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The burden and trend prediction of ischemic heart disease associated with lead exposure: Insights from the Global Burden of Disease study 2021

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Abstract

Aim The purpose of this study was to quantify the global burden of ischemic heart disease associated with lead exposure, utilizing data from the Global Burden of Disease (GBD) Study, 2021.

Methods Data on the burden of ischemic heart disease (IHD) associated with lead exposure were compiled globally from 1990 to 2021. These data were further stratified by dimensions including gender, age, GBD regions, and countries. Utilizing the Joinpoint regression model, we analyzed long-term trends in the burden of IHD disease associated with lead exposure and derived estimated annual percentage changes (EAPC). For future projections, we used an ARIMA model to predict potential trends in the burden of IHD disease associated with lead exposure over the next decade.

Results The study's findings reveal that in 2021, there were 590,370 deaths attributed to IHD (95% UI (Uncertainty interval (UI) is derived from the Bayesian school of statistical analysis used in the GBD studies. Unlike the frequency school of thought, which constructs confidence intervals (CI), the Bayesian school of thought views probability as a measure of confidence in an event, and in this approach the actual mean is viewed as a random variable dependent on the data and prior knowledge, with UI indicating that there is a specific probability (e.g., 95%) that the actual mean will fall within the interval.): -83,778 to 1,233,628) and 11,854,661 disability-adjusted life years (DALYs) (95% UI: -1,668,553 to 24,791,275) globally due to lead exposure, reflecting an increasing and then stabilizing trend from 1990 to 2021. Comparative analysis across study regions indicated a higher disease burden for IHD in regions with lower Socio-Demographic Index (SDI) values, contrasting with the lower burden in regions with higher SDI values. Furthermore, IHD mortality and DALYs peak in the 70–80 age cohort, with males exhibiting higher rates compared to females. Decadal projections indicate a downward trend in IHD mortality and DALYs for regions with higher SDI, in contrast to an anticipated upward trend in regions with lower SDI.

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Conclusion The global burden of ischemic heart disease associated with lead exposure is increasing, particularly in regions with low SDI values and within the elderly population. Considering the profound threat posed by lead exposure to the global burden of IHD, there is an imperative to consistently reinforce and execute robust prevention strategies to mitigate environmental lead exposure.

Keywords Death, Disability-adjusted life-years, Global burden of disease, Ischemic heart disease, Lead exposure

Introduction

Ischemic heart disease (IHD) encompasses a range of chronic cardiovascular conditions characterized by inadequate coronary blood flow to the heart, leading to myocardial damage [1, 2]. It is a major contributor to the global burden of disease (GBD) and significantly impacts global health [3, 4]. According to the World Health Organization, IHD accounts for 16% of all deaths worldwide [5, 6]. The incidence of IHD continues to rise and is projected to remain the leading cause of death globally. The GBD 2021 analysis, published in The Lancet, highlights IHD as a major component of the global disease burden. In 2021, IHD was the second leading cause of disability-adjusted life years (DALYs) globally, accounting for 188.3 million DALYs [7]. DALY is a crucial metric for assessing the global disease burden, combining years of life lost due to premature death (YLL) and years lived with disability (YLD). Specifically, DALY is calculated as DALY = YLL + YLD, providing a comprehensive measure of the disease's impact on individuals and society. A DALY represents one year of healthy life lost due to a health issue. Higher DALY values indicate a greater disease burden, underscoring the significant impact on population health.

IHD is linked to several modifiable risk factors, including hypertension, diabetes, dyslipidemia, and lead exposure. Notably, lead exposure has garnered significant research attention in recent years as a critical factor influencing IHD [8, 9]. Elevated blood lead levels can hinder glutathione production and decrease superoxide dismutase activity [10, 11], leading to an overproduction of free radicals and triggering an oxidative stress response. This response exacerbates lipid peroxidation and disrupts nitric oxide (NO) homeostasis. Consequently, these reactions may impair vascular endothelial function, promoting atherosclerosis [12, 13]. In the human body, lead competes with calcium for calmodulin binding and disrupts intracellular calcium homeostasis. It may also activate the NF-κB signaling pathway, inducing a systemic inflammatory response [14, 15]. This inflammation is characterized by excessive reactive oxygen species (ROS) production and is closely associated with the development of IHD [16, 17].

Notably, the global health impacts of lead exposure are likely much higher than previously estimated [18], with effects on cardiovascular disease comparable to the combined impact of indoor and outdoor PM2.5 air pollution [19], and three times greater than those caused by unsafe drinking water, sanitation, and handwashing [20]. Globally, myocardial ischemia and heart disease deaths due to lead exposure result in significant health and economic losses, particularly in low- and middle-income countries, with lead exposure accounting for 6.56% (−0.94% to 13.79%) of all IHD deaths [21, 22]. Despite the increasing global burden of disease from lead exposure, research on the relationship between lead exposure and IHD remains limited. To address this gap, we conducted a comprehensive analysis of the disease burden of IHD due to lead exposure from 1990 to 2021 using the latest data from the GBD study. This study not only reveals the characteristics of the global distribution of lead-exposure-associated IHD but also tracks its trends over time, providing valuable baseline data for understanding the full impact of lead exposure on IHD and offering a scientific basis for developing future lead exposure control and IHD prevention strategies. Figure 1 illustrates the entire research process.

Materials and methods

Data sources

The primary data for this study were sourced from the GBD database, with the GBD 2021 study recognized as one of the most comprehensive and systematic analyses of global health to date. The study aimed to assess the health impacts of 371 different diseases and injuries from 1990 to 2021 and to monitor trends in these impacts. Additionally, the study considers 88 different health risk factors. GBD 2021 encompasses 21 major domains and integrates data from 204 countries and territories, collecting disease incidence, mortality, and other health-related indicators on a global scale and the reference population used by the Global Burden of Disease Database (GBD) for the calculation of age standardized rates is the age structure of the world's population standardized for 2010–2035. The detailed methodology of data collection, processing, and modeling is fully explained in previous studies [20]. Our study collected data on the burden of ischemic heart disease associated with lead exposure using the online outcomes tool of the U.S. Institute for Health Metrics and Evaluation (IHME). The

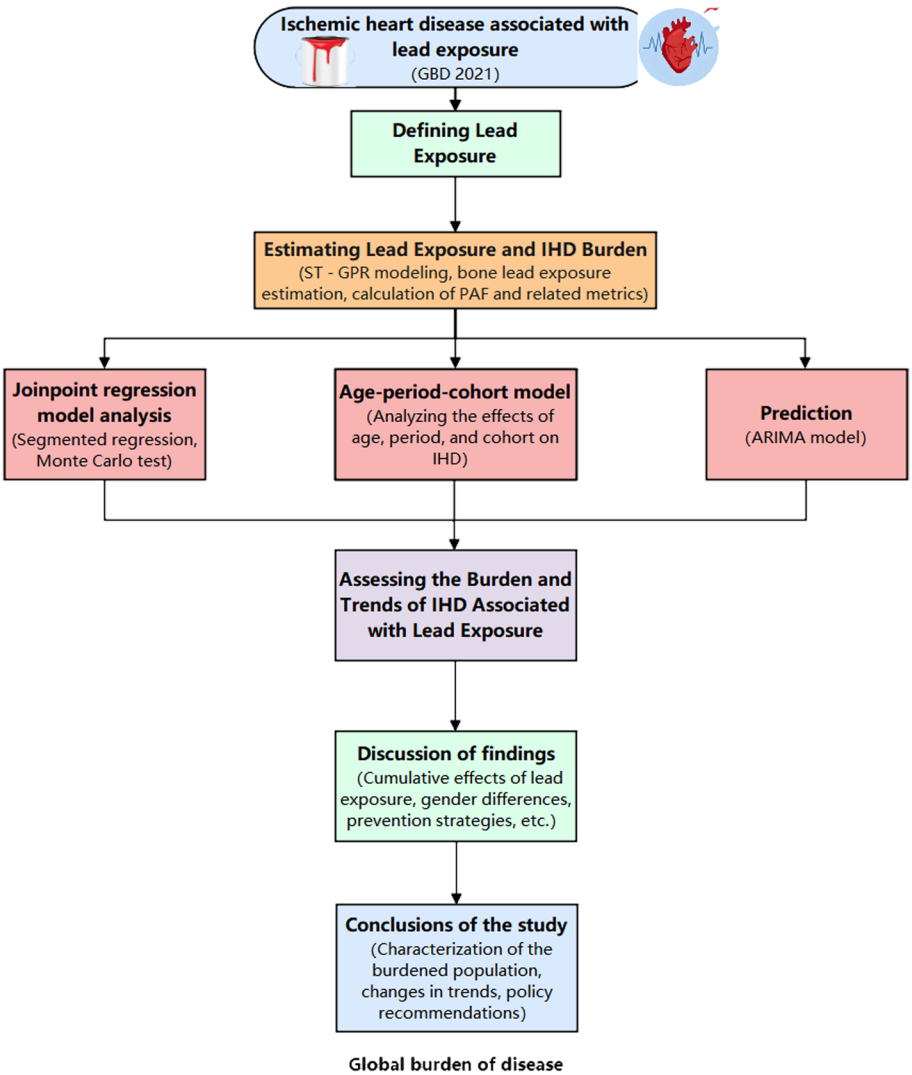

Fig. 1 Flow chart for analysis of ischemic heart disease associated with lead exposure

required datasets were exported through its provided interface and subsequently analyzed using R software. Detailed steps of the study methodology and data collection, including codes and analysis templates can be found in the Supplementary file 1 and 2.

Definitions of lead exposure

In our study, lead exposure was defined as the extent to which an individual is exposed to lead in daily life from sources such as contaminated water, airborne lead particles, and lead levels in soil. Lead exposure can be categorized into two types: acute and chronic. Acute lead exposure is measured in micrograms per deciliter of blood (μg/dL) and is associated with impaired intellectual development in children. Chronic lead exposure, on the other hand, is measured in micrograms of lead per gram of bone (μg/g) and is directly associated with increased systolic blood pressure (SBP) and cardiovascular disease (CVD) risk. The U.S. Centers for Disease Control and Prevention (CDC) has established a blood lead reference value of 3.5 μg/dL for children and 5 μg/dL for adults, which was updated from 5 μg/dL to 3.5 μg/dL in 2021 [23, 24].

Estimation of exposure to lead and its disease burden

In GBD 2021, global lead exposure modeling employed a spatiotemporal Gaussian process regression (ST-GPR) approach, applied to multiple risk variables. Covariates relevant to this study, such as the Socio-Demographic Index (SDI), degree of urbanization, number of cars per capita, and whether leaded gasoline was phased out, were used to predict blood lead levels for years in countries

with insufficient data. From 1970 to 2021, the ST-GPR calculated the mean and standard deviation of blood lead levels for all ages, sexes, and GBD regions, combining them with the global distribution shape to derive the distribution of blood lead exposure. To estimate bone lead exposure, a cumulative blood lead index was calculated using the estimated blood lead exposure, and bone lead was estimated by applying a scalar defined in the literature. The blood lead index was calculated based on literature reports, survey data, and spatial and temporal variations in blood lead exposure, expressed as a curve for each year of life. The cumulative blood lead index was used as the area under the curve to estimate bone lead. We calculated the population attributable fraction (PAF) for lead exposure and its associated outcomes using the predefined GBD formula, generating a sample of 1,000 exposure and relative risk models. The number of deaths and DALYs attributable to lead exposure were calculated by multiplying the PAF by the expected number of deaths or DALYs for each country, age, sex, year, and disease. The number of deaths was estimated in GBD 2021 using the cause-of-death-integrated model (CODEm), which identifies the most appropriate model for the data by creating multiple models. The years lived with disability (YLD) were calculated by multiplying the disability weights by the per-disease prevalence, and years of life lost (YLL) were calculated by multiplying the number of deaths in each age group by the remaining life expectancy for that age group, ultimately summing YLL and YLD to arrive at the disability-adjusted life years (DALY) for each disease [20, 25]. All the estimated values are presented as counts or rates per 100,000 people, accompanied by 95% UI. These UIs were obtained by repeating each calculation step 1,000 times during the statistical process while incorporating uncertainties from multiple sources (such as input data and measurement errors). The construction of the UIs was based on the sorted data points, with the 25th and 975th values selected to determine them. In addition, we also evaluated the burden of ischemic heart disease caused by lead exposure among different SDI levels.

Join-point regression model

The join-point regression model, developed by Kim in 2000, employs segmented regression to analyze temporal trends in disease distribution [26]. This model enables the fitting and optimization of trends over time, facilitating comprehensive analysis of global disease trends. In this study, we applied the join-point regression model to evaluate trends in DALYs rates and mortality rates for IHD, calculating the average annual percentage change (AAPC) and annual percentage change (APC) with corresponding 95% uncertainty interval (UI). The AAPC is calculated based on a connection point regression model. This model takes into account changes in trends in time-series data, and it does a good job of capturing how the data changes over time and consolidating these changes into an average annual percentage change indicator that reflects the overall trend. Specifically, the model incorporates multiple regression stages based on observed disease trends over time, partitioning the study period into intervals defined by specific connection points. Trend optimization within each interval is achieved by setting these connection points to capture distinct patterns of disease progression. Monte Carlo random permutation tests were conducted to determine the number and location of breakpoints, with statistical significance assessed at $\alpha = 0.05$ (two-sided test). The join-point regression models were constructed in both linear and log-linear forms, with a preference for log-linear models in the analysis of population-based DALY rates and mortality rates for IHD: $E[y|x] = e^{\beta 0+\beta 1x+\delta 1(x-\tau 1)^{+}+\cdots+\delta k(x-\tau k)}$, Where x variable primarily represents time, and in analyzing time trends in lead exposure associated with ischemic heart disease, x is measured in years, e is the natural base, k indicates the number of turning points, τk indicates the unknown turning points, $\beta 0$ is the invariant parameter, $\beta 1$ is the regression coefficient, δk indicates the regression coefficient of the segment function in paragraph k. When $(x-\tau k) > 0$,$(x-\tau 1)^{+} = x-\tau k$, otherwise $(x-\tau 1) = 0$. Formula for calculating APC: $APC = \left(e^{\beta 1}-1\right) \times 100$. Formula for calculating AAPC: $AAPC = \left[\exp\left(\frac{\sum wi\beta i}{\sum wi}\right)-1\right] \times 100$. Where $\beta 1$ is the regression coefficient, wi is the width of the interval span (i.e., the number of years included in the interval) for each segmentation function, and $\beta 1$ is the regression coefficient corresponding to each interval.

Age-period-cohort model

The age-period-cohort model is a statistical approach used to analyze the effects of age groups, time periods, and birth cohorts on health outcomes. This model facilitates a more precise understanding of health outcome variability by dissecting and evaluating the distinct and combined impacts of these three factors. Age effects denote variations in health outcome risks at particular ages, while period effects capture synchronous changes in health outcomes across all age groups at various time points. Conversely, cohort effects reveal long-term health outcome trajectories for individuals born in the same year [27]. Arithmetically, the relationship between age, period, and birth cohort is expressed as: $Age = Period(yearofevent) - Cohort(yearofbirth)$. (or birth cohort = period − age). The age-period-cohort model assumes a Poisson distribution of the mortality rates (dependent variable) with age, period,

and birth cohort as the covariates/independent variables. The general equation of the age-period-cohort model is expressed as: $Y = \alpha 0 + \alpha X1 + \beta X2 + \gamma X3 + \epsilon$. where Y is the IHD mortality rate; $X1$, $X2$, and $X3$ are age groups and birth cohorts with corresponding effect estimates of α, β, and γ, respectively; $\alpha 0$ is the intercept; and ε is the residual. In fact, the natural logarithm of the mortality rate in the previous formula is a linear or additive function of age, period and birth cohort, as shown below: $\ln\left[E\left(Mij\right)\right] = \ln\left(\frac{Dij}{Pij}\right) = \mu + \alpha i + \beta i + \gamma k$. Where $E[Mij]$ represents the 5-year expected mortality rate for age group i (20–24, 25–39, 30–34, … 75 + years) and j period (1992–1996, 1997–2001…. …2017–2021); *Dij* and *Pij* denote the number of deaths and the corresponding population size for age group i and period j, respectively. *Dij* and *Pij* denote the number of deaths and the corresponding population size in age group i and period j, respectively. αi denotes the age effect in age group i; βj denotes the period effect in period j; γk corresponds to the cohort effect in the k_{th} $(k = i + j - 1)$ birth cohort, and μ is the intercept.

Age-period-cohort modeling: challenges and strategies

In this study, regarding the application of the age - period - cohort model, we took into account its significant differences from the simple log-linear regression model. Firstly, due to the natural linear relationship among age, period, and cohort, this relationship can lead to covariance problems. For example, for a given cohort, as time passes, the age of the cohort will inevitably increase accordingly. Such an interdependent relationship makes it extremely difficult to directly obtain the pure independent impacts of each factor through traditional regression methods. To address this "identifiability" challenge, we adopted the constrained regression method. Specifically, we set the sum of the age, period, and cohort coefficients to zero. With this constraint condition, the model identification dilemma caused by the covariance was broken, enabling us to effectively estimate the relative contributions of each factor. Taking the disease mortality data as an example, after organizing the data and fitting the structure of the age - period - cohort model, we utilized this constraint condition in the model fitting process and successfully analyzed the inherent patterns of the impacts of age, period, and cohort on the mortality rate of ischemic heart disease. Meanwhile, to further optimize the stability and reliability of the model estimation, we introduced the smoothing technique based on spline functions. This technique is applicable to the trend analysis of age, period, and cohort effects and can effectively alleviate the volatility and instability of the estimation results caused by covariance. Through the smoothing processing of spline functions, the hidden long-term trends and the interactions among various factors can be revealed more accurately. Thus, in the complex situation of covariance, it can provide us with more reasonable and convincing estimated values of the impacts of age, period, and cohort on the research results, thereby ensuring the effective application of the age - period - cohort model and the interpretation of the study results.

Autoregressive integrated moving average model

The Autoregressive Integrated Moving Average (ARIMA) model combines autoregressive (AR) and moving average (MA) components to analyze temporal fluctuations and identify inherent autocorrelations. This approach allows the ARIMA model to capture data dependencies over time. The model's general form is: $Y_t = {}_{\varphi 1}Y_{t-1} + {}_{\varphi 2}Y_{t-2} + ... + {}_{\varphi p}Y_{t-p} + e_t - \theta_1 e_{t-1} - ... - \theta_q e_{t-q}$, where $({}_{\varphi 1}Y_{t-1} + {}_{\varphi 2}Y_{t-2} + ... + {}_{\varphi p}Y_{t-p} + e_t)$ is the AR model part, $e_t - \theta_1 e_{t-1} - ... - \theta_q e_{t-q}$ is the MA model part, Y_{t-p} is the observed value at the period of $(t - p)$, p and q represent the model order of AR and MA, and *et* is the random error at the period of *t*.This model uses historical data to predict future trends. For constructing an ARIMA model, we assume the time series data is stationary, meaning it has a constant mean and variance over time, and we assess this assumption using the Augmented Dickey—Fuller (ADF) test; see Supplementary Figure S1 for more details. This assumption ensures the data has a stable central tendency without significant long-term growth or decline, which is essential for accurate forecasting and model reliability. As a result, the ARIMA model effectively captures time series dynamics, providing a robust framework for forecasting. The construction details of all statistical models can be found in Supplementary File 3.

Statistical analysis

We used age-standardized rates (ASRs) and 95% uncertainty intervals (UIs) to eliminate the effects of differences in the age structure of the population, as well as the effects of temporal variations in age distributions, ensuring data comparability. Therefore, when investigating the effects of lead exposure on IHD, we used age-standardized disability-adjusted life-year rates (ASDR) and mortality rates (ASMR) as the primary measures of disease burden. To examine ASDR and ASMR across countries, regions, and globally from 1990 to 2021, we employed linear regression analyses focusing on the natural logarithm of the age-standardized rate (ASR). Our model is built using the equation: $ln(ASR) = \alpha + \beta X + \lambda$, where α is the intercept, β is the slope, X represents time in years, and ϵ is the error term. The annual average percentage change (EAPC) is an estimate of the overall trend in the data that calculates the average rate of change based on model assumptions and the overall data distribution and it is a key metric to quantify the change in ASR over a

given time period. In the model fitting process, we utilize the natural logarithm of the time variable and the corresponding empirical data. This approach ensures that each piece of data contributes to the calculation of the EAPC, which, along with its 95% uncertainty interval (UI), is determined using the formula $100 \times (exp(\beta) - 1)$, where $exp(\beta)$ represents the exponential function e^{β}. If the 95% uncertainty interval for the EAPC includes 0 (corresponding to a p-value greater than 0.05), the trend is considered stable. This method of analysis contributed to a deeper understanding of the interaction between SDI and health burden. All statistical analyses were conducted using R software version 4.1.1.

Results

Global disease burden of ischemic heart disease associated with lead exposure

Table 1 presents several key health indicators of IHD and their trends globally from 1990 to 2021. In terms of the number of deaths from IHD, 5,367,137 deaths (95% UI: 5,076,404 to 5,562,774) were recorded in 1990, whereas in 2021, this number rose to 8,839,381 deaths (95% UI: 8,156,472 to 9,344,778), indicating a significant growth trend that underscores the increasing global health burden of IHD. Regarding DALYs, the number of DALYs due to IHD in 1990 was 120,931,950 (95% UI: 116,716,077 to 124,967,086), whereas in 2021, this number increased to 188,360,557 (95% UI: 177,036,930 to 198,154,477), again reflecting the growing yearly impact of IHD on human health. The number of deaths and DALYs increased by 64.69% and 55.75%, respectively. Despite the increase in the number of deaths and DALYs, the mortality and DALYs rates of IHD have shown a downward trend over the years. Additionally, we analyzed the changes in global lead exposure levels between 1990 and 2021 and the association between lead exposure and IHD. We observed a gradual decrease in global lead exposure levels from 46.7 (95% UI: 0.01 to 55.43) in 1990 to 38.2 (95% UI: 0 to 45.15) in 2021. Rates of IHD mortality and DALYs associated with lead exposure also showed a downward trend. This phenomenon may be closely related to the evolution of global policies on lead use.

Table 1 Trends in the Global Burden of Ischemic Heart Disease and the Impact of Lead Exposure, 1990–2021

Year	Numbers with uncertainty interval (95% UI)		Lead Exposure-Related IHD DALYs Rates	Age-standardized rate per 100 000 population (95% UI)		Lead Exposure Related IHD Deaths Rates	95% UI
	Number of deaths from IHD	Number of DALYs from IHD		Deaths rate for IHD	DALYs rate for IHD		SEV
1990	5,367,137 (5,076,404,5,562,774)	120,931,950 (116,716,077,124,967,086)	166.11 (−24.29,359.91)	158.9 (148.14,165.3)	3075.86 (2950.54,3185.53)	7.91 (−1.15,16.94)	46.7 (0.01,55.43)
1991	5,447,159 (5,173,861,5,648,149)	119,162,957 (114,547,787,123,454,733)	166.34 (−24.33,352.64)	156.77 (146.58,163.35)	3107.61 (2966.5,3222.67)	7.91 (−1.15,16.77)	46.88 (0.01,55.6)
1992	5,575,981 (5,296,293,5,782,569)	123,852,504 (119,252,601,128,364,192)	167.5 (−24.59,355.97)	156.08 (146.14,162.66)	3073.04 (2938.45,3190.45)	7.97 (−1.17,16.91)	47.03 (0.01,55.74)
2000	6,302,616 (5,962,705,6,520,776)	139,369,364 (134,450,667,143,366,421)	167.64 (−24.36,353.33)	142.54 (133.37,148.15)	2854.63 (2734.3,2941.25)	8.03 (−1.17,17.04)	47.15 (0.01,56.13)
2001	6,410,929 (6,063,644,6,619,307)	141,500,176 (136,281,979,145,642,793)	167.69 (−24.35,353.08)	140.96 (131.58,146.1)	2826.44 (2708.96,2914.2)	8.06 (−1.17,17.12)	47.03 (0.01,55.95)
2002	6,732,157 (6,357,694,6,946,606)	144,695,184 (139,695,690,148,820,505)	168.46 (−24.34,354.72)	140.12 (131.12,145.13)	2818.02 (2707.69,2901.03)	8.13 (−1.18,17.21)	46.88 (0,55.69)
2003	7,429,320 (6,960,145,7,690,364)	147,736,063 (142,517,693,151,856,785)	169.59 (−24.62,359.03)	125 (116.02,129.74)	2807.08 (2689.39,2886.95)	8.24 (−1.2,17.56)	46.7 (0,55.41)
2010	7,566,051 (7,089,927,7,861,225)	159,944,780 (153,875,003,164,898,125)	160.52 (−22.88,336.86)	123.33 (114.56,128.56)	2514.91 (2408.04,2593.89)	7.96 (−1.14,16.84)	44.47 (0,52.59)
2011	7,718,432 (7,241,311,8,023,195)	162,419,585 (155,715,970,167,630,240)	159.88 (−22.92,339.35)	121.82 (113.22,126.95)	2483.93 (2377.05,2567.5)	7.95 (−1.14,16.95)	44 (0.01,52.02)
2012	8,714,715 (8,104,138,9,159,319)	165,499,290 (158,417,291,171,269,215)	159.03 (−22.61,334.09)	110.92 (102.77,116.6)	2460.29 (2343.71,2550.45)	7.91 (−1.13,16.79)	43.5 (0.01,51.42)
2019	8,991,637 (8,264,123,9,531,130)	183,028,388 (173,418,581,191,324,733)	143.48 (−20.51,310.15)	108.73 (99.6,115.38)	2250.97 (2129.72,2352.31)	7.32 (−1.05,15.48)	39.42 (0.01,46.54)
2020	6,569,961 (6,219,604,6,777,359)	185,164,879 (175,081,621,194,414,591)	140.78 (−19.67,301.75)	140.49 (131.67,145.52)	2222.44 (2098.84,2333.49)	7.21 (−1.01,15.42)	38.81 (0,45.86)
2021	8,839,381 (8,156,472,9,344,778)	188,360,557 (177,036,930,198,154,477)	138.57 (−19.52,289.73)	109.47 (100.66,115.89)	2212.16 (2075.54,2327.61)	7.11 (−1.01,14.88)	38.2 (0,45.15)

IHD ischemic heart disease, *DALYs* disability-adjusted life years, *SEV* Summary Exposure Value

Global disease burden of ischemic heart disease associated with lead exposure

In 1990, the global death toll attributed to IHD due to lead exposure reached 277,682, with a 95% uncertainty interval (UI) ranging from −40,556 to 595,671. Concurrently, the DALYs for IHD due to lead exposure totaled 6,484,404, with a 95% UI of −177,012 to 27,414, affecting 4,040 cases (Table 2). By 2021, these figures increased to 590,370 deaths (95% UI: −83,778 to 1,233,628) and 11,854,611 DALYs (95% UI: −1,668,553 to 24,791,275), demonstrating an increase of 112.61% for deaths and 82.8% for DALYs, respectively. Despite the rising death toll and DALYs due to lead exposure, the ASMR and ASDR for lead-associated IHD in 2021 were 7.11 (95% UI: −1.01 to 14.88) and 138.57 (95% UI: −19.52 to 289.73), with corresponding EAPC of −0.32 (95% UI: −0.92 to 0.29) for ASMR and −0.59 (95% UI: −1.27 to 0.10) for ASDR, indicating a downward trend in ASMR and ASDR for lead-associated IHD (Tables 1 and 2).

Regional and national IHD burden and trends and trends, analyzed by sex and age

In the 2021 analysis of age distribution for deaths and DALYs attributable to IHD associated with lead exposure, global data indicate that IHD-related mortality and DALYs increase with age, peaking in specific age groups before declining. In 1990, the age group with the highest number of male deaths was 65–69 years, with 23,553 fatalities, whereas for females, it was 75–79 years, with 17,474 deaths (Fig. 2A). Concurrently, the age group with the highest DALYs for males was 60–64 years, totaling 637,183, and for females, it was 65–69 years, with 317,049 DALYs. By 2021, there was an increase in both mortality and DALYs, with males showing higher numbers than females across both indicators. In the 70–74 age group, male deaths reached 50,521, notably surpassing the 28,983 observed in females (Fig. 2B). Additionally, the highest DALYs were recorded in the 65–69 age group, with 1,099,549 for males and 568,552 for females. Further analyses categorized countries into five SDI based classes: high SDI, upper-middle SDI, lower-middle SDI, medium SDI, and low SDI. Supplementary Figure S2 illustrates that ASDR and ASMR were generally elevated in medium-low and low SDI regions compared to the other classes. Between 1990 and 2013, ASDR and ASMR exhibited an increasing trend annually, peaking in 2014, followed by a yearly decline that eventually stabilized. Conversely, fluctuations in ASDR and ASMR were less pronounced in high SDI and medium SDI regions (Supplementary Figure S2). This disparity may correlate with regional economic development levels and the quality of health care services.

Joinpoint regression analysis

Globally, trends in the incidence of IHD due to lead exposure correlate significantly with SDI. The study demonstrated a significant decrease in ASDR and ASMR for IHD in high SDI areas from 1990 to 2021, with ASDR decreasing from 99 to 35 cases per 100,000 population and ASMR decreasing from 5 to 2 cases per 100,000 population. This trend reflects strict lead management regulations, well-established surveillance systems, and effective public education in high SDI areas. However, IHD ASDRs and ASMRs are generally higher in low-SDI and low-moderate-SDI areas, and the overall upward trend continues despite the decline. For example, in 1990, the IHD ASDR in low-SDI and low-moderate SDI areas was 281 and 251 per 100,000 population, respectively, and by 2021, these numbers had slightly decreased to 274 and 240, respectively. Additionally, IHD ASMR in these regions increased from 12 and 11 cases per 100,000 population in 1990 to a peak of 15 and 13 cases, respectively, in 2014, followed by a slight decline. This difference may be related to the level of economic development and lead exposure management strategies in each region. High SDI regions such as North America and Western Europe have successfully reduced the health impacts of lead exposure through stringent regulations and international cooperation, whereas low SDI regions such as South Asia and some African countries rely on international assistance and localized solutions to cope with lead exposure due to resource and infrastructure constraints. Connection-point regression analysis further revealed gender differences, with males consistently having higher ASDR and ASMR than females across the five SDI regions. For example, in 2021, the global ASDR and ASMR for males were 193 and 10 per 100,000 population, respectively, compared to 90 and 4.5 for females. While ASDR and ASMR continue to decline in high SDI regions, these rates are relatively stable in other regions, reflecting the profound impact of economic development levels on lead exposure management and health outcomes. Through these diverse management strategies, SDI regions are working to reduce the impact of lead exposure on human health (Fig. 3).

Age, period and cohort effects of IHD deaths due to lead exposure

Figure 4 presents a detailed examination of the age, period, and cohort effects on IHD associated with lead exposure across varying SDI regions globally. Upon assessing the period and cohort effects, a uniform trend of increasing age-related mortality is discernible across all regions. In the youngest cohort of 25 to 29 years, the mortality rate was minimal, reported at 0.06 cases per 100,000 population; in contrast, the oldest cohort of 90

Table 2 Changes in the Global Burden of Ischemic Heart Disease Associated with Lead Exposure from 1990 to 2021

location	Numbers with uncertainty interval (95% UI)				Age-standardized rate per 100 000 population (95% UI)					
	1990		2021		1990		2021			
	Numbers of Death	Numbers of DALYs	Numbers of Death	Numbers of DALYs	Death rate	DALY rate	Death rate	EAPC, 95% CI	DALY rate	EAPC, 95% CI
Global	277,682 (−40,556,595,671)	6,484,404 (−947,862,14,078,198)	590,370 (−83,778,1,233,628)	11,854,611 (−1,668,553,24,791,275)	7.91 (−1.15,16.94)	166.11 (−24.29,359.91)	7.11 (−1.01,14.88)	−0.32 (−0.92 to 0.29)	138.57 (−19.52,289.73)	−0.59(−1.27 to 0.1)
High SDI	60,042 (−8491,131,073)	1,260,683 (−177,012,2,741,404)	49,289 (−6958,107,582)	2,027,585 (−275,337,4,329,966)	5.46 (−0.77,11.94)	132.97 (−18.71,289.85)	2.02 (−0.28,4.39)	−3.51 (−4.25 to −2.76)	103.45 (−14.06,220.96)	−3.63(−4.52 to −2.73)
High-middle SDI	21,905 (−3346,45,754)	1,123,444 (−158,081,2,423,687)	48,882 (−7144,102,007)	787,213 (−111,112,1,688,158)	11.55 (−1.79,23.92)	102.41 (−14.39,221.26)	12.23 (−1.8,25.3)	−0.45 (−1.05 to 0.16)	36.18 (−5.1,77.11)	−0.96(−1.69 to −0.23)
Middle SDI	69,709 (−9956,149,892)	1,785,423 (−270,992,3,878,566)	204,073 (−28,950,424,988)	3,874,158 (−552,190,8,296,862)	8.42 (−1.21,17.89)	285.91 (−43.55,614.67)	8.8 (−1.25,18.38)	0.28 (−0.31 to 0.87)	275.71 (−39.54,589.56)	−0.25(−0.91 to 0.42)
Low-middle SDI	58,196 (−8194,126,158)	570,733 (−85,915,1,206,635)	118,372 (−16,282,251,977)	1,143,287 (−165,427,2,416,512)	6.87 (−0.97,14.86)	253.44 (−38.6,532.62)	6.15 (−0.85,13.1)	0.38 (−0.1 to 0.87)	239.69 (−35.02,502.18)	0.01(−0.54 to 0.57)
Low SDI	67,431 (−10,272,143,821)	1,735,489 (−247,537,3,755,519)	169,233 (−24,369,361,479)	4,012,492 (−563,062,8,398,080)	12.64 (−1.93,26.76)	172.53 (−24.69,372.09)	13.54 (−1.96,28.81)	0.33 (−0.12 to 0.77)	157.02 (−22.14,328.22)	−0.14(−0.63 to 0.35)
East Asia	12,590 (−1923,27,066)	955,504 (−132,517,2,058,802)	33,548 (−4808,71,767)	2,653,373 (−369,089,5,784,456)	5.56 (−0.86,11.87)	119.42 (−16.93,255.28)	5.9 (−0.85,12.55)	0.18 (−0.38 to 0.74)	131.24 (−18.33,286.28)	0.62 (−0.04 to 1.29)
Southeast Asia	39,209 (−5555,84,029)	341,089 (−51,041,737,769)	154,245 (−21,706,332,277)	779,602 (−110,930,1,686,169)	6.22 (−0.9,13.52)	127.89 (−19.41,276.33)	8.36 (−1.18,17.97)	1.36 (0.71 to 2.01)	120.62 (−17.25,259.56)	−0.23 (−0.87 to 0.41)
Oceania	114 (−16,254)	3078 (−429,6809)	280 (−37,618)	7062 (−922,15,821)	5.16 (−0.73,11.34)	107.75 (−15.44,239.73)	4.95 (−0.67,10.92)	−0.12 (−0.73 to 0.5)	98.86 (−13.12,218.9)	−0.23 (−0.95 to 0.49)
Central Asia	4513 (−624,9788)	94,132 (−13,029,203,624)	6712 (−945,14,490)	129,489 (−18,083,278,052)	11.02 (−1.52,23.98)	210.33 (−29.11,455.51)	10.51 (−1.49,22.8)	−0.51 (−1.16 to 0.14)	179.01 (−25.16,385.57)	−0.96 (−1.71 to −0.21)
Central Europe	13,042 (−1819,27,760)	275,311 (−38,499,586,645)	13,137 (−1868,28,690)	212,875 (−30,224,459,749)	9.63 (−1.34,20.62)	190.21 (−26.57,404.72)	5.49 (−0.78,11.99)	−2.11 (−2.86 to −1.35)	92.98 (−13.17,200.62)	−2.62 (−3.55 to −1.68)
Eastern Europe	17,161 (−2306,37,247)	352,876 (−47,231,760,937)	23,972 (−3050,52,147)	425,216 (−53,264,938,292)	6.97 (−0.94,15.18)	132.82 (−17.78,286.75)	6.66 (−0.85,14.5)	−0.65 (−1.35 to 0.06)	120.1 (−15.03,265.2)	−0.9 (−1.81 to 0.01)
High-income Asia Pacific	3872 (−537,8464)	73,846 (−10,155,160,384)	5140 (−726,11,489)	72,226 (−10,190,159,243)	2.18 (−0.3,4.78)	38.4 (−5.29,83.71)	0.81 (−0.11,1.79)	−3.26 (−3.88 to −2.64)	13.88 (−1.95,30.6)	−3.48 (−4.3 to −2.65)

Table 2 (continued)

location	Numbers with uncertainty interval (95% UI)				Age-standardized rate per 100 000 population (95% UI)					
	1990		2021		1990		2021			
	Numbers of Death	Numbers of DALYs	Numbers of Death	Numbers of DALYs	Death rate	DALY rate	Death rate	EAPC, 95% CI	DALY rate	EAPC, 95% CI
Western Europe	2309 (−325,5046)	565,101 (−79,351,1,207,274)	1636 (−234,3537)	304,534 (−42,616,669,077)	10.15 (−1.43,22.15)	98.17 (−13.75,210.05)	2.6 (−0.37,5.64)	−4.67 (−5.32 to −4.01)	29.37 (−4.08,64.63)	−4.18 (−5.11 to −3.24)
Australasia	30,816 (−4344,66,304)	43,637 (−6123,95,018)	21,234 (−2973,46,930)	23,769 (−3388,51,396)	5.2 (−0.73,11.2)	187.73 (−26.31,408.89)	1.79 (−0.25,3.94)	−3.73 (−4.48 to −2.96)	41.29 (−5.85,89.29)	−5.16 (−5.99 to −4.33)
Southern Latin America	1834 (−248,4098)	38,949 (−5279,86,268)	1743 (−244,3879)	31,898 (−4454,70,213)	4.27 (−0.58,9.55)	85.84 (−11.63,190.41)	1.92 (−0.27,4.27)	−2.27 (−3.05 to −1.49)	36.24 (−5.05,79.82)	−2.54 (−3.53 to −1.54)
High-income North America	23,760 (−3412,51,694)	425,210 (−60,568,919,725)	17,022 (−2390,37,150)	273,647 (−38,082,589,745)	6.53 (−0.94,14.2)	120.9 (−17.16,261.61)	2.35 (−0.33,5.12)	−3.66 (−4.41 to −2.91)	40.19 (−5.57,86.36)	−3.87 (−4.74 to −3)
Caribbean	3487 (−519,7506)	74,607 (−11,140,160,140)	5397 (−769,11,485)	106,837 (−15,057,232,685)	14.62 (−2.17,31.49)	293.34 (−43.78,629.73)	9.88 (−1.41,21.02)	−1.26 (−1.7 to −0.82)	197.46 (−27.83,430.53)	−1.26 (−1.77 to −0.75)
Andean Latin America	877 (−119,1973)	18,954 (−2499,42,348)	1940 (−263,4306)	36,479 (−4908,81,566)	4.83 (−0.65,10.81)	94.79 (−12.62,212.47)	3.46 (−0.47,7.67)	−1.3 (−1.72 to −0.88)	62.94 (−8.5,140.41)	−1.55 (−2.09 to −1)
Central Latin America	7424 (−1049,15,602)	160,322 (−22,449,337,278)	20,489 (−2980,44,941)	369,802 (−53,225,804,469)	10.64 (−1.51,22.48)	202.14 (−28.51,423.79)	8.71 (−1.27,19.11)	−0.8 (−1.24 to −0.36)	151.51 (−21.87,329.58)	−1.15 (−1.72 to −0.58)
North Africa and Middle East	6800 (−949,14,597)	858,565 (−127,181,1,840,440)	9899 (−1448,21,307)	1,434,262 (−202,240,3,105,385)	8.6 (−1.21,18.51)	515.95 (−76.83,1109.53)	3.97 (−0.58,8.54)	−2.31 (−2.85 to −1.76)	335.84 (−47.91,725.26)	−1.45 (−1.79 to −1.12)
Tropical Latin America	34,785 (−5185,74,837)	165,881 (−23,010,355,596)	66,488 (−9522,143,314)	209,468 (−30,529,449,535)	24.69 (−3.69,53.31)	182.35 (−25.44,390.62)	18.16 (−2.63,39.14)	−1.03 (−1.3 to −0.77)	81.53 (−11.9,175.13)	−2.49 (−3.14 to −1.83)
South Asia	64,718 (−9936,138,448)	1,783,337 (−271,123,3,853,628)	184,304 (−26,477,388,248)	4,254,075 (−605,200,9,047,993)	12.64 (−1.95,26.67)	296.1 (−45.34,633.39)	14.3 (−2.06,29.94)	0.6 (0.23 to 0.97)	293.64 (−42,622.01)	0.11 (−0.31 to 0.52)
Central Sub-Saharan Africa	1362 (−191,2868)	35,614 (−4986,74,965)	3186 (−469,6816)	77,869 (−11,612,165,337)	7.71 (−1.1,16.21)	163.64 (−22.97,342.78)	7.98 (−1.16,17.16)	0.03 (−0.51 to 0.58)	156.05 (−22.92,334.88)	−0.26 (−0.91 to 0.39)

Table 2 (continued)

location	Numbers with uncertainty interval (95% UI)				Age-standardized rate per 100 000 population (95% UI)					
	1990		2021		1990		2021			
	Numbers of Death	Numbers of DALYs	Numbers of Death	Numbers of DALYs	Death rate	DALY rate	Death rate	EAPC, 95% CI	DALY rate	EAPC, 95% CI
Eastern Sub-Saharan Africa	3502 (−520,7336)	88,865 (−12,939,189,686)	7087 (−956,15,096)	165,385 (−22,321,351,561)	5.75 (−0.87,11.91)	122.88 (−18.21,258.82)	5.55 (−0.75,11.71)	−0.25 (−0.98 to 0.5)	106.96 (−14.53,227.42)	−0.6(−1.42 to 0.23)
Southern Sub-Saharan Africa	892 (−121,1958)	22,446 (−3069,49,405)	2071 (−289,4497)	47,598 (−6645,102,435)	3.73 (−0.51,8.19)	81.87 (−11.19,179.54)	4.36 (−0.61,9.47)	0.69 (−0.29 to 1.68)	86.09 (−12.05,185.94)	0.41(−0.69 to 1.53)
Western Sub-Saharan Africa	4615 (−666,9876)	107,080 (−15,420,229,559)	10,842 (−1545,23,308)	239,145 (−33,805,523,083)	6.39 (−0.92,13.57)	127.96 (−18.48,273)	7.35 (−1.05,15.71)	0.45 (0.14 to 0.76)	135.55 (−19.37,292.71)	0.18(−0.2 to 0.55)

DALYs disability-adjusted life years, *EAPCs* estimated annual percentage changes

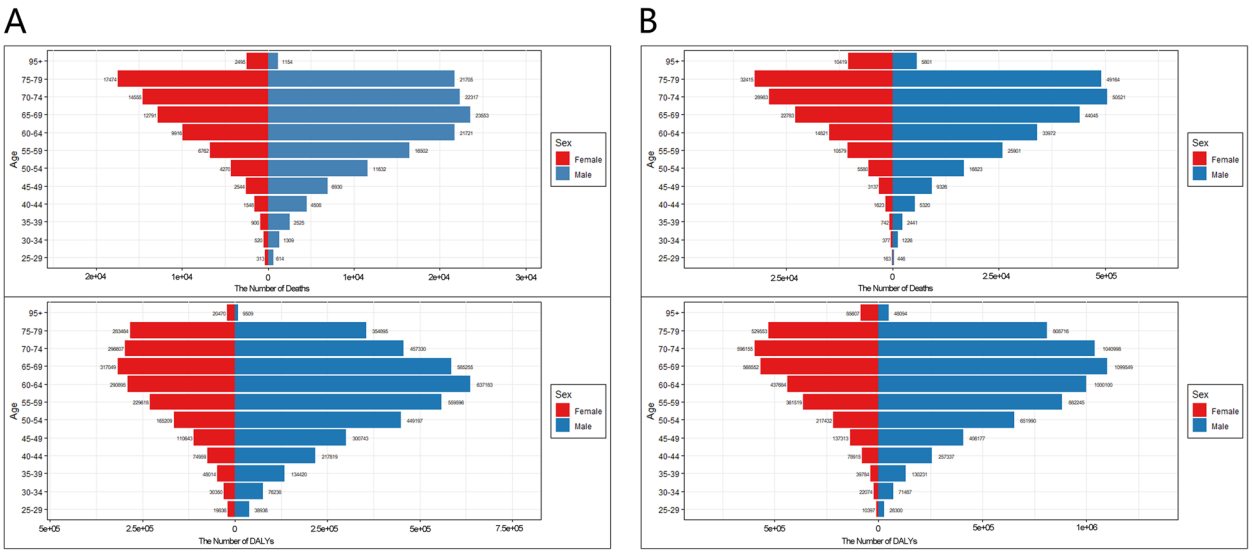

Fig. 2 DALYs and deaths from ischemic heart disease due to lead exposure at different times and age groups. **A** DALYs and deaths in 1990 (**B**) DALYs and deaths in 2021

to 94 years exhibited a substantially elevated rate of 277.8 cases per 100,000 population. Across all age groups, mortality rates were typically lower in high SDI regions compared to those with lower SDI levels (Fig. 4). Globally, the mortality risk reached its zenith between 1995 and 2000, subsequently declining to its nadir between 2015 and 2021. Notably, in low and lower-middle SDI regions, the mortality risk commenced its decline post-peak between 1995 and 2000, achieving its lowest ebb between 2015 and 2019. Concurrently, mortality risk in medium, high, and low SDI regions exhibited a similar downward trajectory. It is important to note that individuals born between 1935 and 1945 are at the greatest risk of mortality. The patterns across varying SDI regions align with the global mean, manifesting an initial ascent followed by a descent. Individuals born between 1910 and 1920 exhibit the peak mortality risk within high SDI regions. The mortality risk for those born between 1921 and 1929 reached its apex within the upper-middle SDI region. The cohort born between 1935 and 1946 recorded the highest mortality risk in medium SDI regions. Furthermore, individuals born between 1936 and 1942 encountered the maximum mortality risk in low, medium, and lower-middle SDI regions (Fig. 4). These findings underscore substantial disparities in mortality risk from myocardial ischemia associated with lead exposure among individuals born in various decades and across SDI regions. Likewise, the DALYs for myocardial ischemia due to lead exposure paralleled this mortality risk trend (Supplementary Figure S3). The resulting data from the model calculations can be found in Supplementary Tables S1 through S6.

Socio-Demographic Index related to ASDR and ASMR of IHD

In 2021, an examination of SDI regions revealed that the ASMR and ASDR for IHD associated with lead exposure were highest in low SDI regions and lowest in high SDI regions (Table 1). Between 1990 and 2021, ASMR increased across all SDI regions, yet it declined in high SDI regions, with an EAPC of −3.51 (95% UI: −4.25 to −2.76) and −0.45% (95% UI: −1.05 to 0.16), respectively. Concurrently, ASMR in other SDI areas exhibited an escalating trend. Furthermore, the IHD ASDR related to lead exposure displayed a marginal increase solely in low and medium SDI areas, with an EAPC of 0.01 (95% UI: −0.54 to 0.57), in contrast to a downward trend in other regions. Figure 5C and D provide additional clarity on the national trends in ASMR and ASDR in relation to SDI from 1990 to 2021. Collectively, the IHD burden associated with lead exposure escalates with rising socioeconomic status; however, this upward trajectory starts to decelerate as the SDI nears 0.65, and the burden begins to incrementally diminish as the SDI ascends further. Notably, IHD burdens were considerably higher than anticipated in certain countries like Iran and Morocco, whereas others, including the United States and the United Kingdom, displayed markedly lower burdens than projected.

ASDR and ASMR for predicting lead exposure-Related IHD in the next decade

We utilized ARIMA models to forecast trends in DALYs and mortality associated with IHD due to lead exposure

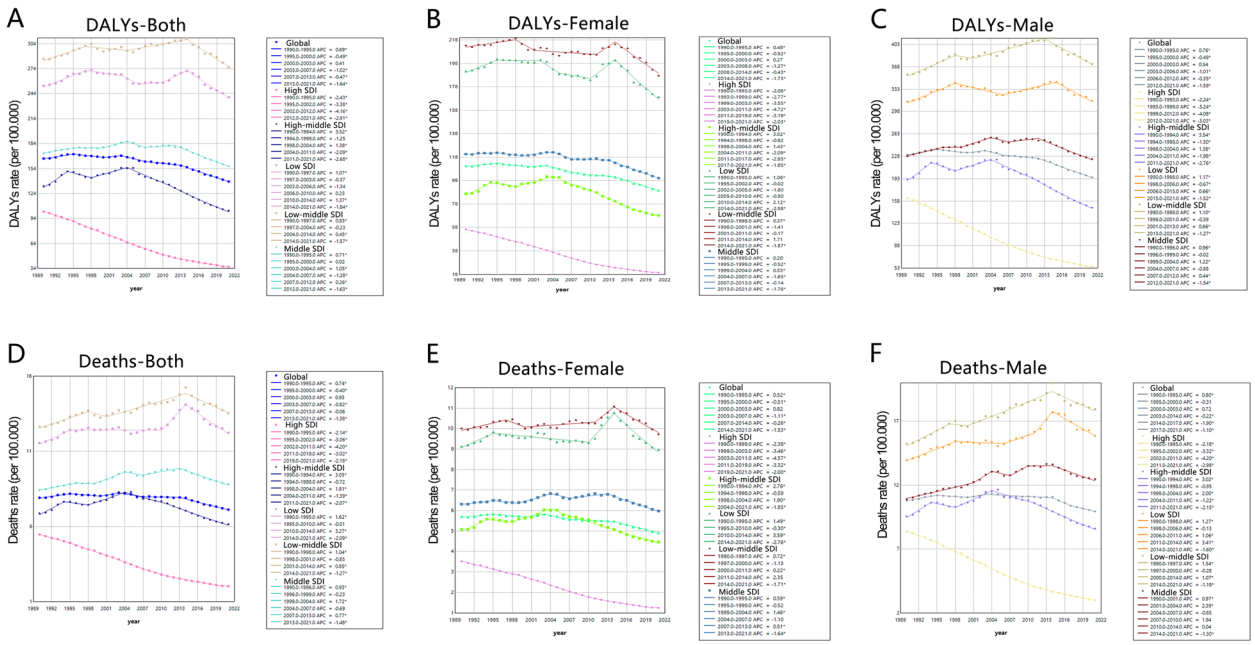

Fig. 3 Trends in global age standardized DALYs rates and mortality from IHD due to lead exposure, 1990–2021. **A** age-standardized rates of DALYs; (**B**) age-standardized rates of DALYs for IHD in females; (**C**) age-standardized rates of DALYs for IHD in males; (**D**) age-standardized mortality rates; (**E**) age-standardized mortality rates for IHD in females; (**F**) age-standardized mortality rates for IHD in males

across various SDI regions over the next decade. The auto.arima() function was employed for model selection, identifying optimal ARIMA models with corresponding Akaike Information Criterion (AIC) values for different SDI levels. The optimal global model was ARIMA (1,2,1) with an AIC of 94.05. For the high SDI region, the optimal model was ARIMA(1,1,2) with an AIC of 60.8; for the medium-high SDI region, ARIMA(1,2,1) with an AIC of 146.8; for the low SDI region, ARIMA(1,2,2) with an AIC of 166.13; for the medium-low SDI region, ARIMA(0,1,2) with an AIC of 165.27; and for the medium SDI region, ARIMA(1,2,2) with an AIC of 113.24, AIC values for the other ARIMA models for each SDI region are shown in Supplementary Table S7. Analysis of normal Q-Q plots, autocorrelation function (ACF), and partial autocorrelation function (PACF) plots confirmed the normal distribution properties of the residuals (Supplementary Figures S4-S5). Additionally, the Ljung-Box test indicated that the residuals for all SDI regions conformed to a white noise process (all p-values > 0.05, Supplementary Figure S6), supporting the models' validity. Using a similar methodology, we constructed an ARIMA model for the IHD death rate and verified its stability through the Ljung-Box test. Across SDI regions, ASDR projections are consistent with observations (Fig. 6). Specifically, in high SDI areas, the ASDR for IHD is projected to decline from 35 cases per 100,000 population in 2021 to 30 cases per 100,000 population in 2031 (Fig. 6B). This downward trend is also observed in the medium and medium-high SDI regions. The most pronounced decline is in the medium-low SDI region, projected to decrease from 275 cases per 100,000 persons in 2021 to 210 cases per 100,000 persons in 2031 (Fig. 6E). Regarding ASMR, there is consistency between projected and actual observations. Across the SDIs, ASMR is projected to show a downward trend from 2021 to 2031, with the most significant decrease in the lower and middle SDI, projected to fall from 13.5 cases per 100,000 population in 2021 to 12.1 cases per 100,000 population in 2031 (Supplementary Figure S7).

Socio-demographic indicators related to ASDR and ASMR of IHD

Globally, the ASMR and ASDR for IHD due to lead exposure exhibited varying trends from 1990 to 2021, with notable regional differences (Table 1). In high SDI countries, both ASMR and ASDR associated with IHD significantly decreased, with EAPCs of −3.51 (95% UI: −4.25 to −2.76) and −3.63 (95% UI: −4.52 to −2.73), respectively. Similarly, high-intermediate SDI countries experienced a downward trend, with EAPCs of −0.45 (95% UI: −1.05 to 0.16) and −0.96 (95% UI: −1.69 to −0.23), respectively. Conversely, in medium, low-middle, and low-SDI countries, ASMR and ASDR for IHD related to lead exposure continued to rise, with EAPCs of 0.28 (95% UI: −0.31 to 0.87), 0.38 (95% UI: −0.10 to 0.87), and 0.33 (95% UI:

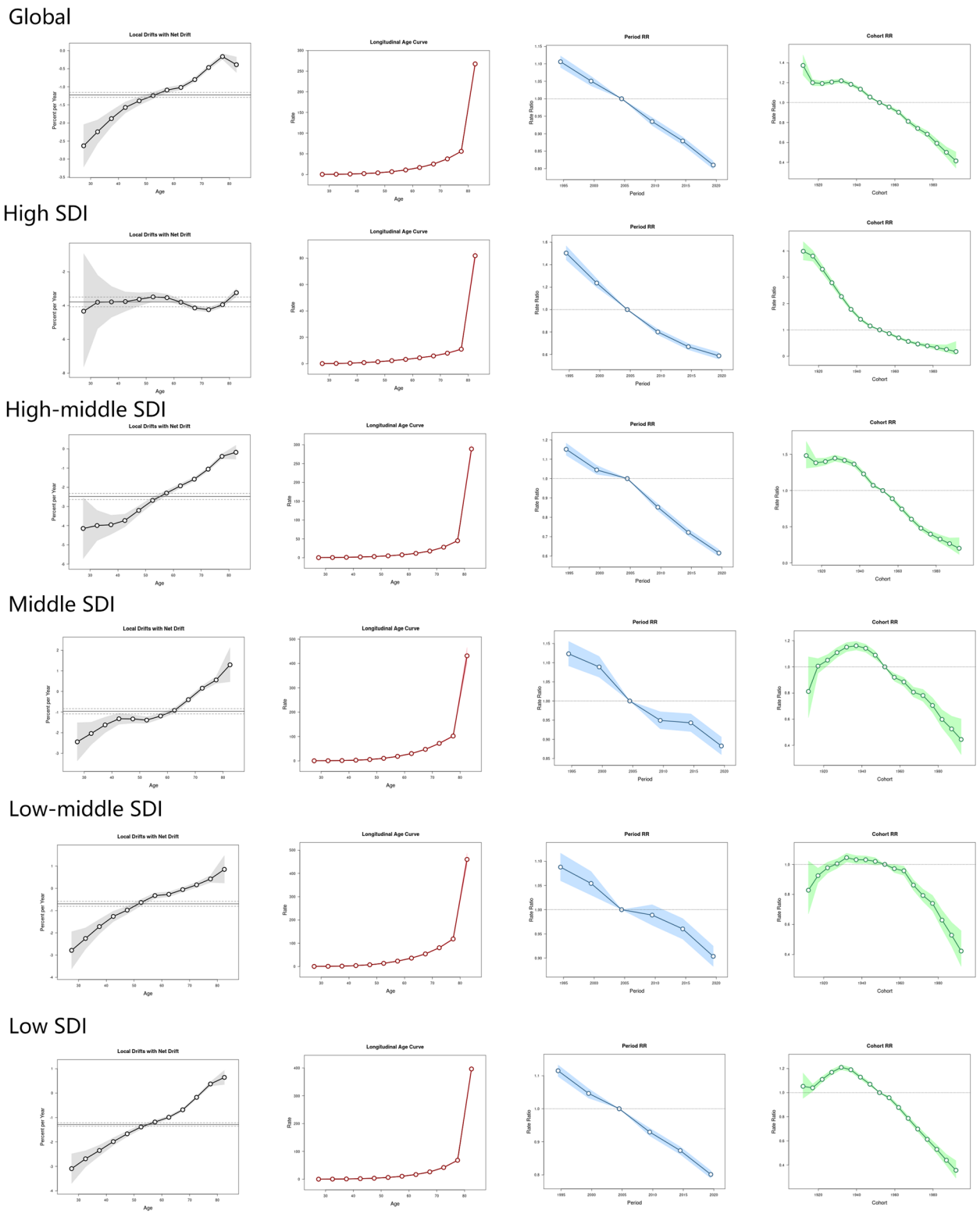

Fig. 4 Age, period, and cohort effects on ischemic heart disease mortality due to lead exposure globally and across SDI regions. Longitudinal Age Curve: Fitted longitudinal age-specific rates in reference cohort c0 adjusted for period deviations. Period RR: Ratio of age-specific rates in period p relative to reference period p0. Cohort RR: Ratio of age-specific rates in cohort c relative to reference cohort c0. Local Drifts with Net Drift: Estimated annual percentage change over time specific to age group a

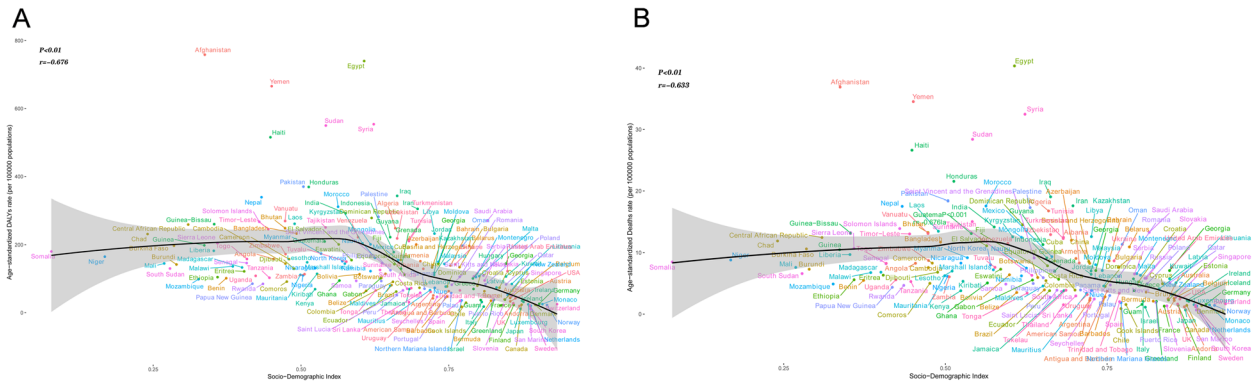

Fig. 5 ASDRs and ASMRs for lead-exposure-related IHD by SDI for 204 countries and territories in 2021.The black line is the expected value. Each dot shows the observed age-standardized DALY rate and mortality rate for a given country in 2021. ASDR: age-standardized disability-adjusted life year rate; ASMR: age-standardized mortality rate; SDI: sociodemographic index

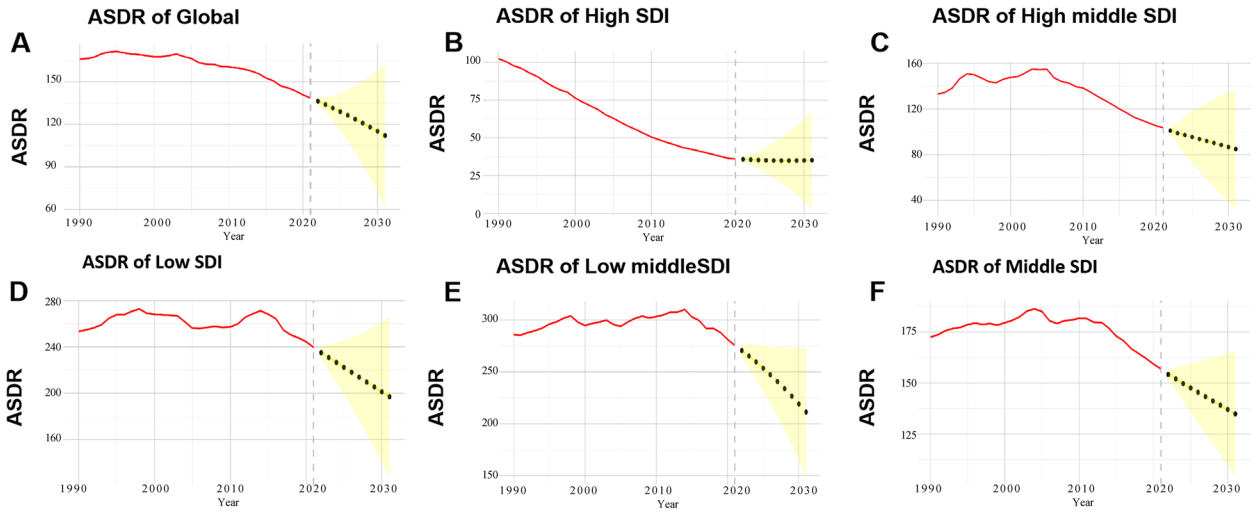

Fig. 6 Projected trends in global age-standardized disability-adjusted life-year rates from IHD due to lead exposure over the next 10 years. The red line represents the true trend in ischemic heart disease mortality over the period 1990–2021; the yellow dashed line and shaded area represent the projected trend and its 95% UI

−0.12 to 0.77), respectively. As of 2021, ASDR varied significantly across countries, ranging from 758.43 cases per 100,000 people in Afghanistan to 11.28 cases per 100,000 people in San Marino (Fig. 7A). ASMR also showed wide variation, from 2.82 cases per 100,000 people in Lesotho to −5.56 cases per 100,000 people in Israel (Fig. 7B). A total of 47 countries exhibited an upward trend in ASMR and ASDR (EAPC > 0), with Lesotho and Zimbabwe showing the most significant increases, with EAPC values of 2.89 (95% UI: 1.84 to 3.95) and 2.82 (95% UI: 1.93 to 3.72) for ASMR, and 2.04 (95% UI: 1.13 to 2.97) and 1.95 (95% UI: 1.17 to 2.74) for ASDR. Conversely, 157 countries demonstrated decreasing trends in ASMR and ASDR. Among these, Israel, Denmark, the United Kingdom, Norway, Australia, and the Netherlands showed the most significant reductions in ASMR (Fig. 7C), with EAPC values below −4 (Supplementary Table S8). In terms of ASDR, Ireland, Israel, Denmark, the United Kingdom, and Switzerland exhibited the most substantial downward trends (Fig. 7D), with EAPC values also below −4 (Supplementary Table S9).

Discussions

Upon a thorough examination of the most recent GBD data, specifically GBD2021, it was observed that mortality and ASDR for IHD due to lead exposure exhibit significant variability over time and across regions. In high and upper-middle SDI regions, the burden of IHD associated with lead exposure, as measured by ASMR and ASDR, demonstrated a declining trend from 1990 to

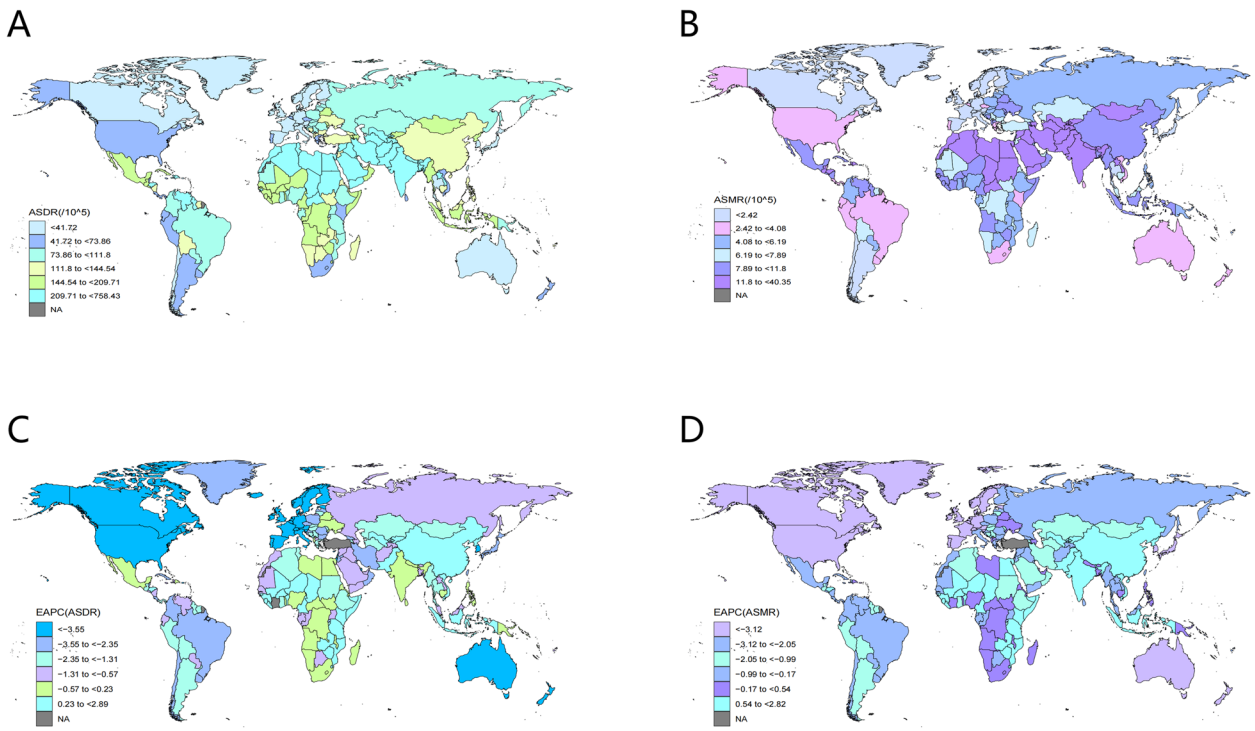

Fig. 7 Sum of age-standardized mortality and disability-adjusted life-year rates for ischemic heart disease due to lead exposure for men and women in each country in 2021 (**A**, **B**); and combined EAPC for men and women in age-standardized mortality and disability-adjusted life-year rates for ischemic heart disease due to lead exposure for men and women in each country from 1990 to 2021 (**C**, **D**)

2021. Conversely, in low, lower-middle, and middle SDI areas, the ASMR and ASDR burden of IHD related to lead exposure increased from 1990 to 2014, subsequently stabilizing post-2014. Furthermore, the data indicate that certain populations, including males, older adults, and those residing in low and lower-middle SDI regions, are at an elevated risk for the burden of IHD due to lead exposure. These findings have significant implications for guiding policy development, prioritizing resource allocation, and implementing effective preventive measures to mitigate the risk of IHD from lead exposure.

Despite the global phase-out of leaded gasoline and leaded paint, lead exposure pathways remain widespread [28], particularly in activities such as mining and smelting of metals, waste incineration, and battery recycling [29]. Although the use of leaded gasoline in automobiles has been halted globally, lead is still added to aviation gasoline, posing a continuing threat to the environment and health. Additionally, lead paint is not banned worldwide, especially in countries with low SDI, which may lack adequate regulatory and enforcement capacity, leading to the widespread use of lead paint. Even in countries where lead paint is officially banned, there is evidence of its sale through unofficial markets. These factors collectively pose a major challenge in managing lead exposure globally, particularly in middle-income and low-income countries [30]. The World Health Organization lists lead as one of the ten hazardous chemicals requiring priority attention and ranks it fourth among major environmental health risk factors [25, 31]. Lead exposure increases the risk of developing cardiovascular diseases, including elevated blood pressure, plaque formation in arterial walls, and coronary artery disease [9]. Lead is harmful as it inhibits the normal production of glutathione, increases lipid oxidation, disrupts nitric oxide (NO) levels, and impairs vascular endothelial function, potentially leading to atherosclerotic lesions [32]. Several studies have shown associations between lead exposure and ischemic heart disease [33]; however, comprehensive and in-depth research on the health burden related to lead exposure and ischemic heart disease remains scarce.

In the present study, we found that the cumulative effect of lead exposure on the burden of IHD varied significantly across age groups. Notably, the impact of lead exposure on IHD mortality was particularly significant among individuals born between 1910 and 1920. This finding may be related to the cumulative effect of lead exposure, which refers to the long-term impact on cardiovascular health from the total amount of lead an individual is exposed to over their lifetime. Lead is a known

neurotoxin and cardiovascular toxin, and long-term exposure may lead to atherosclerosis, elevated blood pressure, and myocardial damage, thereby increasing the risk of IHD. Although older age groups typically have higher mortality rates for various reasons, the cumulative effects of lead exposure may exacerbate the burden of IHD in these groups. Additionally, the risk of death associated with myocardial ischemia increases with age [34]. The efficiency of the body's metabolism declines with advancing age, increasing the likelihood of developing chronic conditions such as hypertension and diabetes [35, 36]. Concurrently, the comparatively compromised immune system of older adults, along with pre-existing health conditions and external environmental factors, predisposes them to an increased risk of developing IHD [37] Furthermore, males exhibit a higher incidence of IHD compared to females, potentially due to increased exposure to environmental risk factors and unhealthy lifestyle habits. For instance, males are more frequently employed in high-risk occupations such as mining, metal smelting, and welding, which pose an elevated risk of lead exposure. Concurrently, behaviors detrimental to heart health, such as smoking and alcohol consumption [38, 39], which are established risk factors for cardiovascular disease, are more prevalent among males. Therefore, gender disparities in susceptibility to lead-induced IHD may be significantly associated with these factors [40].

Utilizing the joinpoint regression model in our analysis, we identified a significant correlation between IHD associated with lead exposure and the SDI. The health burden of IHD due to lead exposure has shown a declining trend from 1990 to 2021, particularly in high SDI countries and regions. Effective ambient air pollution control measures and sufficient health service resources are pivotal in addressing these disparities. Beginning in the 1970s, several high-income countries, including the United Kingdom, the United States, Switzerland, and Poland, enacted regulations strictly prohibiting the inclusion of lead in fuel [41, 42]. Some countries, such as Sweden and Spain, have expanded these bans to include paints or have established stringent limits on lead content in paints, similar to practices in the United States. These measures have significantly reduced blood lead levels [42]. Compared to high-income countries, regions with lower SDI experienced an initial increase followed by a reduction in the burden of IHD due to lead exposure, potentially due to the delayed adoption of environmental control measures [21]. The relatively poor socioeconomic conditions in these regions, coupled with scarce medical resources and less advanced technology, pose significant challenges to effectively managing IHD caused by lead exposure. Concurrently, developed countries benefit from robust healthcare systems, encompassing comprehensive medical services, nutritional support, and healthcare, all contributing to mitigating the effects of lead exposure on IHD. Over the past few decades, several nations in the developing and least developed categories have implemented policies and regulations aimed at reducing the risk of lead exposure [43]. However, in low- and middle-income countries with higher levels of lead contamination, lead exposure remains a significant health challenge [23]. A critical imperative for these nations is implementing effective measures to mitigate lead exposure. Strengthening environmental monitoring and providing heightened vigilance for vulnerable populations are among the recommended strategies [44]. These strategies are essential not only for alleviating the burden of IHD but also for significantly contributing to the mitigation of other diseases [45]. Additionally, enhancing the quality of primary health care services, including diagnosis, treatment, and referral, is crucial for improving life quality [46]. In conclusion, variations in preventive and therapeutic approaches to tackle lead exposure and its cardiovascular implications vary by region, primarily driving the disparity in IHD burden. Hence, there is an imperative for more comprehensive prospective studies, particularly in low- and middle-income countries, to precisely evaluate the impact of lead exposure on IHD risk [47]. This will facilitate the development of more efficacious prevention and intervention strategies to curtail the public health ramifications of lead exposure.

Based on the outcomes of the Age-Period-Cohort (APC) model, IHD mortality associated with lead exposure demonstrates a significant positive relationship with age. The bodily accumulation of lead toxins increases with age, leading to sustained chronic exposure [16]. The mortality rate associated with IHD due to lead exposure shows a marked escalation after the age of 70 to 80 years. The increased susceptibility of the older population to conditions such as hypertension, diabetes, and cardiovascular disease, along with the cumulative effects of lead exposure, heightens their risk of developing IHD [34]. The cyclical impact on the IHD burden presents as a fluctuating pattern over time, potentially correlated with advancements in medical technology, diagnostic improvements, and shifts in economic and cultural factors [18, 48, 49]. Our study findings indicate an overall downward trend in the cyclical impact of IHD, likely due to socioeconomic improvements and advances in medical technology that have effectively controlled and mitigated the adverse health effects of lead exposure, thereby reducing the mortality rate [4, 50]. Cohort analyses robustly demonstrate the diverse early-life exposures to socioeconomic status, behavioral practices, and environmental factors that differ across birth years. The current study observed an initial increase in IHD deaths across

birth cohorts, followed by a decrease, with earlier-born individuals facing a higher IHD risk compared to those born later. This reduction in risk is likely attributed to recent policies effectively restricting lead use [51], as well as the younger generation's advantage of superior education and heightened health consciousness [28].

Furthermore, we employed the Autoregressive Integrated Moving Average (ARIMA) model to forecast the mortality and DALYs rates of IHD associated with lead exposure for the forthcoming decade. Our analysis indicates that in countries and regions with a high SDI, IHD mortality is anticipated to exhibit a declining trend over the next decade. Nonetheless, in regions with a lower SDI, this downward trend is less pronounced. Consistent with prior research, a negative correlation exists between SDI and the disease burden associated with lead exposure [18, 21]. Moreover, common risk factors for IHD, including adverse lifestyle practices and environmental exposures, are significantly correlated with socioeconomic status, rendering low- and middle-income nations more susceptible to the IHD burden [52]. Significantly, the DALYs rates for IHD linked to lead exposure are anticipated to rise markedly in the next decade, particularly in regions with low and middle SDI. This underscores the urgency of addressing lead exposure in low SDI regions as a critical environmental issue that necessitates effective prevention and mitigation strategies to curtail the disease burden induced by lead exposure.

Our study found a significant association between lead exposure and IHD, filling a crucial knowledge gap in the existing literature and providing a valuable reference point for public health policy development. By quantifying the impact of lead exposure on the burden of heart disease, our findings reveal potential points of intervention, urging policymakers to prioritize lead exposure control in future health strategies. Additionally, the results offer new directions for future research, suggesting that more systematic longitudinal studies are necessary to investigate the specific effects of lead exposure in different populations, thereby developing more effective preventive measures. Although our study identified a significant association between lead exposure and IHD, the cross-sectional nature of the GBD data limits our ability to determine causality. This limitation necessitates caution in interpreting the results. Therefore, future research should incorporate longitudinal data or experimental designs to further explore how lead exposure influences the pathogenesis of IHD.

In addition, due to the observational nature of the data, our study may be influenced by sample selection bias and changes in the external environment, which could potentially limit the generalizability of the results. Therefore, we are cautious when interpreting these findings and suggest that future research adopt more rigorous experimental designs, such as randomized controlled trials, and longitudinal data to further validate these relationships and explore potential causal mechanisms. Despite these limitations, we believe that this study provides new insights into the relationship between lead exposure and IHD and offers valuable preliminary evidence for public health interventions. We fully recognize that our policy recommendations should be regarded as initial investigations based on the current data. Their implementation demands evaluation within a broader scope of empirical research and specific socio-cultural contexts. Future studies ought to incorporate randomized controlled trials and longitudinal studies to furnish a more solid evidence foundation that can support the validity and applicability of these policy suggestions. In general, our research has provided novel perspectives on the relationship between lead exposure and ischemic heart disease and has furnished a preliminary basis for formulating relevant policies. Nevertheless, we stress the necessity for additional research to corroborate these findings and conduct a comprehensive impact assessment prior to implementing any policy recommendations. We anticipate that future research will be able to offer more profound insights to assist policymakers in making decisions regarding the reduction of lead exposure and associated health risks.

Conclusion

Our study found that the burden of lead-exposure-related IHD was greater among older adults, men, and in low-to-moderate SDI regions, particularly in Tropical Latin America. In addition, age-standardized mortality rates and DALY rates for lead-exposure-associated IHD declined progressively from 1999 to 2021 globally. Based on our findings, we suggest that governments in low SDI regions should strengthen the implementation of lead exposure prevention strategies and gradually increase the awareness of self-protection among lead-exposed individuals to reduce the burden of IHD due to long-term lead exposure.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01155-w.

Supplementary Material 1: Supplementary Tables S1-S6. The result data of the age-period cohort model.

Supplementary Material 2: Supplementary Table S7. AIC values for other ARIMA models for each SDI region.

Supplementary Material 3: Supplementary Table S8. EAPC in age standardized mortality from ischemic heart disease due to lead exposure in 204 countries worldwide, 2021.

Supplementary Material 4: Supplementary Table S9. EAPC in age standardized DALYs rate from ischemic heart disease due to lead exposure in 204 countries worldwide, 2021.

Supplementary Material 5: Supplementary Figure S1. The Augmented Dickey - Fuller (ADF) test result. The data always fluctuated around the horizontal line without any significant upward and downward trend, indicating that the good data is stable, and the P value is less than 0.05.

Supplementary Material 6: Supplementary Figure S2. Global trends in the burden of ischemic heart disease due to lead exposure, 1990-2021.

Supplementary Material 7: Supplementary Figure S3. Age, Period, and Cohort Effects of Lead Exposure on Ischemic Heart Disease Disability-Adjusted Life Years Rates, Globally and by SDI Region.

Supplementary Material 8: Supplementary Figure S4. Autocorrelation function and partial autocorrelation graphs after differencing. Truncated: the autocorrelation or partial autocorrelation of a time series quickly becomes 0 after reaching a certain order. trailing: the autocorrelation or partial autocorrelation of a time series gradually decreases to 0 after reaching a certain order.

Supplementary Material 9: Supplementary Figure S5. Residual Q-Q plots, autocorrelation function and partial autocorrelation graphs of the ARIMA models. The residuals of the model satisfy a normal distribution with mean 0 (i.e., there is no correlation between the residuals).

Supplementary Material 10: Supplementary Figure S6. Ljung-Box test result graph. All values of the white noise test are above 0.05, indicating that the model fit is accurate, all information has been extracted, and the model has good validity and predictive ability.

Supplementary Material 11: Supplementary Figure S7. Projected trends in global age-standardized disability-adjusted life-year rates for ischemic heart disease due to lead exposure over the next 10 years.

Supplementary Material 12: Supplementary Figure file 1. Data Extraction Steps.

Supplementary Material 13: Supplementary Figure file 2. Raw code for data analysis.

Supplementary Material 14: Supplementary Figure file 3. The construction details of all statistical models.

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Authors' contributions
YD: Conceptualization, Writing – original draft. AD: Formal Analysis, Methodology, Supervision, Writing—original draft, Writing – original draft. HY: Conceptualization, Writing – original draft. TQ: Conceptualization, Methodology, Writing – original draft. LW：conceptualization, Methodology, Validation, Writing–original draft, HZ: Methodology, Validation, Writing – review & editing.

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Data availability
The data that support the findings of this study are openly available in Institute for Health Metrics and Evaluation IHME website at [http://ghdx.healthdata.org/gbd-results-tool].

Declarations

Ethics approval and consent to participate
Ethical approval and consent to participate were not necessary for this study. This study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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