Global Burden, Socio-demographic Index Correlations, and Mendelian Randomization Analysis of Risk Factors in Ischemic Heart Disease: A Comprehensive Study Based on GBD 2021 Data

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Abstract

Objective   Based on GBD 2021 data, to analyze the global trends in the burden of ischemic heart disease (IHD) from 1990 to 2021, its association with the Socio-demographic Index (SDI), and to evaluate the causal effects of risk factors.   **Methods**   IHD epidemiology and risk factor data from 204 countries and territories globally were extracted. Age-standardized rates (ASR) and average annual percentage change (AAPC) were calculated. Joinpoint regression, Mendelian randomization (MR), and ARIMA models were employed for trend analysis, causal inference, and prediction.   **Results**   Globally, the age-standardized incidence, mortality, and DALY rates of IHD declined (AAPC: -0.379, -1.200, and -1.083, respectively), while the prevalence rate slightly increased (AAPC: 0.040).North Africa, the Middle East, and Central Asia had the heaviest burden, while low-middle SDI regions had the highest incidence and prevalence rates.MR showed that smoking, high BMI, high waist-to-hip ratio, and high triglycerides increase IHD risk, while LDL-C had a protective effect (OR=0.996, p=0.006). Predictions indicate that the disease burden among females will continue to worsen in the future.   **Conclusions**   The burden of IHD is closely associated with SDI, necessitating targeted prevention and control strategies for low-middle SDI regions and addressing gender disparities.

Keywords: Ischemic heart disease; Global Burden of Disease; Socio-demographic Index; Risk factors; Mendelian randomization

1. Introduction

Ischemic heart disease (IHD) is a cardiac disorder resulting from the narrowing or obstruction of coronary arteries, primarily due to atherosclerosis, which reduces blood supply to the myocardium. As the foremost cause of mortality worldwide, IHD imposes a substantial clinical and public health burden, with persistently increasing global impact [1]. Despite widespread public health initiatives, annual IHD-related deaths continue to escalate. Currently, an estimated 126.5 million individuals are affected globally, accounting for more than 9 million fatalities annually, representing a major threat to human health [2]. The pathogenesis of IHD is multifactorial and challenging to predict; current preventive strategies mainly target modifiable risk factors. Conventional risk factors include hypertension, elevated low-density lipoprotein cholesterol, and smoking [3]. In addition, amid rapid socioeconomic development and increasingly demanding lifestyles,

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psychosocial factors—such as chronic stress, depression, and social isolation—are increasingly recognized as significant contributors to the development and progression of IHD[4]. Elucidating the relative influence and temporal trends of these modifiable risk factors is essential for global IHD prevention and control. Such insights are crucial for informing public health policy and enhancing clinical practice, thereby mitigating the global health burden imposed by IHD.

As living standards rise, public attention to personal health has grown considerably. Among various health concerns, the epidemiological profile and disease burden of ischemic heart disease (IHD) remain major focuses of global health research. IHD not only substantially impairs patients' quality of life but also imposes considerable burdens on families and societies. In recent years, its incidence has gradually increased, particularly among middle-aged and elderly populations. This trend has garnered significant attention from the medical community and elicited multifaceted societal responses, ranging from lifestyle modifications to advances in medical technology. For example, Marco et al. analyzed trends in premature IHD mortality in Italy [5], while Federico et al. used GBD 2019 data to examine temporal changes in IHD incidence and mortality across Western Europe, observing a modest decline [6]. Duygu et al. focused on IHD mortality in Turkey [7], and Eng Joo et al. investigated urban–rural disparities in IHD burden in Australia [8]. Nevertheless, comprehensive analyses of the global IHD burden using GBD 2021 data are still lacking—a gap that may impede the formulation of effective, region-specific prevention strategies.

To systematically investigate the global epidemiology and disease burden of ischemic heart disease (IHD), this study used the most recent Global Burden of Disease (GBD) 2021 data to analyze its epidemiological burden across regions, age groups, sexes, and Socio-Demographic Index (SDI) levels from 1990 to 2021. We comprehensively evaluated age-standardized rates and average annual

percentage changes (AAPCs) across 204 countries and 21 regions worldwide to elucidate spatiotemporal distributions and temporal trends. Furthermore, a two-sample Mendelian randomization (MR) analysis was applied to infer potential causal effects of exposure risk factors on IHD, thereby clarifying their etiological roles. This methodology offers a scientific foundation for understanding global IHD trends and supports the development of targeted prevention and treatment strategies.

The Autoregressive Integrated Moving Average (ARIMA) model demonstrates strong efficacy in predicting disease incidence, prevalence, and mortality. It is particularly well-suited for analyzing data with distinct temporal patterns, cyclical variations, or abrupt public health anomalies, thereby furnishing an evidence-based foundation for public health policymaking. Utilizing data from the Global Burden of Disease (GBD) study, this research applies the ARIMA time-series model to systematically assess long-term trends in the global incidence, mortality, prevalence, and disability-adjusted life years (DALYs) of ischemic heart disease, with additional stratification to examine sex-specific variations.

2.Methods

2.1 Data Source

The ischemic heart disease (IHD) data used in this study were sourced from the Global Burden of Disease (GBD) 2021 database. This repository comprehensively and systematically documents a wide range of diseases worldwide, employing multidimensional health assessments by quantifying key epidemiological metrics — including incidence, mortality, and prevalence—to evaluate the global burden of diseases and injuries. From this source, we extracted IHD-related incidence, prevalence, mortality, disability-adjusted life years (DALYs), and their corresponding 95% uncertainty intervals for the period 1990–2021. The data encompass all age groups and associated risk factors.

2.2 Average Annual Percentage Change

To accurately assess temporal trends in age-

standardized rates, we utilized Joinpoint regression software to calculate the average annual percentage change (AAPC) and its corresponding 95% confidence interval. These calculations were performed for the age-standardized incidence rate (ASIR), prevalence rate (ASPR), mortality rate (ASMR), and disability-adjusted life year (DALY) rate (ASDR). The software identifies significant turning points within time-series data and employs segmented regression models to fit distinct trend segments. This analytical approach elucidates key characteristics in the dynamic evolution of disease burden metric.

2.3 Socio-demographic Index

The Socio-demographic Index (SDI) is a comprehensive indicator of regional development, developed by the Global Burden of Disease (GBD) research team. It integrates multidimensional attributes such as population size, structure, distribution, and key socioeconomic factors. The 2021 global SDI data utilized in this analysis were obtained from the official GBD repository (https://ghdx.healthdata.org/record/global-burden-disease-study-2021-gbd-2021-socio-demographic-index-sdi-1950–2021).

2.4 Mendelian Randomization

Building upon the established ischemic heart disease (IHD) risk factors reported in the Global Burden of Disease (GBD) 2021 study—including high body mass index (BMI), smoking, high low-density lipoprotein (LDL) cholesterol, and high fasting blood glucose—we performed a two-sample Mendelian randomization (MR) analysis to investigate their causal relationships with IHD. Genome-wide association study (GWAS) summary statistics for all exposures and the outcome were obtained from publicly available databases. The outcome data consisted of a chronic ischemic heart disease dataset (ukb-b-8184), including 5,861 cases and 457,149 controls of European ancestry.

3.Results

3.1 Global Burden Analysis from 1990 to 2021

Between 1990 and 2021, the global burden of ischemic heart disease (IHD) exhibited an overall decline. Age-standardized incidence (ASIR), mortality (ASMR), and disability-adjusted life years (ASDR) rates all demonstrated decreasing trends, with average annual percentage changes (AAPCs) of −0.379, −1.200, and −1.083, respectively. In contrast, the age-standardized prevalence rate (ASPR) showed a slight increase, with an AAPC of 0.040. Specifically, the incidence per 100,000 population decreased from 420 to 373, while the mortality rate declined from 159 to 109. Conversely, the prevalence rate increased from 2,905 to 2,947 per 100,000.

Regionally in 2021, North Africa and the Middle East recorded the highest ASIR and ASPR, whereas Central Asia reported the highest ASDR and ASMR (Table 1). Notably, North Africa and the Middle East ranked among the top three regions for all four metrics: ASIR (896 per 100,000), ASPR (6,405 per 100,000), ASDR (4,024 per 100,000), and ASMR (203 per 100,000). An upward trend in ASMR was observed in East Asia, Southern Sub-Saharan Africa, South Asia, Eastern Sub-Saharan Africa, and Western Sub-Saharan Africa, with AAPCs of 0.450, 0.308, 0.271, 0.126, and 0.021, respectively. Although these increases were modest, they warrant continued monitoring.

Nationally, Uzbekistan (1,207 per 100,000), the Syrian Arab Republic (1,131 per 100,000), and the United Arab Emirates (1,085 per 100,000) had the highest ASIR. The highest ASPR was observed in Kuwait (7,807 per 100,000), the United Arab Emirates (7,609 per 100,000), and Saudi Arabia (7,342 per 100,000). The highest ASMR was found in Nauru (433 per 100,000), Ukraine (374 per 100,000), and Syria (354 per 100,000), while the highest ASDR was recorded in Nauru (10,682 per 100,000), Vanuatu (7,190 per 100,000), and Egypt (6,925 per 100,000). Particular attention should be paid to countries including Uzbekistan, Lesotho, Zimbabwe, and Zambia, where several IHD burden indicators demonstrated a significant upward trend, with AAPC values exceeding 1 (Table 2, Figure 1).

Table 1　The regions ranked among the top three in age-standardised rates (ASRs) in 2021 across 21 areas, along with the corresponding average annual percent chang (AAPC).

Indicator	Location	ASR（95%Uncertain interval）	AAPC（95%Confidence interval）
Incidence	North Africa and Middle East	895.85（786.65-1043.49）	-0.311（-0.324 ~ -0.299）*
	Central Asia	801.56（731.97-893.80）	0.741（0.700 ~ 0.793）*
	Eastern Europe	714.22（578.98-859.74）	0.031(-0.006 ~ 0.053)
Prevalence	North Africa and Middle East	6404.84（5872.02-7041.08）	-0.022(-0.029 ~ -0.016) *
	Eastern Europe	4942.65（4299.13-5766.77）	0.280(0.274 ~ 0.284) *
	South Asia	4455.73（3796.73-5339.20）	0.147(0.140 ~ 0.153) *
Deaths	Central Asia	265.51（240.67-290.42）	-0.661(-0.758 ~ -0.586) *
	Eastern Europe	252.89（226.96-277.15）	-0.723(-0.857 ~ -0.588) *
	North Africa and Middle East	202.85（180.59-223.68）	-0.971(-1.029 ~ -0.923) *
DALYS	Central Asia	4864.49（4415.55-5338.75）	-0.783(-0.877 ~ 0.691) *
	Eastern Europe	4687.70（4267.79-5115.68）	-0.783(-0.948 ~ -0.607) *
	North Africa and Middle East	4023.23（3581.71-4507.47）	-1.162(-1.195 ~ --1.126) *

Table 2 Countries and regions with an average annual percentage change (AAPC) exceeding 1% between 1990 and 2021.

| Indicator	Location	AAPC (95%Confidence interval)
ASIR	Uzbekistan	2.3972（2.291 to 2.520）*
	Lesotho	2.242（2.140 to 2.314）*
ASDR	Zimbabwe	1.543(1.489 to 1.603) *
	Cabo Verde	1.420(1.187 to 1.640) *
	Kenya	1.304(1.279 to 1.330) *
	Mozambique	1.122(1.190 to 1.253) *
	Zambia	1.217(1.176 to 1.261) *
	United Republic of Tanzania	1.077(1.050 to 1.101) *
	Honduras	1.058(0.981 to 1.122) *
	Lesotho	2.044(1.952 to 2.119) *
	Cabo Verde	1.833(1.563 to 2.037) *
ASMR	Kenya	1.401(1.377 to 1.427) *
	Honduras	1.368(1.271 to 1.449) *
	Zambia	1.325(1.274 to 1.370) *
	Zimbabwe	1.206(1.104 to 1.310) *
	United Republic of Tanzania	1.188(1.163 to 1.210) *
	Mozambique	1.125(1.078 to 1.166) *
	Montenegro	1.068(0.906 to 1.220) *
	Indonesia	1.037(0.999 to 1.067) *
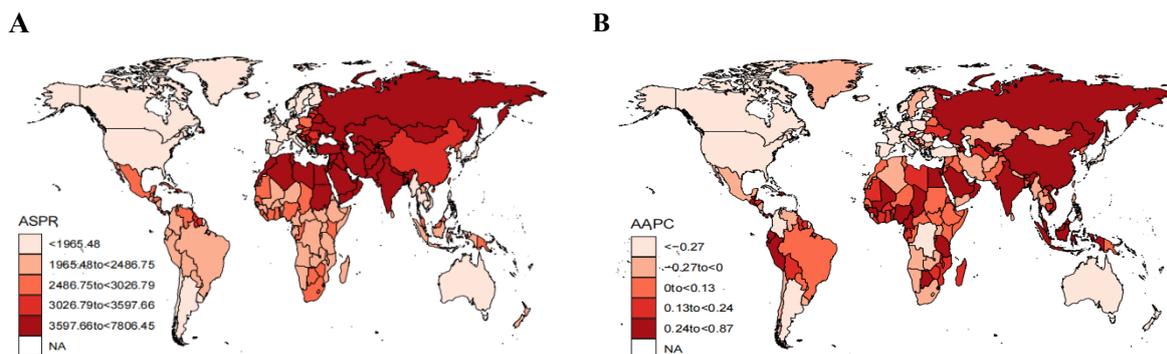
Figure 1   The age-standardized prevalence and AAPC of Ischemic Heart Disease from 204 countries and regions.

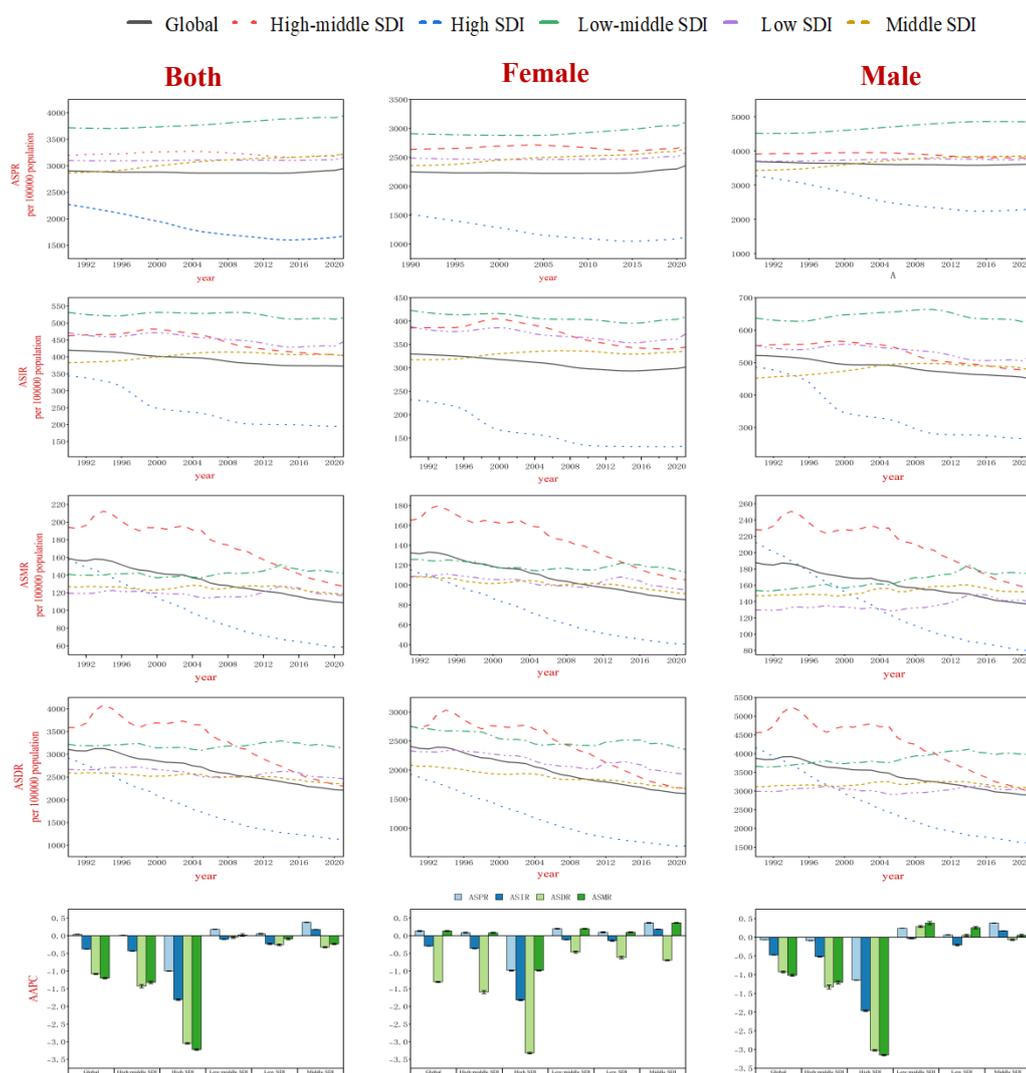**Note:** A) Age-standardized prevalence in 2021   B) AAPC of age-standardized prevalence from 1991 to 2021.

Figure 2 The temporal trends of ASPR,ASIR,ASDR,and ASMR for Ischemic Heart Disease burden globally and across five SDI levels (high,high-middle,middle,low-middle,and low SDI) from 1991 to 2021.The AAPC of global and SDI levels from 1991 to 2021 are also shown.ASIR:Age-standardized incidence rate. ASPR:Age-standardized prevalence rate. ASDR:Age-standardized DALY rate. ASMR:Age-standardized mortality rate. AAPC:Annual average percentage change.

3.2 Disparities in IHD Burden Across SDI Levels

From 1990 to 2021, the global burden of ischemic heart disease (IHD) exhibited an overall declining trend, albeit with significant disparities across regions of varying Socio-demographic Index (SDI) levels. Low-middle SDI regions consistently demonstrated the highest age-standardized incidence (ASIR) and prevalence (ASPR) rates. Concerning mortality-related metrics, high-middle SDI regions reported the highest age-standardized disability-adjusted life years (ASDR) rate until 2008, after which low-middle SDI regions assumed the highest burden; a similar transition occurred for the age-standardized mortality rate (ASMR), with a turning point in 2013. High SDI regions consistently recorded the lowest values for all IHD burden metrics, each remaining below the global average. In 2021, low-middle SDI regions continued to report the highest ASIR and ASPR, at 516 and 3,942 per 100,000 population, respectively.

Although the overall ASDR trend declined across all SDI regions—with the most pronounced decrease in high SDI areas—an upward trend was observed for ASDR among males in low-middle SDI regions. Furthermore, the most notable increase in ASMR was identified among males in low-middle SDI regions, whereas the largest increase for females occurred in middle SDI regions. Of particular concern is the high-middle SDI region, where females experienced rising trends in both ASPR and ASMR, while males exhibited a declining trend (Figure 2).

Further analysis of the correlation between disease burden and SDI revealed that higher SDI levels were associated with lower ASDR and ASMR; the average annual percentage change (AAPC) for all four metrics (ASIR, ASPR, ASDR, and ASMR) decreased as SDI increased, demonstrating a significant negative correlation. However, no significant correlation was found between SDI and either ASIR or ASPR (Figure 3).
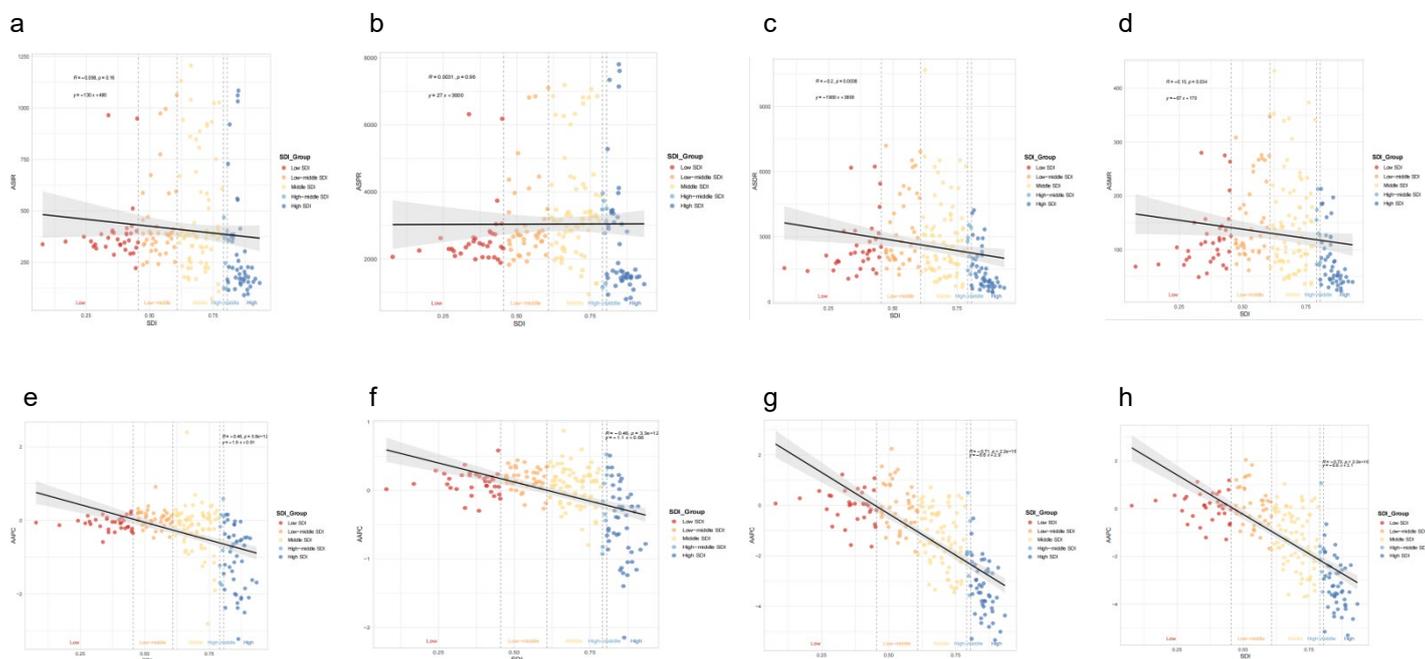

Figure 2 **The association between SDI and the age-standardized incidence rate, prevalence rate, DALY rate,and mortality rate of Ischemic Heart Disease in 2021, as well as the corresponding AAPC from 1991 to 2021.**

Note:(A)ASPR and SDI.(B)ASIR and SDI.(C)ASDR and SDI.(D)ASMR and SDI.(E)AAPC of ASPR and SDI.(F)AAPC of ASIR and SDI.(G)AAPC of ASDR and SDI.(H)AAPC of ASMR and SDI.Note:SDI:Socio-demographic Index.AAPC:Annual Average Percentage Change.ASPR:Age-standardized prevalence rate.ASIR:Age-standardized incidence rate.ASDR:Age-standardized DALY rate.ASMR:Age-standardized mortality rate.
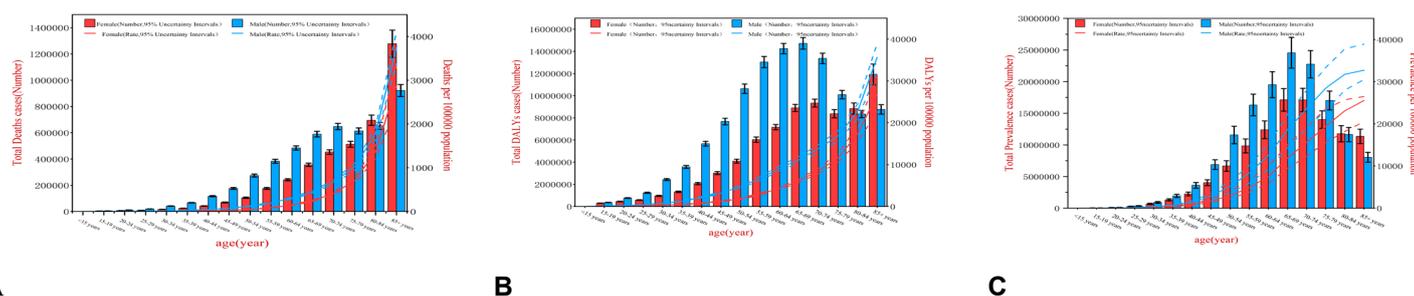
A   **B**   **C**

Figure 3 **The age-standardized prevalence,mortality,and DALY rate of IHD in 2021.**

Note:(A) Number of Ischemic Heart Disease cases and age-standardized Deaths (B)DALYs of Ischemic Heart Disease and age-standardized DALY rate. (C)Number of Ischemic Heart Disease prevalence and age-standardized mortality rate.

3.3 Disparities in IHD Burden by Age and Sex

Significant disparities in the burden of ischemic heart disease (IHD) were observed across age and sex groups. Incidence, mortality, and disability-adjusted life year (DALY) rates were markedly low in individuals under 20 years of age. The highest prevalence rates were observed among adults aged 85 years and older, reaching 32,702 per 100,000 in males and 25,530 per 100,000 in females. However, the largest number of prevalent cases occurred in the 65–69-year age group, comprising approximately 2.456 million male and 1.712 million female patients. The number of male patients exceeded that of females until 80 years of age, after which this trend reversed. Both mortality rates and death counts peaked in the 85+ age group: the mortality rate was 3,747 per 100,000 with approximately 920,000 deaths in males, and 2,873 per 100,000 with roughly 1.277 million deaths in females. Although the absolute number of deaths and prevalent cases among females aged 80 years and above surpassed those of males, their corresponding age-standardized rates remained lower. Furthermore, the highest number of DALYs was observed in males aged 65–69 years (14,726,170 person-years), whereas for females, the peak occurred in the 85+ year age group (11,916,229 person-years) (Figure 4).

3.4 Impact of Risk Factors on IHD Burden

In 2021, the global burden of ischemic heart disease (IHD) was primarily attributable to several modifiable risk factors, namely high body mass index (BMI), high low-density lipoprotein (LDL) cholesterol, smoking, and high fasting blood glucose. These factors accounted for 12.70%, 35.44%, 18.84%, and 13.76% of IHD-related disability-adjusted life years (DALYs), respectively. High LDL cholesterol was the dominant risk factor, contributing to 36.52% and 33.76% of risk-attributable DALYs in males and females, respectively.

Between 1990 and 2021, the burden attributable to high BMI demonstrated a consistent upward trend across all regions, with the most substantial increase in DALYs observed in Sub-Saharan Africa (exceeding 5%). Smoking remained the leading risk factor for IHD burden among males. High fasting blood glucose had a pronounced impact in high-income North America, accounting for 22.20% and 19.06% of DALYs in males and females in this region, respectively. The distribution and temporal evolution of these risk factors underscore the necessity for targeted IHD prevention and control strategies that account for regional and sex-based disparities.

To further evaluate the causal relationship between these risk factors and IHD, we employed Mendelian randomization (MR) analysis. The inverse variance weighted (IVW) method served as the primary analytical approach, supplemented by MR-Egger and weighted median methods for validation and sensitivity analyses. The MR results indicated that smoking, higher BMI (OR = 1.007, 95% CI: 1.00–1.01, p = 0.001), increased waist-to-hip ratio (OR = 1.004, 95% CI: 1.00–1.01, p = 0.010), and elevated triglyceride levels (OR = 1.002, 95% CI: 1.00–1.00, p = 0.018) were positively associated with IHD risk.

Conversely, LDL cholesterol was negatively associated with IHD risk (OR = 0.996, 95% CI: 0.99–1.00, p = 0.006). MR analyses for fasting blood glucose and high-density lipoprotein cholesterol revealed no statistically significant causal relationship with IHD.

3.5 ARIMA Projections of ASR

From 2022 to 2050, the age-standardized prevalence rate (ASPR) of ischemic heart disease is projected to increase gradually for both sexes. By 2050, the ASPR is estimated to reach 3,890 per 100,000 in males and 4,035 per 100,000 in females. Notably, while the age-standardized incidence rate (ASIR) is projected to increase consistently in females, it is expected to continue declining in males. This divergence highlights a potential disproportionate future disease burden for female populations (Figures 5).
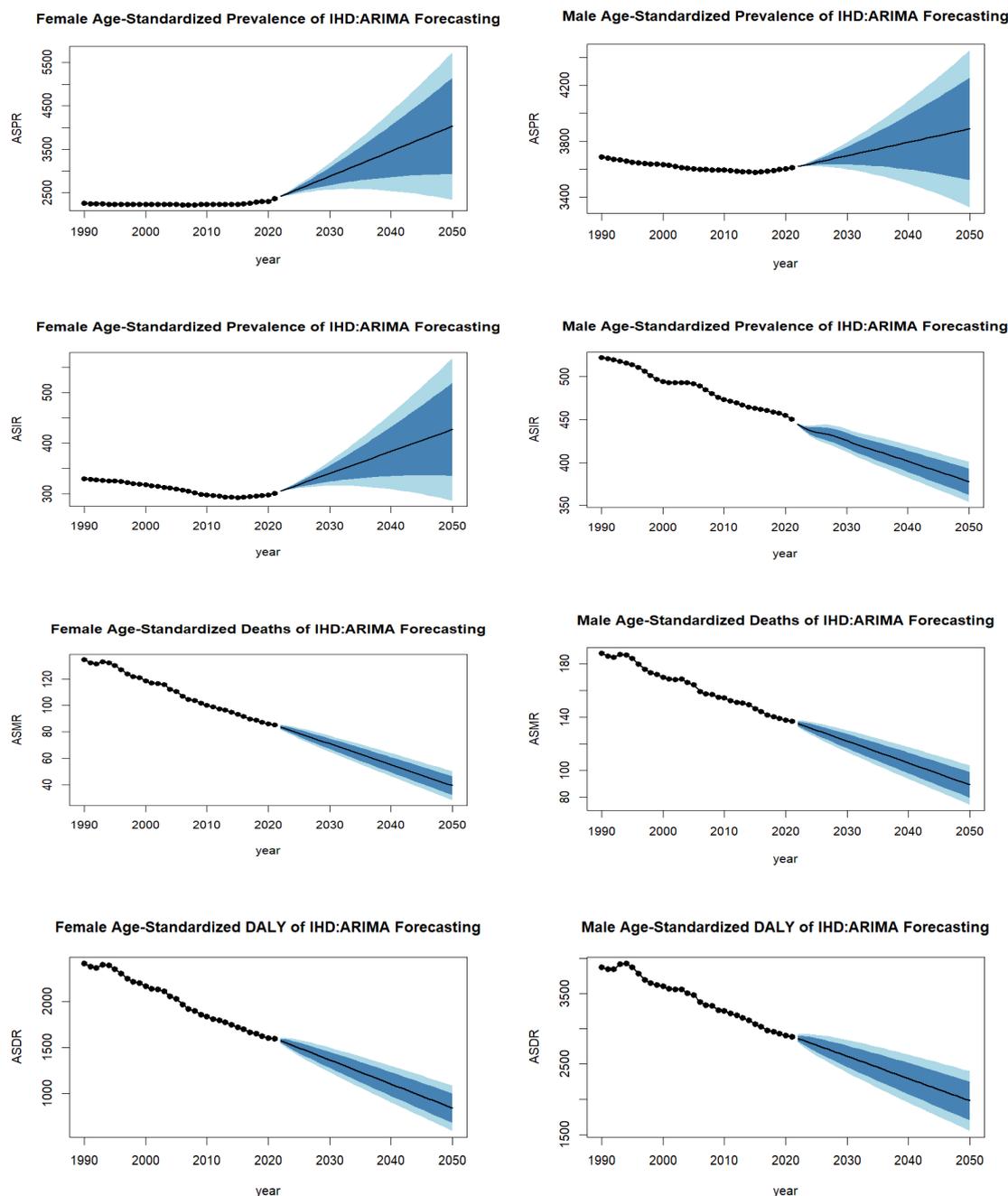
Figures 5 ARIMA model forecasting the male,and female ASIR,ASPR,ASMR,and ASDR from 2022 to 2050.

4.Discussion

This study corroborates that these factors elevate the risk of ischemic heart disease (IHD). The findings indicate a particularly severe IHD burden in the Middle East and North Africa, where multiple metrics—including the age-standardized incidence rate (ASIR), prevalence rate (ASPR), mortality rate (ASMR), and disability-adjusted life years rate (ASDR)—rank among the highest globally. Although the overall growth trend in these regions remained relatively moderate from 1990 to 2021, their standardized rates were still among the top five worldwide by 2021. Concurrently, increasing ASMR trends were observed in East Asia, Southern Sub-Saharan Africa, South Asia, and Eastern and Western Sub-Saharan Africa, warranting focused attention. Regarding Socio-demographic Index (SDI) levels, the IHD burden was significantly heavier in low-middle SDI regions, whereas high SDI regions exhibited the lightest burden. Further analysis revealed a negative correlation between SDI and both ASDR and ASMR. In contrast, no significant association was found between SDI and either ASIR or ASPR. Established cardiovascular risk factors—such as smoking, high low-density lipoprotein (LDL) cholesterol, and high triglycerides—were also validated in this study through Mendelian randomization analysis as significant contributors to increased IHD risk.

The pathogenesis of IHD is a protracted process initiated by endothelial dysfunction, driven primarily by lipid-induced inflammation, and pathologically characterized by atherosclerotic plaque formation. This process can culminate in acute clinical events triggered by plaque rupture and thrombosis. The disease predominantly affects middle-aged and older adults, with notable sex-based differences in clinical presentation, treatment response, and prognosis. Studies indicate that factors like premature menopause and adverse pregnancy outcomes elevate IHD risk in women, who often experience poorer post-diagnosis health status [9][10]. This study similarly identified significant sex-based disparities: before age 80, men exhibited higher prevalence, incidence, and mortality rates than women, a trend that reversed after age 80. Research further shows that non-obstructive coronary artery disease is more common in women, while obstructive epicardial disease predominates in men [11][12][13]. Additionally, peripheral microvascular dysfunction combined with mental stress is associated with an increased risk of adverse events in women, a correlation not observed in men [14]. These differences highlight the critical need for sex-specific diagnostic and therapeutic strategies. For instance, single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) may exhibit reduced sensitivity for detecting ischemia and assessing transient ischemic dilation in women due to smaller heart size; its specificity is also limited by breast tissue attenuation. In contrast, stress positron emission tomography (PET) allows simultaneous evaluation of the microvascular and macrovascular systems through quantification of myocardial blood flow and coronary flow reserve, thereby enhancing diagnostic accuracy [15][16].

The amplified risks of ischemic heart disease (IHD) associated with smoking, high body mass index (BMI), an elevated waist-to-hip ratio (independent of BMI), and high triglyceride levels underscore the critical importance of lifestyle interventions. Supporting this, a Korean study reported that a two-fold increase in triglyceride levels was associated with a 1.22-fold increase in IHD mortality [17]. Furthermore, the triglyceride-glucose index has been significantly correlated with myocardial ischemia and adverse prognostic outcomes, highlighting the value of dietary management and physical activity [18]. Smoking accelerates IHD progression through diverse pathways, including the promotion of inflammation, endothelial dysfunction, and impaired platelet activity [19][20]. In the present study, the IHD burden attributable to smoking was greater in males than in females. This finding aligns with a Japanese study which indicated that secondhand smoke exposure elevates IHD risk among middle-aged female never-smokers [21]. Although our Mendelian randomization (MR) analysis did not identify a

causal relationship between fasting blood glucose and IHD, extant research has established that elevated glycated hemoglobin (HbA1c) levels are positively correlated with the formation of vulnerable atherosclerotic plaques [22].

This study provides a comprehensive evaluation of recent trends in the global burden of IHD and analyzes its association with the Socio-demographic Index (SDI). The results demonstrate a significant negative correlation between SDI and both the age-standardized death rate (ASDR) and age-standardized mortality rate (ASMR). In contrast, no significant association was observed between SDI and the age-standardized incidence rate (ASIR) or age-standardized prevalence rate (ASPR). Notably, the average annual percentage change (AAPC) of the age-standardized rates (ASRs) exhibited a significant negative correlation with increasing SDI. Risk factors conclusively identified include smoking, high BMI, elevated waist-to-hip ratio, and high triglyceride levels, whereas LDL cholesterol demonstrated a protective effect. These findings enhance our understanding of IHD pathogenesis and offer a scientific foundation for developing targeted public health prevention strategies.

This study is subject to several limitations. First, the GBD data are derived from modeled estimates, and the quality of the original data varies across countries and regions. Incomplete healthcare infrastructure and surveillance policies in some nations may lead to the underdiagnosis or misreporting of IHD, potentially introducing bias. Second, the Socio-demographic Index (SDI) data were obtained from the GBD 2021 database; recent fluctuations in SDI values for certain countries may have affected our analysis. Third, as the genome-wide association studies (GWAS) databases used predominantly comprise individuals of European ancestry, their applicability to populations in less developed countries is limited, thereby constraining the generalizability of our Mendelian randomization findings.

Ischemic heart disease continues to pose a major global health challenge, disproportionately affecting middle-aged and older adults. The implementation of targeted early prevention and intervention strategies is urgently needed. Maintaining a healthy lifestyle, including weight management and smoking cessation, constitutes a proven effective approach to reducing IHD incidence and should be promoted as a cornerstone of public health initiatives.

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