies have established strong links between lead exposure and hypertension and coronary artery disease [15]. Mechanistic research indicates that lead may promote atherosclerosis through pathways involving vascular calcification, oxidative stress, and inflammation [16]. Notably, even low levels of lead exposure have been implicated in heightened cardiovascular risk, offering significant public health implications [17].

However, current research on the association between environmental lead exposure and PAD has the following limitations: First, existing research mainly comes from high-income countries, and there is a relative lack of research on populations in low- and middle-income countries [18, 19]. Considering that these countries often face more serious environmental pollution problems and have limited medical resources, relevant evidence is urgently needed to guide disease prevention [20]. Secondly, traditional observational studies are difficult to effectively control the influence of confounding factors, which limits the inference of causal relationships [21]. Third, there is a lack of systematic global comparative research, making it difficult to reveal the regional differences in environmental factors and PAD patterns [22, 23]. Especially in developing countries with rapid industrialization, environmental lead exposure levels are often significantly higher than those in developed countries, but there is a serious lack of research on related health risks. By using genetic variation as an instrumental variable, the Mendelian Randomization (MR) method can overcome the confounding bias in observational studies to a certain extent and provide more reliable evidence for causal inference [24, 25]. Recent studies have discovered multiple genetic loci related to blood lead levels, providing a basis for MR analysis. In addition, the US National Health and Nutrition Examination Surveys (NHANES) have accumulated a large amount of high-quality environmental exposure data [26], while the GBD study has provided comprehensive global disease burden estimates [27]. Integrating these data sources is expected to provide more comprehensive evidence. It is worth noting that recent genomic studies have found that the genetic determinants of blood lead levels differ among different ethnic groups, suggesting that the health effects of environmental exposure may be ethnic-specific [28].

This study innovatively integrated NHANES data, GBD database and MR method to systematically evaluate the association between environmental lead exposure and PAD on a global scale for the first time, and to compare and analyze the differences between countries with different income levels. Specifically, this study aims to: (1) evaluate the strength of the association between lead exposure and PAD in the NHANES population; (2) infer the causal relationship between lead exposure and PAD through MR analysis; (3) analyze the spatiotemporal distribution characteristics of PAD disease burden in 195 countries and regions around the world; (4) compare the heterogeneity of the association between environmental lead exposure and PAD between countries with different income levels; (5) explore potential interactions and mechanisms. Recent studies have shown that the interaction between environmental factors and genetic

susceptibility may play an important role in the pathogenesis of PAD.

The findings of this study will provide important insights into the following aspects: (1) improving the PAD risk factor assessment system and taking environmental exposure into consideration; (2) guiding global environmental health policy formulation, especially heavy metal pollution prevention and control in low- and middle-income countries; (3) promoting the optimization of PAD prevention strategies and achieving precision intervention; (4) promoting international collaborative research in the field of environmental health. These contributions have important public health significance for reducing the global PAD disease burden.

Materials and methods

Study design and data sources

This study adopted a cross-sectional study design integrating multiple data sources. As shown in Fig. 1, 31 and 126 participants were initially included in the NHANES database from 2011 to 2018. After excluding participants with missing LEPAD information ($n = 21{,}981$) and missing blood lead test data ($n = 411$), 8,735 eligible participants were finally included for analysis. In addition, the study also integrated the GBD database and GWAS data based on the European population. The study was approved by the relevant ethics committee, and all participants signed informed consent.

Study population

Inclusion criteria: (1) adults aged ≥ 18 years; (2) complete LEPAD and blood lead data. Exclusion criteria: (1) pregnant women; (2) patients with severe liver and kidney dysfunction; (3) patients with missing key data. GBD data analysis covers 195 countries and regions around the world, and countries are divided into four categories according to World Bank standards: high-income, upper-middle-income, lower-middle-income, and low-income. The GWAS data used in the Mendelian randomization analysis were from people of European descent.

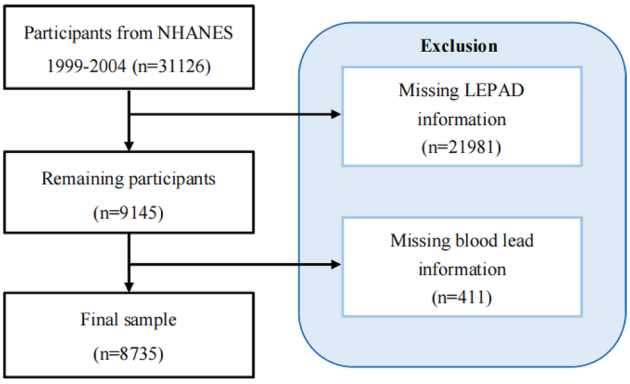

Fig. 1 Nhanes database workflow

Exposure and outcome assessment

Lead exposure assessment

Fasting venous blood samples from the NHANES population were used to measure blood lead concentrations using inductively coupled plasma mass spectrometry (ICP-MS). Participants were divided into four groups, Q1-Q4, according to the quartiles of blood lead levels. Quality control included blank samples, standards, and repeated sample analysis.

PAD diagnosis

PAD diagnosis is based on ankle-brachial index (ABI) measurement. ABI ≤ 0.9 is defined as PAD when measured by trained technicians using standardized methods. PAD burden indicators in the GBD database include age-standardized incidence, prevalence, mortality, and disability-adjusted life years (DALYs).

Covariate collection

Information on demographic characteristics (age, sex, race), socioeconomic status (education level, marital status, income), lifestyle factors (smoking, alcohol consumption, body mass index), and medical history (hypertension, diabetes) was collected through standardized questionnaires. Income levels were standardized using the income-to-poverty ratio (PIR). To capture the detailed characteristics and potential impacts of variables, we transformed continuous variables into categorical variables. Age was categorized into 20–40, 40–60, and ≥ 60 years; the PIR (Poverty Income Ratio) was divided into < 1.3, 1.3–1.85, 1.85–3.5, and ≥ 3.5; and BMI was categorized into Underweight (< 18.5), Normal weight (18.5–24.9), Overweight (25-29.9), and Obese (≥ 30).

Statistical analysis

Descriptive analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables were expressed as number of cases (percentage). The t-test, Mann-Whitney U test, or $\chi 2$ test was used for comparison between groups.

Association analysis

Multivariate logistic regression models were used to analyze the association between blood lead levels and PAD. Three stepwise adjusted models were constructed: Model 1 was unadjusted; Model 2 adjusted for demographic characteristics; and Model 3 further adjusted for socioeconomic status, lifestyle, and comorbidities. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI).

Stratified and interaction analyses

Stratified analysis was performed on pre-specified subgroups (sex, age, race, education level, etc.), and interactions were tested. Forest plots were used to present the results of subgroup analysis.

Spatiotemporal analysis

Based on GBD data, a Bayesian spatiotemporal model was used to evaluate the geographical distribution characteristics and temporal trends of the global PAD burden, focusing on analyzing the differences between different SDI regions. According to the World Bank's country income classification standards (https://blogs.worldbank.org/), GBD data were stratified into high-income, upper-middle-income, middle-income, lower-middle-income, and low-income countries to assess differences across regions with varying socioeconomic levels.

Mendelian randomization analysis

This study employed a bidirectional MR approach to analyze the causal relationship between lead exposure and PAD. First, we selected SNPs significantly associated with blood lead levels from large-scale GWAS studies ($P < 5 \times 10 - 6$) and ensured that these SNPs were not in linkage disequilibrium (r2 < 0.001). The F-statistics for all selected SNPs were greater than 10, indicating sufficient strength of the instrumental variables. We used the inverse-variance weighted (IVW) method as the primary analysis, supplemented by MR-Egger and weighted median methods for sensitivity analysis. Additionally, we validated the robustness of the results through leave-one-out analysis.

All statistical analyzes were completed using R software (version 4.0.3). A two-sided test was used, and $P < 0.05$ was considered a statistically significant difference. Type I error was controlled using multiple comparison correction. Missing data were handled using multiple imputation. Sensitivity analysis assesses the robustness of the results.

Results

Baseline characteristics of the study population

As shown in Table 1, a total of 8,636 participants were included in this study, of which 618 (7.2%) had PAD. The average age of the PAD patient group (71.00 ± 11.54 years old) was significantly higher than that of the non-PAD group (60.36 ± 13.40 years old) ($P < 0.001$). Compared with the non-PAD group, the PAD group was African American (22.33% vs. 17.76%), had a low education level (25.40% vs. 19.63%), had a low income (30.10% vs. 24.24%), and smoked (65.70% vs. 51.78%), hypertension (61.33% vs. 42.04%) and diabetes (22.65% vs. 13.78%) were all significantly higher (all $P < 0.001$). There was no statistically significant difference in gender and BMI distribution between the two groups ($P > 0.05$). It is worth noting that the blood lead level in the PAD group (3.01 ± 2.07 μg/dL) was significantly higher than that in the non-PAD group (2.52 ± 1.89 μg/dL) ($P < 0.001$), which provides a basis for further exploring the association between blood lead exposure and PAD. provides the basis.

Association between blood lead level and PAD

As shown in Table 2, in unadjusted model 1, for every 1 unit increase in blood lead level, the risk of PAD increased by 11% (OR = 1.11, 95%CI: 1.07–1.15). After adjusting for demographic characteristics (Model 2), this association still existed but was attenuated (OR = 1.06, 95%CI: 1.02–1.10). After further adjusting for socioeconomic status, lifestyle and comorbid conditions (model 3), the association between blood lead level and PAD is still statistically significant (OR = 1.04, 95%CI: 1.00-1.09). Classification analysis showed that compared with the lowest quartile group, the risk of PAD in the highest quartile group was increased by 36% (OR = 1.36, 95%CI: 1.03–1.79), and there was a significant dose-response relationship (P for trend = 0.021). This persistent association and dose-dependent trend support the hypothesis that blood lead exposure may be an independent risk factor for PAD.

The incidence of PAD is highest in developed countries such as the United States, Canada, and the United Kingdom (Fig. 2), but in terms of mortality, Russia and some Eastern European countries have the highest mortality rates in the world (Fig. 2).In addition, Fig. 3 further analyzes the trend of PAD mortality in different regions from 1990 to 2020 by social development index (SDI). The results show obvious regional differences: PAD mortality in high SDI and high-medium SDI regions showed a continuous downward trend, from about 1.8 and 2.2 in 1990 to 1.3 and 1.0 in 2020, respectively; medium SDI regions were relatively stable, maintaining at around 0.4; while low SDI and low-medium SDI regions showed an upward trend, from about 0.5 and 0.25 in 1990 to 0.7 and 0.4 in 2020, respectively. This difference is more obvious in the male population, suggesting that gender may be an important factor affecting the burden of PAD disease.

Stratified analysis results

Figure 4 demonstrates the heterogeneity in the association between blood lead levels and PAD in different subgroups. The results showed that there were significant interactions in terms of gender (P for interaction < 0.001), education level (P for interaction < 0.001), income level (P for interaction < 0.001) and hypertension status (P for interaction = 0.008). The association between blood lead and PAD is higher among men (OR = 1.07, 95%CI: 1.05–1.09), those with high education level (OR = 1.24, 95%CI:

Table 1 Baseline characteristics of participants from National health and nutrition examination survey (NHANES) 1999–2004

Variables	Overall	PAD		*P*-value
	(*n* = 8636)	NO (*n* = 8108)	YES (*n* = 618)	
Sex, n (%)				0.727
Male	4309 (49.38%)	4008 (49.43%)	301 (48.71%)	
Female	4417 (50.62%)	4100 (50.57%)	317 (51.29%)	
Age, Mean + SD	61.11 ± 13.55	60.36 ± 13.40	71.00 ± 11.54	
Age strata, n (%)				< 0.001
20–40	3994 (45.77%)	3900 (48.10%)	94 (15.21%)	
40–60	3630 (41.60%)	3298 (40.68%)	332 (53.72%)	
≥ 60	1102 (12.63%)	910 (11.22%)	192 (31.07%)	
Race, n (%)				< 0.001
Mexican American	1852 (21.22%)	1754 (21.63%)	98 (15.86%)	
Other Hispanic	339 (3.88%)	324 (4.00%)	15 (2.43%)	
Non-Hispanic White	4689 (53.74%)	4336 (53.48%)	353 (57.12%)	
Non-Hispanic Black	1578 (18.08%)	1440 (17.76%)	138 (22.33%)	
Other Race	268 (3.07%)	254 (3.13%)	14 (2.27%)	
Education level, n (%)				< 0.001
Less than 9th grade	1749 (20.04%)	1592 (19.63%)	157 (25.40%)	
9-11th grade	1397 (16.01%)	1284 (15.84%)	113 (18.28%)	
High school graduate	2003 (22.95%)	1850 (22.82%)	153 (24.76%)	
Some college or associates degree	2034 (23.31%)	1911 (23.57%)	123 (19.90%)	
College graduate or above	1543 (17.68%)	1471 (18.14%)	72 (11.65%)	
Marital status, n (%)				< 0.001
Married/Living with a partner	5577 (63.91%)	5245 (64.69%)	332 (53.72%)	
Divorced/Separated/Widowed	2604 (29.84%)	2342 (28.89%)	262 (42.39%)	
Never married	545 (6.25%)	521 (6.43%)	24 (3.88%)	
Income-to-poverty ratio, n (%)				< 0.001
< 1.3	2151 (24.65%)	1965 (24.24%)	186 (30.10%)	
1.3–1.85	1039 (11.91%)	935 (11.53%)	104 (16.83%)	
1.85–3.5	2833 (32.47%)	2628 (32.41%)	205 (33.17%)	
≥ 3.5	2703 (30.98%)	2580(31.82%)	123 (19.90%)	
BMI, n (%)				0.170
Underweight	98 (1.12%)	88 (1.09%)	10 (1.62%)	
Normal weight	2252 (25.81%)	2078 (25.63%)	174 (28.16%)	
Obese	3539 (40.56%)	3286 (40.53%)	253 (40.94%)	
Overweight	2837 (32.51)	2656 (32.76%)	181 (29.29%)	
Alcohol use, n (%)				0.770
Yes	5512 (63.17%)	5125 (63.21%)	387 (62.62%)	
No	3214 (36.83%)	2983 (36.79%)	231 (37.38%)	
Smoking, n (%)				< 0.001
Yes	4604 (52.76%)	4198 (51.78%)	406 (65.70%)	
No	4122 (47.24%)	3910 (48.22%)	212 (34.30%)	
Hypertension, n (%)				< 0.001
Yes	3788 (43.41%)	3409 (42.04%)	379 (61.33%)	
No	4938 (56.59%)	4699 (57.96%)	239 (38.67%)	
Diabetes, n (%)				< 0.001
Yes	1257 (14.41%)	1117 (13.78%)	140 (22.65%)	
No	7469 (85.59%)	6991 (86.22%)	478 (77.35%)	
LEAD, Mean + SD	2.55 ± 1.91	2.52 ± 1.89	3.01 ± 2.07	< 0.001

BMI: Body Mass Index

Table 2 Association of blood lead and PAD

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Lead			
Continuous	1.11 (1.07, 1.15)	1.06 (1.02, 1.10)	1.04 (1.00, 1.09)
Categories			
Q1	Reference	Reference	Reference
Q2	1.35 (1.03, 1.76)	1.13 (0.86, 1.49	1.11 (0.84, 1.46)
Q3	1.61 (1.24, 2.09)	1.18 (0.90, 1.56)	1.16 (0.88, 1.53
Q4	2.23 (1.74, 2.85)	1.45 (1.11, 1.90)	1.36 (1.03, 1.79)
P for trend	< 0.001	0.003	0.021

Model 1: no covariates were adjusted

Model 2: Sex, age, race, education level, marital status were adjusted

Model 3: Sex, age, race, education level, marital status, PIR, BMI, alcohol use, smoking, diabetes, and hypertension were adjusted

PIR: Poverty Income Ratio, BMI: Body Mass Index

1.16–1.32), and those with high income (OR = 1.10, 95% CI: 1.04–1.16) and patients with hypertension (OR = 1.07, 95%CI: 1.05–1.09) were more significant. It is particularly worth noting that in the body mass index stratified analysis, underweight people showed the strongest association (OR = 1.32, 95%CI: 1.09–1.59), which suggests that nutritional status may moderate the effect of blood lead exposure on vascular health. Influence.

Analysis of global PAD disease burden trend

Figure 5 shows the forecast trend of the age-standardized incidence of PAD worldwide from 1990 to 2050. Overall, the incidence rate showed a downward trend, from about 630/100 000 in 1990 to 550/100 000 in 2020. However, the forecast after 2020 showed a significant increase in uncertainty, reflecting the potential impact of multiple factors such as environmental factors on the future disease burden.

The Fig. 6 shows the gender difference in PAD mortality in different SDI regions. In all SDI levels, the mortality rate of men was higher than that of women, but the degree of difference varied by region. The gender difference in high SDI and high-medium SDI regions was relatively stable, while the gender difference in low SDI and low-medium SDI regions showed a trend of widening over time. This difference may reflect differences in access to medical and health resources, lifestyles, and environmental exposure levels between different regions. In particular, in terms of environmental lead exposure, factors such as occupational exposure may lead to higher risks for men.

From the GBD database, we analyzed the possible causes of death from PAD in people over 55 years old (Fig. 7). Behavioral risks (26.77), smoking (21.28) and tobacco (21.28) were the main causes of death.

Causal association between blood lead concentration and PAD

In the analysis of blood lead concentration (qb3C-4cvxDM) and PAD (bbj-a-144), a total of 8 SNPs (rs2415030, rs2887641, rs12101120, rs10991100, rs60698614, rs45576138, rs11639885, rs12617786) were ultimately included as instrumental variables (IVs) to assess the causal relationship between blood lead concentration and PAD. The F-statistics for all included SNPs were greater than 10, indicating the absence of weak IVs. As shown in Supplemental Fig. 1A, blood lead concentration is negatively correlated with peripheral vascular atherosclerosis in East Asian population (OR = 0.892, 95%CI: 0.806, 0.987, $P = 0.027$). MR Egger analysis shows that there is no significant heterogeneity between blood lead concentration and peripheral vascular atherosclerosis ($P = 0.28$), further supporting the robustness of the results. Supplemental Fig. 1B shows the forest plot results of the inverse-variance weighted analysis of 8 SNPs related to blood lead concentration ($P = 0.027$), showing a negative correlation. Additionally, the results exhibited low dependence on individual SNPs. Supplemental Fig. 1C shows that the 8 SNPs can be evenly distributed on both sides of the inverse-variance weighted. Supplemental Fig. 1D expresses that the 8 SNPs may have a linear relationship with peripheral vascular atherosclerosis. The leave-one-out analysis showed that the results did not change significantly after sequentially removing each SNP (Supplementary Fig. 1E).

These findings not only reveal the important association between blood lead exposure and PAD, but also show the global distribution characteristics of PAD disease

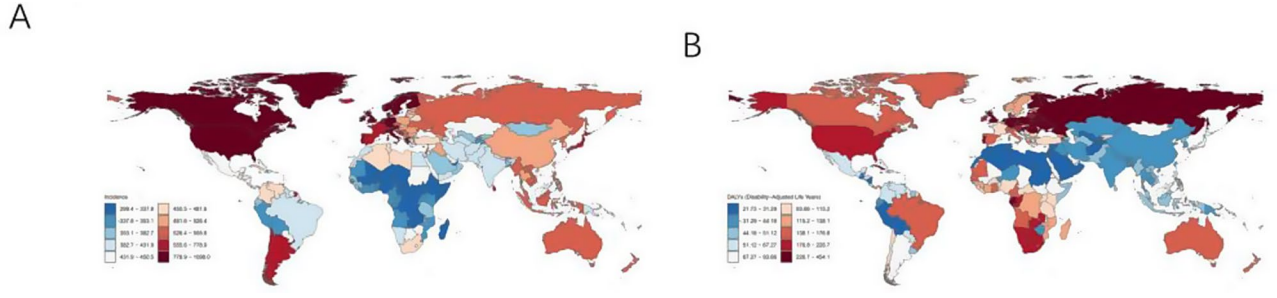

Fig. 2 Global PAD incidence and mortality distribution map in 2021

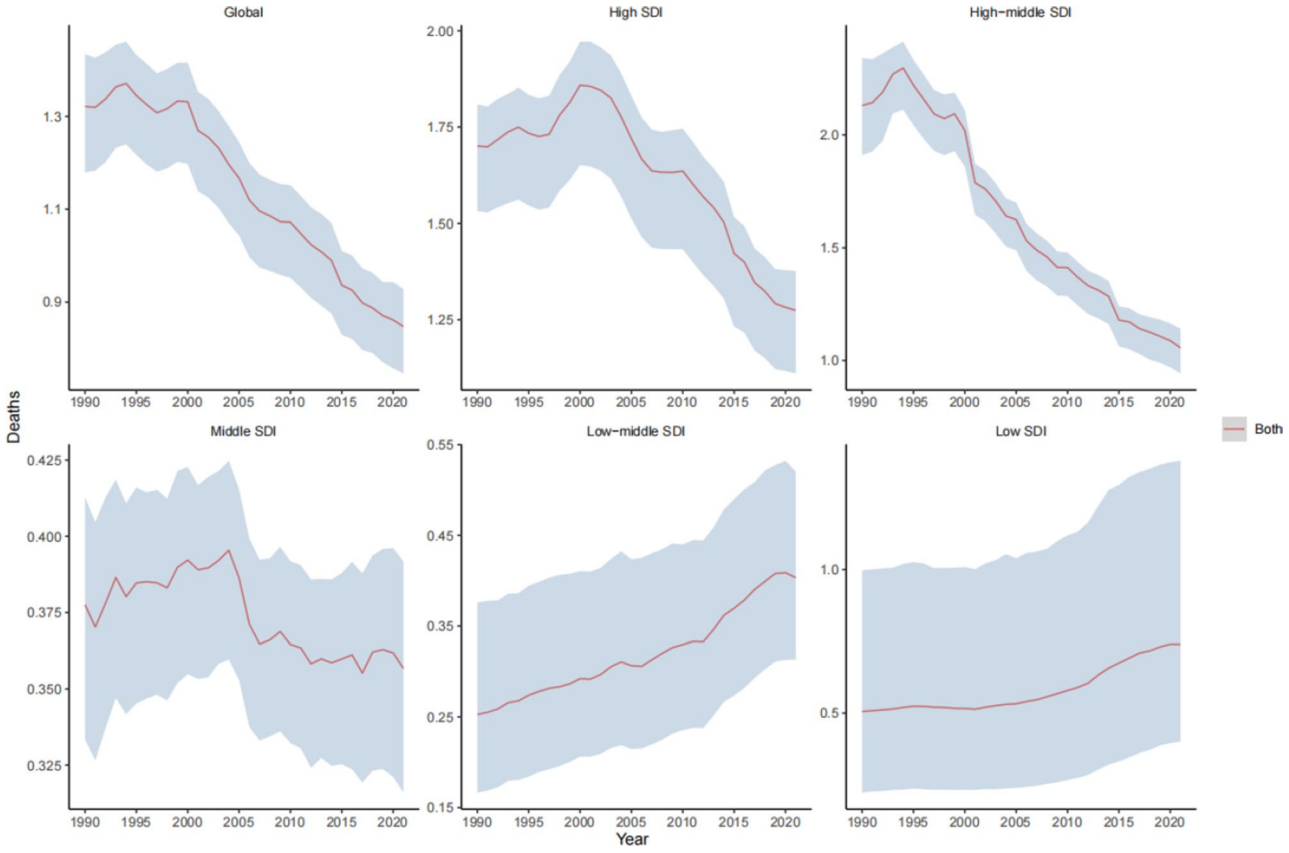

Fig. 3 Trends of deaths in different regions around the world, especially in relation to blood lead exposure and peripheral arterial disease (PAD). The chart is d.ivided into four parts, showing data for the world, high sociodemographic index (SDI), medium-high SDI, and low-medium SDI regions

burden and its evolution trend. The results emphasize the necessity of adopting differentiated prevention strategies in different populations, and provide important clues for further exploring the role of environmental factors in the onset of PAD. These evidences are of great significance for the formulation of targeted public health policies.

Discuss

This study is the first to integrate multi-source data and systematically evaluate the association between environmental lead exposure and PAD and its global disease burden trend. The main innovations are: first, by integrating NHANES individual-level data and GBD population-level data, it provides multi-level evidence support from individuals to populations; second, it is the first time to use the Mendelian randomization method to explore the causal relationship between environmental lead exposure and PAD, effectively reducing the confounding bias and reverse causality of observational studies; finally, it is the first time to compare the heterogeneity of the association between lead exposure and PAD between countries with different income levels, providing a scientific basis for the formulation of differentiated prevention strategies [34, 35].

This study found a significant dose-response relationship between blood lead levels and PAD risk, and this association remained even after adjusting for traditional cardiovascular risk factors. Johnson et al.'scross-sectional study in Canada found that even in areas with low environmental pollution levels (average NO2 concentration 5.4 ± 1.6 ppb), environmental exposure is still significantly associated with carotid atherosclerosis [29]. For every 1 ppb increase in NO2 concentration, the carotid artery plaque area increased by 3.4 mm2. The prospective cohort study by Hennig et al. also confirmed that long-term air pollution exposure is related to the progression of atherosclerosis, especially among people with mild baseline lesions [30]. These findings consistently support the hypothesis that environmental exposures may play an important role in the early stages of atherosclerosis.

Existing studies have shown that lead exposure may increase the risk of cardiovascular diseases through mechanisms such as oxidative stress, inflammatory responses, vascular calcification, and endothelial dysfunction. Lead exposure can induce excessive generation of reactive oxygen species (ROS) and inhibit the production of nitric oxide (NO), leading to vascular endothelial cell damage and impaired vasodilation, thereby

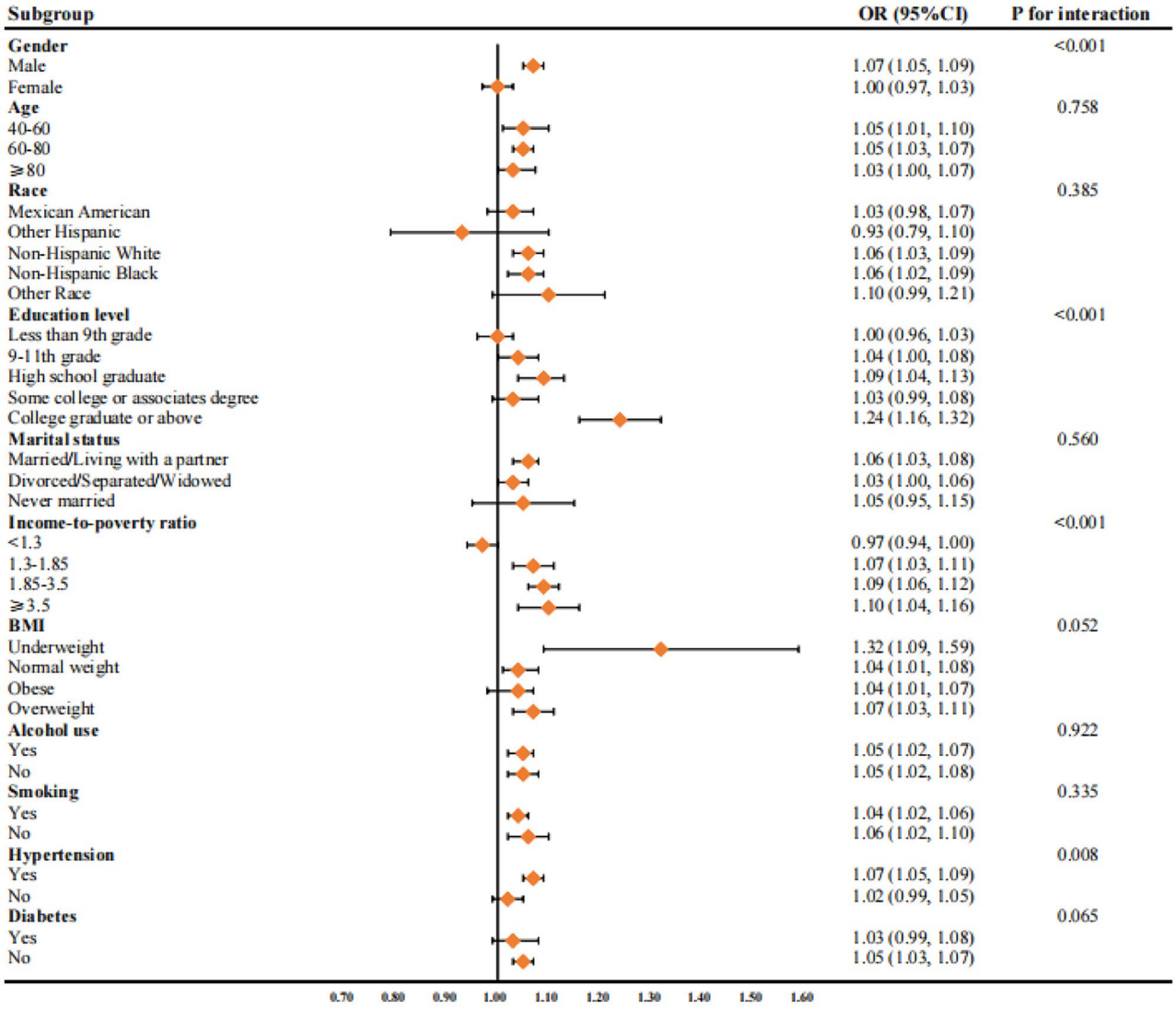

Fig. 4 shows the results of heterogeneity analysis of the association between blood lead levels and PAD in different subgroups.Patients were categorized and compared based on age, race, education level, marital status, income to poverty ratio, BMI, alcohol use, smoking, hypertension, and diabetes.*P* < *0.05* was considered statistically significant

promoting the development and progression of atherosclerosis [31–33]. Simões MR et al. found that lead exposure can activate inflammatory pathways, such as NF-κB and TNF-α signaling pathways, increasing the levels of inflammatory markers, such as C-reactive protein and IL-6, thereby exacerbating vascular inflammation and plaque formation [34]. Additionally, lead exposure can disrupt calcium metabolism and promote osteogenic transformation of vascular smooth muscle cells, leading to vascular calcification and increasing the risk of vascular diseases [35]. Therefore, we hypothesize that lead exposure may also increase the risk of PAD through the aforementioned four mechanisms.

Significant gender differences were observed in this study. In stratified analysis, the association between lead exposure and PAD was more substantial among men, those with higher education levels, and those with hypertension. This is consistent with the research results of Maugeri et al., who found that gender may moderate the association between environmental factors and atherosclerosis. Their research showed that antioxidant nutritional intake has a more obvious protective effect on carotid artery intima-media thickness in women [38]. This gender difference may be related to the following factors: (1) Differences in occupational exposure patterns: Men are more likely to engage in high-exposure occupations; (2) Differences in lifestyle habits: Smoking, drinking and other behaviors are more common among men; (3) Differences in biological mechanisms: Estrogen may have certain protective effect. Min et al.'s (2020) study further supported the gender-specific effect, and they found that indoor air pollution caused by

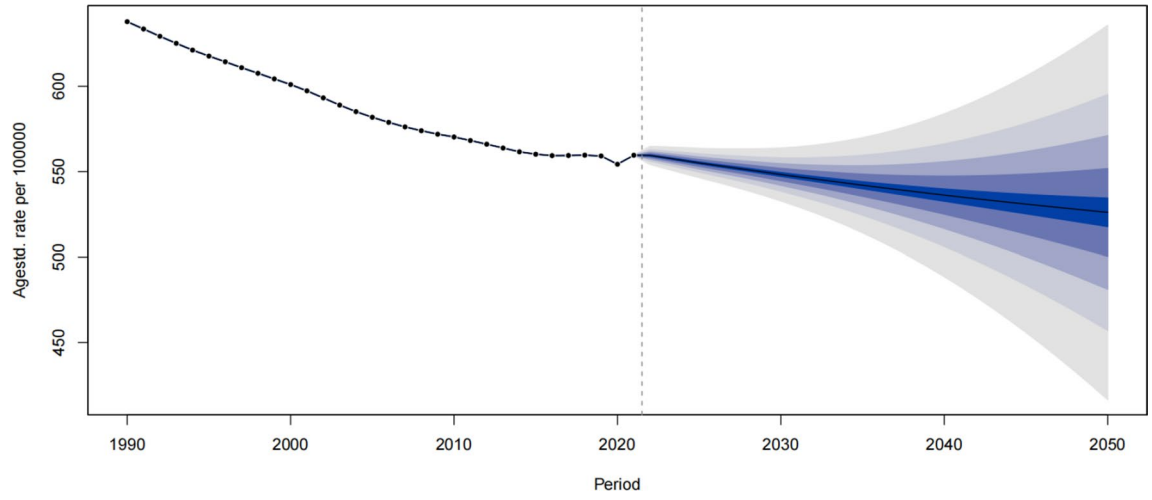

Fig. 5 By 2025, the age-standardized incidence of PAD

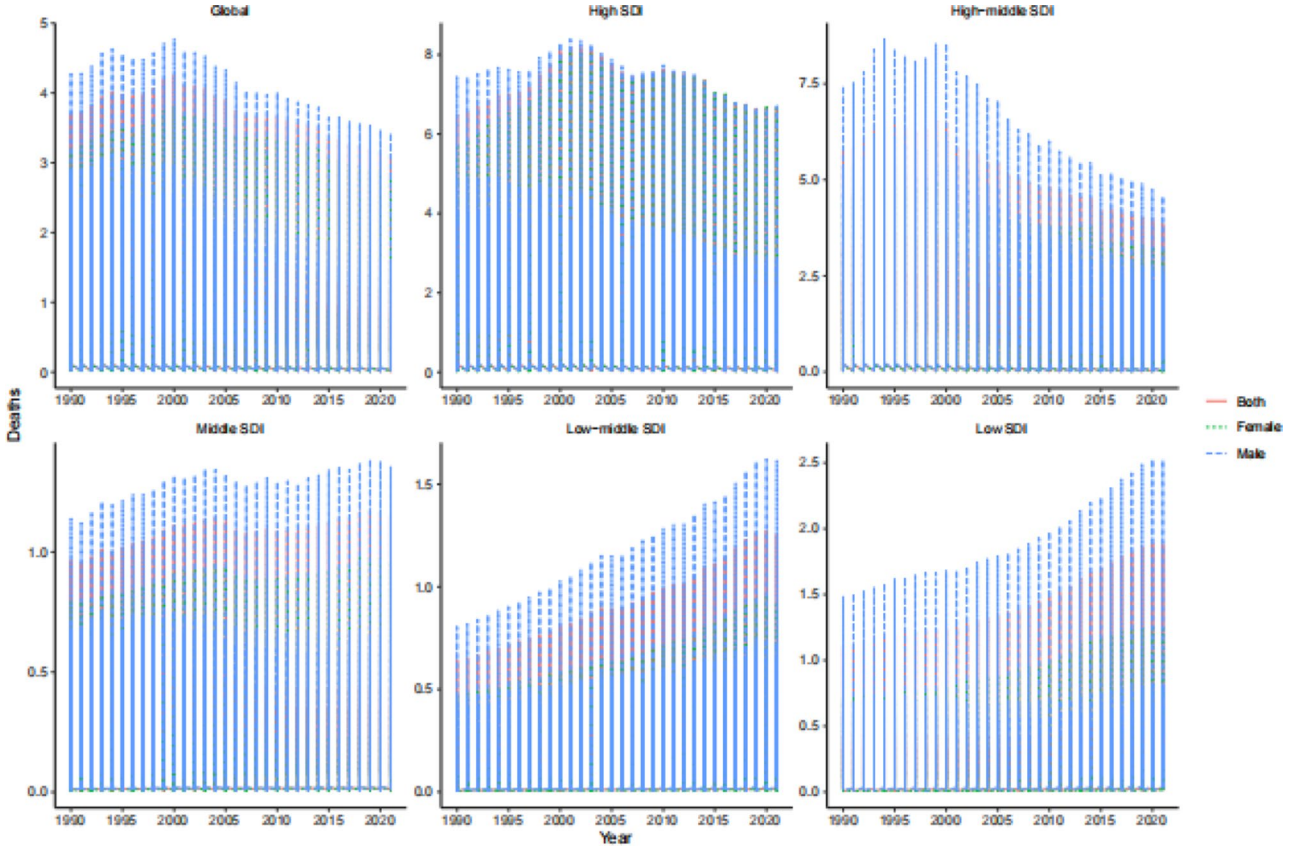

Fig. 6 Trends in PAD Mortality by SDI Level from 1990 to 2020.The chart is divided into global, high SDI, high-middle SDI, middle SDI, middle-low SDI and low SDI according to different SDI. Each part shows the disease mortality trends by sex

household cooking fuel use was significantly associated with increased carotid artery intima-media thickness in women during early pregnancy [39]. This study found that people over 55 years old showed higher sensitivity to environmental lead exposure, which is consistent with previous research results. The sensitivity of vascular endothelial function to environmental toxicants in the elderly is significantly higher than that in the young. This age-related difference in susceptibility may be related to the following mechanisms: (1) vascular repair ability decreases with age; (2) oxidative stress response increases; (3) chronic inflammatory state worsens; and (4) detoxification ability weakens. This finding has important implications for the environmental health protection

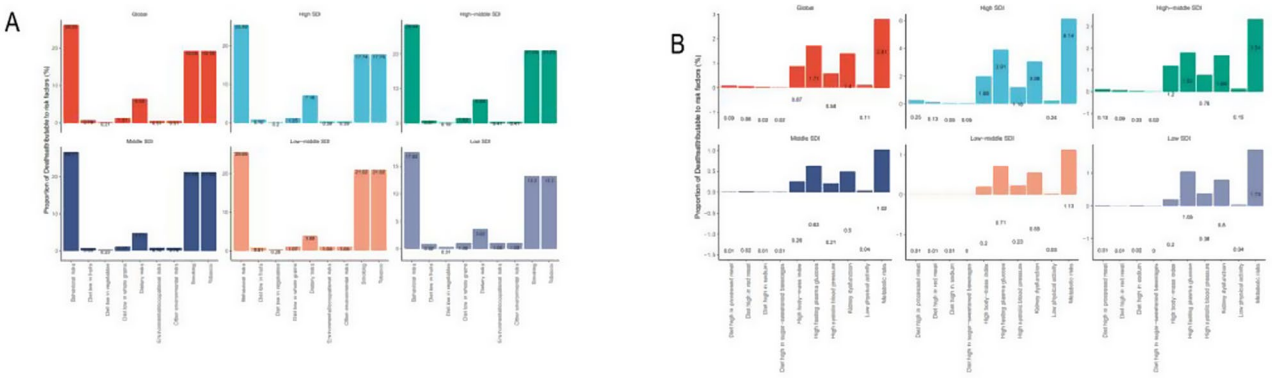

Fig. 7 Different hazard ratios of PAD patients aged 55 years and above in GBD database

of the elderly, and it is recommended to strengthen environmental exposure monitoring and intervention for the elderly.

However, the finding that individuals with higher education levels are more sensitive to lead exposure is inconsistent with typical socioeconomic models. We speculate that this may be due to their heightened awareness of health issues, leading to more frequent health checkups and earlier detection of elevated blood lead levels and their health impacts. Additionally, it is possible that genetic background or epigenetic modifications make them more sensitive to lead exposure. For example, a study has shown that aminolevulinic acid dehydratase (ALAD) gene polymorphism (G177C) significantly affects individual sensitivity to lead exposure, with carriers of the ALAD-2 allele being more sensitive [36]. Future research could further explore this hypothesis. As for hypertensive patients, their increased sensitivity to lead exposure may be attributed to impaired vascular endothelial function, elevated oxidative stress levels, and chronic inflammatory states [37]. Lead exposure may exacerbate vascular endothelial dysfunction and inflammatory responses, further increasing the risk of PAD [23].

In terms of socioeconomic differences, this study found that the burden of PAD continues to increase in low-income countries, while it shows a downward trend in high-income countries. This "double burden" phenomenon is consistent with the findings of Hasslof et al. [40]. Their research shows that socioeconomic status not only affects environmental exposure levels but may also modify its health effects. This difference may be due to: (1) unequal access to medical resources; (2) differences in health literacy levels; (3) differences in the implementation of environmental policies; (4) differences in lifestyle and eating habits. The research of Ward-Caviness et al. provided new insights. They found that epigenetic age acceleration may be a biomarker of sensitivity to environmental pollution [38, 39], which suggests that socioeconomic factors may affect the health effects of environmental exposure through epigenetic mechanisms. This study also reveals multiple health effects of environmental exposures. McNeely et al.'s study of airline flight attendants showed that occupational second-hand smoke exposure is still significantly associated with an increased risk of cardiovascular disease even many years after the exposure has ceased [40]. This "legacy effect" emphasizes the importance of early intervention. In addition, Blum et al.'s research showed that environmental particulate matter exposure is associated with albuminuria and decreased renal function [41], suggesting that environmental exposure may affect cardiovascular health through damage to multiple organ systems.

The association between blood lead exposure and PAD is not only significant in the U.S. population but has also been observed in countries such as China, South Korea, India, and Bangladesh. In China, a study analyzing survey results from eight provinces in the eastern, western, and central regions between 2009 and 2010 found that the geometric mean of blood lead concentration in the general population was 34.90 μg/L, and the geometric mean of urinary lead concentration was 1.05 μg/L. The study indicated that long-term exposure to lead compounds can reduce vascular dilation function, impair vascular generation and damage repair, and promote atherosclerosis and thrombosis. In South Korea, data from the 2008 National Health and Nutrition Examination Survey revealed that the geometric mean of blood lead concentration in the general population was 19.10 μg/L. Additionally, Korean studies have found that blood lead levels are associated with an increased risk of cardiovascular diseases, including coronary artery disease, PAD, and electrocardiogram abnormalities. Similarly, a study on blood lead levels and attributable disease burden in India confirmed that lead exposure increases the risk of cardiovascular diseases [42]. Furthermore, Jenna E. Forsyth et al. found elevated blood lead levels in rural maternal populations in Bangladesh, which were associated with an increased risk of cardiovascular diseases [37, 43]. These findings suggest that blood lead exposure also increases

the risk of PAD in populations across Asia and some low- and middle-income countries.

Notably, due to the limitations of the NHANES database, this study only included blood lead concentration as the exposure indicator and did not consider other potential sources of lead exposure, such as drinking water contamination, airborne lead particles, or occupational exposure, which are also common pathways of exposure [44–46]. Blood lead concentration, as a sensitive biomarker of recent lead exposure, may be higher in individuals exposed to these additional sources compared to the general population. Consequently, the relationship between blood lead levels and PAD may vary depending on these exposure pathways. Future studies should integrate multi-source exposure data, such as environmental monitoring data and occupational exposure records, and explore the potential impact of different exposure pathways on the study results to provide a more comprehensive assessment of the effects of environmental lead exposure.

This study has the following main advantages: (1) Based on large-scale population data, the sample is representative and the results have good extrapolation; (2) Multiple statistical methods are used for cross-validation, which enhances the reliability of the results; (3) It provides evidence from a global perspective, filling the regional gap in previous studies; (4) The innovative use of Mendelian randomization method to explore causal relationships has obvious methodological advantages.

The main limitations include: (1) It is difficult to determine the temporal relationship in the cross-sectional design; (2) It is not possible to obtain information on all potential confounding factors, such as dietary patterns and physical activity; (3) NHANES data primarily represent the U.S. population and may not fully capture the context of low-income countries, while the GBD database also has limitations in data quality and coverage for these regions. To enhance the global applicability of our findings, future studies should incorporate more regional data (e.g., from low-income countries in Africa and Asia) and explore additional data sources, such as the World Health Organization's global environmental monitoring system, to address these gaps; (4) Although this study provides evidence for a causal relationship between lead exposure and PAD using MR methods, the findings are based on genetic data from East Asian populations and have not been validated in other ethnic groups. Further research is needed to verify these findings in more diverse populations.

The results of this study have important implications for public health practice: (1) Even at the current low exposure level, environmental lead exposure may still increase the risk of PAD, and it is recommended to further lower the exposure standard while establishing cost-effective lead pollution monitoring systems using low-cost technologies and community-based approaches; (2) Differentiated prevention strategies should be adopted according to the differences in susceptibility of different populations; (3) The rising trend of PAD burden in low-income countries deserves attention. It is recommended to ensure policy adoption and enforcement through legislative support, interdepartmental collaboration, and public education campaigns, while leveraging international support and cooperation to provide technical and financial assistance to low-income countries; (4) It is recommended to incorporate environmental exposure screening into the cardiovascular disease prevention system. For example, Bangladesh successfully reduced lead pollution levels in drinking water by introducing low-cost water quality testing technologies and community participation models. This case demonstrates that even in resource-limited environments, effective lead pollution prevention and control measures can be implemented through innovative methods and multi-party collaboration [47].

Suggested future research directions include: (1) Conduct multicenter prospective cohort studies to further clarify the causal relationship; (2) Explore the interaction mechanism between environmental factors and genetic susceptibility; (3) Evaluate the cost-effectiveness of different prevention strategies; (4) Study the molecular mechanism by which environmental exposure affects cardiovascular health, such as validating the impact of lead exposure on vascular function through animal models or cell experiments; (5) Conduct randomized controlled trials to evaluate the effects of environmental improvement measures; (6) Establish a long-term monitoring system to evaluate the effects of policy interventions.

Conclusion

By integrating NHANES individual data, GBD population data, and Mendelian randomization analysis methods, this study is the first to systematically evaluate the association between environmental lead exposure and PAD and its global disease burden distribution characteristics. The study found that even at the current relatively low exposure levels, blood lead levels still show a significant dose-response relationship with the risk of PAD. This association is more significant among men, those with higher education levels, and those with hypertension, suggesting important population differences in susceptibility. Analysis of the global burden of PAD disease shows significant differences between regions with different levels of socioeconomic development. The burden of PAD is declining in high-income countries, while it continues to rise in low-income countries. This "double burden" phenomenon reflects the problem of environmental health inequality. Mendelian randomization

analysis provides more reliable evidence support for the causal relationship between environmental lead exposure and PAD.

The findings have important implications for public health practice. First, it is recommended to lower environmental lead exposure standards further and strengthen protection for occupational groups; second, differentiated prevention strategies should be developed for different susceptible groups; third, special attention should be paid to the rising trend of PAD burden in low-income countries, and environmental health policy support and support should be strengthened. international cooperation. In addition, it is recommended that environmental exposure screening be incorporated into the cardiovascular disease prevention system and targeted intervention be carried out. This study provides new scientific evidence for understanding, the association between environmental lead exposure and PAD, and, emphasizes the need to take active preventive measures. Future prospective studies are needed to further verify these findings and explore potential biological mechanisms to provide more basis for the optimization of prevention strategies.

Supplementary Information

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Supplementary Material 1

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Congzhi Yan: conceptualization, methodology, writing– original draft. Jiahao Chen: analyzed and interpreted the data.Xinbing Xu: Edit the article and organize the data. Hua Wei and Jinjiao Li: project administration.

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Data availability
The data that are discussed in the study are included in the paper.

Declarations

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Not applicable. Only publicly available summary statistics were used.

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Competing interests
The authors declare that they have no competing interests.

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References

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116:1509–26.
2. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–40.
3. Writing Committee M, Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary. Vasc Med. 2017;22:NP1–43.
4. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA. 2004;292:453–61.
5. Sampson UK, Fowkes FG, McDermott MM, Criqui MH, Aboyans V, Norman PE, Forouzanfar MH, Naghavi M, Song Y, Harrell FE Jr., et al. Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. Glob Heart. 2014;9:145–58. e121.
6. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, Rudan I. Global, regional, and National prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health. 2019;7:e1020–30.
7. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2020;396:1204–22.
8. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured National population. J Vasc Surg. 2014;60:686–e695682.
9. Fowkes FG, Thorogood M, Connor MD, Lewando-Hundt G, Tzoulaki I, Tollman SM. Distribution of a subclinical marker of cardiovascular risk, the ankle brachial index, in a rural African population: SASPI study. Eur J Cardiovasc Prev Rehabil. 2006;13:964–9.
10. Rivera-Andrade A, Luna MA. Trends and heterogeneity of cardiovascular disease and risk factors across Latin American and Caribbean countries. Prog Cardiovasc Dis. 2014;57:276–85.
11. Ankle Brachial Index C, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, et al. Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.
12. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Balde AB, Bertollini R, Bose-O'Reilly S, Boufford JI, et al. The lancet commission on pollution and health. Lancet. 2018;391:462–512.
13. Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC State-of-the-Art review. J Am Coll Cardiol. 2018;72:2054–70.
14. Chowdhury R, Ramond A, O'Keeffe LM, Shahzad S, Kunutsor SK, Muka T, Gregson J, Willeit P, Warnakula S, Khan H, et al. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 2018;362:k3310.
15. Solenkova NV, Newman JD, Berger JS, Thurston G, Hochman JS, Lamas GA. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. Am Heart J. 2014;168:812–22.
16. Araujo JA, Nel AE. Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. Part Fibre Toxicol. 2009;6:24.
17. Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health. 2018;3:e177–84.
18. Macchi C, Sirtori CR, Corsini A, Mannuccio Mannucci P, Ruscica M. Pollution from fine particulate matter and atherosclerosis: A narrative review. Environ Int. 2023;175:107923.
19. Wildman RP, McGinn AP, Lin J, Wang D, Muntner P, Cohen HW, Reynolds K, Fonseca V, Sowers MR. Cardiovascular disease risk of abdominal obesity vs. metabolic abnormalities. Obes (Silver Spring). 2011;19:853–60.

20. Bhatnagar A. Environmental determinants of cardiovascular disease. Circ Res. 2017;121:162–80.
21. VanderWeele TJ, Tchetgen Tchetgen EJ, Cornelis M, Kraft P. Methodological challenges in Mendelian randomization. Epidemiology. 2014;25:427–35.
22. Zhang K, Brook RD, Li Y, Rajagopalan S, Kim JB. Air pollution, built environment, and early cardiovascular disease. Circ Res. 2023;132:1707–24.
23. Yao X, Steven Xu X, Yang Y, Zhu Z, Zhu Z, Tao F, Yuan M. Stratification of population in NHANES 2009–2014 based on exposure pattern of lead, cadmium, Mercury, and arsenic and their association with cardiovascular, renal and respiratory outcomes. Environ Int. 2021;149:106410.
24. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, Hemani G, Tansey K, Laurin C, Early G, et al. LD hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;33:272–9.
25. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med. 2008;27:1133–63.
26. Johnson CL, Paulose-Ram R, Ogden CL, Carroll MD, Kruszon-Moran D, Dohrmann SM, Curtin LR. National health and nutrition examination survey: analytic guidelines, 1999–2010. Vital Health Stat *2* 2013:1–24.
27. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982–3021.
28. Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators. Am J Epidemiol. 2013;178:1177–84.
29. Maugeri A, Hruskova J, Jakubik J, Kunzova S, Sochor O, Barchitta M, Agodi A, Bauerova H, Medina-Inojosa JR, Vinciguerra M. Dietary antioxidant intake decreases carotid intima media thickness in women but not in men: A cross-sectional assessment in the Kardiovize study. Free Radic Biol Med. 2019;131:274–81.
30. Min M, Taneepanichskul N. Cooking fuels use and carotid intima-media thickness during early pregnancy of women in Myanmar. PLoS ONE. 2020;15:e0236151.
31. Lee JW, Choi H, Hwang UK, Kang JC, Kang YJ, Kim KI, Kim JH. Toxic effects of lead exposure on bioaccumulation, oxidative stress, neurotoxicity, and immune responses in fish: A review. Environ Toxicol Pharmacol. 2019;68:101–8.
32. Silveira EA, Siman FD, de Oliveira Faria T, Vescovi MV, Furieri LB, Lizardo JH, Stefanon I, Padilha AS, Vassallo DV. Low-dose chronic lead exposure increases systolic arterial pressure and vascular reactivity of rat aortas. Free Radic Biol Med. 2014;67:366–76.
33. Sun Y, Zhao Z, Zhang H, Li J, Chen J, Luan X, Min W, He Y. The interaction of lead exposure and CCM3 defect plays an important role in regulating angiogenesis through eNOS/NO pathway. Environ Toxicol Pharmacol. 2020;79:103407.
34. Simoes MR, Aguado A, Fiorim J, Silveira EA, Azevedo BF, Toscano CM, Zhenyukh O, Briones AM, Alonso MJ, Vassallo DV, Salaices M. MAPK pathway activation by chronic lead-exposure increases vascular reactivity through oxidative stress/cyclooxygenase-2-dependent pathways. Toxicol Appl Pharmacol. 2015;283:127–38.
35. Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. Am J Physiol Heart Circ Physiol. 2008;295:H454–465.
36. Montenegro MF, Barbosa F Jr., Sandrim VC, Gerlach RF, Tanus-Santos JE. A polymorphism in the delta-aminolevulinic acid dehydratase gene modifies plasma/whole blood lead ratio. Arch Toxicol. 2006;80:394–8.
37. Gambelunghe A, Sallsten G, Borne Y, Forsgard N, Hedblad B, Nilsson P, Fagerberg B, Engstrom G, Barregard L. Low-level exposure to lead, blood pressure, and hypertension in a population-based cohort. Environ Res. 2016;149:157–63.
38. McNeely E, Mordukhovich I, Staffa S, Tideman S, Coull B. Legacy health effects among never smokers exposed to occupational secondhand smoke. PLoS ONE. 2019;14:e0215445.
39. Blum MF, Surapaneni A, Stewart JD, Liao D, Yanosky JD, Whitsel EA, Power MC, Grams ME. Particulate matter and albuminuria, glomerular filtration rate, and incident CKD. Clin J Am Soc Nephrol. 2020;15:311–9.
40. Ilmiawati C, Reza M, Yanni M, Rusjdi DA. Blood cd levels and carotid intima-media thickness in young adults living in Padang, Indonesia. BMC Res Notes. 2020;13:202.
41. Hennig F, Geisel MH, Kalsch H, Lucht S, Mahabadi AA, Moebus S, Erbel R, Lehmann N, Jockel KH, Scherag A, et al. Air pollution and progression of atherosclerosis in different vessel Beds-Results from a prospective cohort study in the Ruhr area, Germany. Environ Health Perspect. 2020;128:107003.
42. Ericson B, Dowling R, Dey S, Caravanos J, Mishra N, Fisher S, Ramirez M, Sharma P, McCartor A, Guin P, et al. A meta-analysis of blood lead levels in India and the attributable burden of disease. Environ Int. 2018;121:461–70.
43. Forsyth JE, Saiful Islam M, Parvez SM, Raqib R, Sajjadur Rahman M, Marie Muehe E, Fendorf S, Luby SP. Prevalence of elevated blood lead levels among pregnant women and sources of lead exposure in rural Bangladesh: A case control study. Environ Res. 2018;166:1–9.
44. Ono A, Horiguchi H. Relationship between personal-sampled air lead and blood lead in low-lead-exposure workers in Japan to apply multiple regression models determining permissible air lead concentration. J Occup Health. 2021;63:e12264.
45. Wilson J, Dixon SL, Wisinski C, Speidel C, Breysse J, Jacobson M, Crisci S, Jacobs DE. Pathways and sources of lead exposure: Michigan children's lead determination (the MI CHILD study). Environ Res. 2022;215:114204.
46. Levallois P, Barn P, Valcke M, Gauvin D, Kosatsky T. Public health consequences of lead in drinking water. Curr Environ Health Rep. 2018;5:255–62.
47. Hulland KR, Leontsini E, Dreibelbis R, Unicomb L, Afroz A, Dutta NC, Nizame FA, Luby SP, Ram PK, Winch PJ. Designing a handwashing station for infrastructure-restricted communities in Bangladesh using the integrated behavioural model for water, sanitation and hygiene interventions (IBM-WASH). BMC Public Health. 2013;13:877.

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