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Research Article

Global Trends and Health Inequalities in Non-Rheumatic Heart Disease Burden, 1990–2021: A Systematic Analysis of the Global Burden of Disease 2021

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Abstract: Objective: To comprehensively analyze global epidemiological trends, health disparities, and future projections of non-rheumatic valvular heart disease (NRVHD), including calcific aortic valve disease (CAVD) and degenerative mitral valve disease (DMVD), from 1990 to 2021, and to forecast disease burden through 2052.

Methods: Using data from the Global Burden of Disease (GBD) 2021, we extracted estimates and 95% uncertainty intervals (UI) for incidence, prevalence, deaths, and disability-adjusted life years (DALYs) of NRVHD (including CAVD and DMVD) from 1990 to 2021. We analyzed epidemiological trends at global, regional, and national levels, assessed health inequalities, and employed Bayesian modeling to project future disease burden through 2052.

Results: In 2021, an estimated 2,206,928 global incident cases of non-rheumatic valvular heart disease (NRVHD) were recorded (95% UI: 2,048,267–2,375,325), with calcific aortic valve disease (CAVD) and degenerative mitral valve disease (DMVD) accounting for 47.32% and 52.68% of cases, respectively. Prevalence reached 28,389,034 cases (95% UI: 26,323,458–30,585,670), of which CAVD and DMVD comprised 46.92% and 54.58%. Disability-adjusted life years (DALYs) attributable to NRVHD totaled 3,238,185 (95% UI: 2,934,104–3,594,474), with CAVD contributing 69.27% and DMVD 29.13%. The burden was disproportionately concentrated in high sociodemographic index (SDI) regions, such as high-income North America, whereas low SDI regions, including sub-Saharan Africa, exhibited the lowest burden. Health inequalities widened between 1990 and 2021, evidenced by a rise in absolute disparities (the slope index of inequality increased from 99.35 to 135.92). Decomposition analysis identified population growth (55.95%) and aging (52.73%) as primary drivers of the increase in DALYs. Projections suggest a 24–26% decline in age-standardized incidence, prevalence, mortality, and DALY rates by 2052.

Conclusion: The escalating burden of NRVHD reflects demographic shifts and persistent health inequities, with high-SDI regions bearing the greatest burden. Despite projected declines in age-standardized rates, absolute case numbers will rise due to population aging. Targeted interventions—emphasizing early diagnosis, equitable resource allocation, and management of modifiable risk factors—are critical to mitigate disparities, particularly in aging high-income populations.

Keywords: Non-rheumatic valvular heart disease; Calcific aortic valve disease; Degenerative mitral valve disease; GBD 2021; Health inequalities; Disability-adjusted life years.

1. Introduction

The cardiac cycle relies on the integrity of heart valves to maintain unidirectional blood flow, ensuring adequate circulation and oxygen delivery throughout the body[1]. To fulfill this critical role, heart valves must exhibit exceptional strength and durability to endure decades of repetitive and intense mechanical stress[2]. However, when valve dysfunction occurs, the unidirectional flow of blood is disrupted, compromising cardiovascular efficiency. Historically, rheumatic heart disease (RHD) was the predominant cause of valvular heart disease worldwide. However, with the widespread adoption of antibiotics in the late 20th century, the incidence of RHD has significantly declined[3,4]. In contrast, non-rheumatic valvular heart diseases (NRVHD) have emerged as a growing public health concern, driven by factors such as population aging and demographic shifts[5]. Among NRVHD, calcific aortic valve disease (CAVD) and degenerative mitral valve disease (DMVD) are the most prevalent forms[5,6]. Recent epidemiological data highlight the escalating burden of NRVHD. In 2019, the age-standardized prevalence rate (ASPR) of CAVD was estimated at 116.3 cases per 100,000 population (95% UI: 37.6–54.7 per 100,000), while the DALYs of DMVD reached at 34,000 cases[7]. These figures underscore the increasing significance of NRVHD as a pressing public health challenge that demands attention.

CAVD is a chronic and progressive disorder, characterized by the dysregulation of extracellular matrix production, leading to fibrosis, calcification, and thickening of the valve leaflets, which ultimately disrupts their normal function and results in aortic stenosis. The resulting stenosis imposes increased pressure on the left ventricle, reducing ejection volume and compromising coronary blood flow, thereby precipitating clinical manifestations such as angina pectoris, syncope, and heart failure[8,9]. Degenerative Mitral Valve Disease (DMVD) is a chronic progressive cardiac disease characterized by degenerative changes in the mitral valve structure, including leaflet thickening, fibrosis, and calcification, which ultimately leads to abnormal valve function and triggers mitral regurgitation or stenosis. This pathological change is usually closely associated with abnormal remodeling of the extracellular matrix and dysregulation of collagen metabolism [10,11]. As the disease progresses, mitral valve dysfunction leads to increased left ventricular volume loading, which in turn causes left atrial dilatation and pulmonary hypertension[12-14]. CAVD and DMVD can significantly contribute to the global burden of cardiovascular disease, increasing the risk of severe complications, including heart failure, arrhythmias, and sudden cardiac death16980116. The therapeutic strategies for both conditions are determined by factors such as disease severity, symptomatic presentation, hemodynamic impact on cardiac chambers and pulmonary circulation, and the potential for durable valve repair or replacement, whether through surgical intervention or transcatheter techniques[15,16].

In this study, we use the latest Global Burden of Disease (GBD) data to conduct a comprehensive analysis of the epidemiological trends, health inequalities, burden distribution and future projection of NRVHD, including its two predominant subtypes – CAVD and DMVD, across global, regional, and national levels from 1990 to 2021. By integrating comprehensive GBD data with advanced analytical methodologies, systematic examination of temporal trends and geographical variations, the study not only offering novel insights into the complex interplay between demographic transitions, healthcare accessibility, and disease burden, but also identifies critical gaps in current prevention and treatment paradigms, thereby contributing substantially to the field of cardiovascular disease research and public health policy formulation.

Method

Data Resource

The methodological framework of this study leveraged the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 database, which incorporates comprehensive epidemiological data and advanced standardized methodologies to evaluate health burden metrics across 204 countries and territories. Through sophisticated analytical approaches addressing temporal trends and confounding variables, the GBD 2021 provides detailed age- and sex-stratified assessments for 369 diseases and

injuries, alongside 88 risk factors, with methodological specifications extensively documented in previous publications[17]. From this robust dataset, epidemiological estimates including incidence, prevalence, mortality, and disability-adjusted life years (DALYs) were extracted for specific NRVHD (including CAVHD and DMVHD) from 1990 to 2021. These estimates were accompanied by their corresponding age-standardized rates (ASR) and 95% uncertainty intervals (UI). Furthermore, the analytical framework incorporated the SDI, a composite metric that quantifies regional development levels through the integration of income, educational attainment, and fertility indicators, categorized into quintiles representing low, low-middle, middle, high-middle, and high development strata[18]. The utilization of de-identified data from the GBD study was conducted under the ethical approval of the University of Washington Institutional Review Committee, which granted a waiver of informed consent due to the study's retrospective nature and use of anonymized data[19].

Trend Analysis

To evaluate trends in the age-standardized rates (ASR) of incidence, prevalence, deaths and DALYs and of NRVHD (including CAVD and DMVD), the estimated annual percentage change (EAPC), a robust and widely utilized metric, was employed[20]. A linear regression model was constructed using the equation $y = \alpha + \beta x$, where y represents the natural logarithm of the ASR $\ln(\text{ASR})$ and x denotes the calendar year. The EAPC was calculated as $(\exp(\beta)-1) * 100\,\%$, with its 95% confidence interval (CI) derived from the regression model[21]. An upward trend in ASR was inferred if both the EAPC estimate and the lower bound of its 95% CI exceeded zero, whereas a downward trend was indicated if both the EAPC estimate and the upper bound of its 95% CI were below zero. In cases where these conditions were not met, the ASR was classified as stable.

To further characterize trends in the burden of NRVHD (including CAVD and DMVD), age-period-cohort (APC) analyses were conducted. Given the potential interactions between age, period, and birth cohort effects, an intrinsic estimator (IE) approach based on principal component regression analysis was applied to disentangle these temporal influences and provide efficient estimates[22]. Within the APC framework, age-specific incidence or deaths were stratified into consecutive 5-year age groups (15–19, 20–24, ..., 95+), 5-year periods (1992–1996, 1997–2001, ..., 2017–2021), and corresponding 5-year birth cohorts (1894–1899, 1900–1904, ..., 2000–2004). The APC model, formulated as $ln\,(Y_{i,j,k}) = \mu + \alpha_i + \beta_j + \gamma_k + \varepsilon_{i,j,k}$, , where $Y_{i,j,k}$ represents the incidence or deaths of (i, j, k) group, α_i, β_j and γ_k, which represent the age effect of i-th age group, the period effect of j-th period group and the birth cohort effect in the k-th birth cohort group[23]. These coefficients were subsequently exponentiated to derive relative risks (RR) for incidence and deaths, comparing specific age groups, periods, or birth cohorts to the average levels across all categories[22,23].

Decomposition Analysis

Decomposition analysis was conducted by examining population size, age structure, and epidemiologic changes to elucidate the contributing to changes in DALYs attributable to NRCAVD (including CAVD and DMVD) From 1990 to 2021, followed by the equation: The analysis was performed using the following equation: $DALYs_{ay,\,py,\,ey} = \sum i=1n\,(a_{i,y} * p_y * e_{i,y})$ [24]. $DALYs_{ay,\,py,\,ey}$ referred to the number of DALYs according to the factors of age structure, population size, and DALYs rate in year y. py is the total population in year y; ei,y represents the DALYs rate of the i age category in year y. The contribution of each factor to the change in DALYs from 1990 to 2021 is defined as the effect of one factor changing while the other factors remain constant[22].

Cross-country Inequality Analysis

To assess disparities in the burden of NRVHD（including CAVD and DMVD）across countries, two standardized metrics, the slope index of inequality (SII) and the concentration index (CI)were employed to quantify absolute and relative gradient inequality, respectively[25].The SII was derived by performing a regression analysis of the national age-standardized DALY rate for all age groups against a relative positional scale based on sociodemographic development. The CI, reflecting the degree of inequality in disease burden distribution, was computed by numerically integrating the area under the Lorenz

concentration curve. This curve was constructed by plotting the cumulative proportion of age-standardized DALY rate against the cumulative proportion of the population, ranked according to the SDI. Both indices provide complementary insights into the socioeconomic gradients of disease burden, with the SII capturing absolute differences and the CI measuring relative inequalities[26].

Projection Analysis

To estimate the future burden of NRVHD (including CAVHD and DMVHD) in the next 30 years (from 2022 to 2052), a Bayesian age-period-cohort (BAPC) analysis was employed, incorporating integrated nested Laplace approximation (INLA) models for enhanced computational efficiency. All analyses were conducted using R software (version 4.4.2) within the R Studio environment, utilizing specialized packages including nordpred (version 1.1), BAPC (version 0.0.36), and INLA (version 24.05.10) to implement the projection models[27].

Result

Global Level

In 2021, the global incidence of NRVHD reached 2,206,928 cases (95% UI: 2,048,267–2,375,325), reflecting a 129.11% increase since 1990. The age-standardized incidence rate (ASIR) rose slightly from 23.9 per 100,000 (95% UI: 21.98–26.0) in 1990 to 25.0 per 100,000 (95% UI: 23.17–26.92) in 2021, with an EAPC of 0.34 (95% CI: 0.28–0.40) (Table 1, Figure 1).

Table 1: The incidence, prevalence, deaths, disability-adjusted life years and their age-standardized rate of non-rheumatic valvular heart disease in global and reginal from1990 to 2021

Location	1990		2021		EAPC_95%CI
	Number	ASR	Number	ASR	
Incidence					
Global	963242 (885978, 1047599)	23.9(21.98,26)	2206928 (2048267, 2375325)	25(23.17,26.92)	0.34(0.28,0.41)
High SDI	547094 (500018, 597009)	49.31(45.19,53.71)	1195688 (1106085, 1288386)	58.47(54.45,62.86)	0.75(0.68,0.82)
High-middle SDI	272226 (251103, 296620)	26.14(24.19,28.44)	577630 (535619, 619126)	28.14(26.1,30.15)	0.43(0.35,0.51)
Middle SDI	96529 (88517, 105023)	8.92(8.21,9.71)	307973 (282242, 333637)	10.96(10.04,11.86)	0.85(0.78,0.93)
Low-middle SDI	37267 (33493, 41196)	5.94(5.39,6.57)	101633 (91823, 111879)	6.86(6.23,7.54)	0.5(0.46,0.55)
Low SDI	8942 (8104, 9823)	3.79(3.46,4.13)	21658 (19775, 23602)	4.05(3.73,4.39)	0.25(0.21,0.29)
Andean Latin America	1594 (1381, 1850)	7.36(6.35,8.5)	6988 (6127, 7859)	11.54(10.09,13)	1.48(1.45,1.51)
Australasia	9208 (8215, 10227)	37.9(33.92,41.98)	25426 (22770, 28386)	47.09(42.22,52.55)	0.83(0.79,0.88)
Caribbean	2578 (2256, 2918)	9.67(8.44,10.93)	6716 (5895, 7522)	12.45(10.93,13.91)	1(0.92,1.09)

Central Asia	16638 (13750, 20248)	34.19(28.53,41.49)	41779 (36129, 48324)	46.94(40.7,53.92)	1.31(1.14,1.48)
Central Europe	51603 (45244, 58568)	33.02(29.11,37.33)	101960 (91978, 112506)	48.31(43.52,52.94)	1.63(1.38,1.87)
Central Latin America	9356 (8083, 10760)	10.66(9.12,12.27)	37597 (32473, 43344)	14.57(12.63,16.72)	1.31(1.18,1.43)
Central Sub-Saharan Africa	773 (687, 875)	3.31(2.97,3.7)	1937 (1739, 2166)	3.34(3.03,3.68)	0.01(-0.07,0.09)
East Asia	95629 (89302, 102418)	10.37(9.71,11.09)	303606 (285972, 323035)	12.81(12.08,13.66)	0.9(0.81,0.99)
Eastern Europe	81226 (73738, 89618)	28.13(25.61,30.95)	136802 (121955, 154010)	38.53(34.26,43.06)	1.24(1.12,1.36)
Eastern Sub-Saharan Africa	2405 (2169,2648)	3.06(2.77,3.36)	5515 (4959,6059)	3.06(2.78,3.34)	-0.06(-0.12,0)
High-income Asia Pacific	98155 (89465, 107912)	47.4(43.22,52.15)	206663 (188271, 226570)	51.13(47.07,55.78)	0.34(0.28,0.39)
High-income North America	244395 (220215, 269807)	69.15(62.98,75.89)	540168 (500532, 581828)	80.25(74.58,86.04)	0.63(0.55,0.71)
North Africa and Middle East	16117 (14352, 18075)	8.85(7.91,9.99)	47461 (42391, 53035)	9.79(8.77,10.92)	0.47(0.42,0.53)
Oceania	228 (189,272)	7.37(6.17,8.96)	596(510,706)	7.78(6.65,9.24)	0.07(0.03,0.1)
South Asia	27641 (25192, 30117)	4.78(4.39,5.21)	80940 (74042, 88299)	5.39(4.93,5.87)	0.44(0.4,0.47)
Southeast Asia	18425 (16322, 20883)	7.1(6.31,8.09)	59913 (53761, 67695)	8.72(7.84,9.78)	0.68(0.65,0.72)
Southern Latin America	11689 (10365, 13260)	24.95(22.18,28.22)	28899 (26069, 32466)	33.23(29.89,37.13)	0.94(0.82,1.06)
Southern Sub-Saharan Africa	950 (862,1043)	3.24(2.94,3.53)	2118 (1899,2353)	3.55(3.16,3.94)	0.18(0.13,0.23)
Tropical	11943		37982		

Latin America	(10479, 13614)	12.17(10.64,13.93)	(32293, 43996)	14.51(12.35,16.79)	0.69(0.61,0.77)
Western Europe	260393 (239821, 281064)	45.67(42.05,49.2)	528050 (489529, 568174)	61.24(56.9,65.82)	1.12(0.97,1.26)
Western Sub-Saharan Africa	2294 (2072,2501)	2.29(2.1,2.49)	5811 (5263,6354)	2.38(2.18,2.58)	0.08(0.07,0.1)
Prevalence					
Global	11670353 (10755209, 12710746)	318.94 (294.11,345.46)	28389034 (26323458, 30585670)	335.29 (311.34,361.05)	0.31(0.25,0.38)
High SDI	6804927 (6279564, 7416779)	596.9 (551.49,650.61)	15706968 (14626860, 16896603)	701.43 (652.84,754.32)	0.67(0.6,0.74)
High-middle SDI	3371574 (3117547, 3675733)	354.03 (327.57,384.34)	7808022 (7253399, 8404433)	390.45 (363.31,419.85)	0.51(0.43,0.58)
Middle SDI	1020335 (925119, 1120132)	111.18 (101.02,121.5)	3544917 (3218658, 3883188)	137.45 (124.91,149.79)	0.87(0.8,0.94)
Low-middle SDI	378078 (334286, 422590)	69.57(61.65,77.88)	1093767 (978378, 1223533)	81.26(72.55,90.48)	0.56(0.51,0.6)
Low SDI	80083 (70799, 90317)	38.31(34.18,42.78)	201828 (179669, 225920)	42.44(38.14,47.25)	0.38(0.33,0.42)
Andean Latin America	19439 (16649, 23054)	98.68(84.88,116.45)	93716 (81226, 106171)	160.83 (139.57,181.86)	1.59(1.55,1.62)
Australasia	99780 (88656, 111244)	412.5(367.25,459.7)	303585 (270530, 341285)	526.64 (468.55,591.03)	0.92(0.88,0.96)
Caribbean	33060 (28762, 37972)	128.49 (111.95,147.13)	92523 (81571, 104662)	171.3 (151.06,193.63)	1.12(1.03,1.21)
Central Asia	200828 (167122, 243268)	456.87 (382.4,549.88)	470030 (408341, 548303)	637.65 (555.56,731.12)	1.42(1.23,1.61)
Central Europe	684705 (601755, 776671)	458.28 (404.67,517.99)	1522618 (1364168, 1672529)	661.9(592.4,728.12)	1.55(1.33,1.78)
Central Latin America	111085 (95194, 129056)	141.03 (120.13,163.81)	486518 (415465, 563180)	197.3 (168.79,227.87)	1.38(1.25,1.52)
Central Sub-Saharan Africa	6048 (5067,7072)	28.27 (24.02,32.68)	15034 (12718, 17527)	28.43(24.13,32.92)	0.01(-0.11,0.12)

East Asia	972315 (902509, 1047756)	128.93 (120.57,138.51)	3410421 (3215856, 3622872)	157.06 (148.33,166.92)	0.85(0.77,0.94)
Eastern Europe	1024879 (935452, 1127599)	370.76 (339.52,406.37)	1867600 (1662768, 2086612)	518.32 (462.85,578.44)	1.31(1.19,1.44)
Eastern Sub-Saharan Africa	19263 (16697, 21994)	26.16(22.67,29.85)	45050 (38875, 51324)	27.01(23.45,30.76)	0.04(-0.02,0.11)
High-income Asia Pacific	1227041 (1122930, 1348837)	617.99 (566.98,677.33)	3331745 (3079932, 3612705)	665.64 (617.88,719.82)	0.31(0.26,0.36)
High-income North America	3080862 (2825533, 3361126)	832.23 (764.74,905.35)	6542606 (6108039, 6984839)	943.53 (883.74,1004.39)	0.53(0.47,0.59)
North Africa and Middle East	167569 (145763, 190335)	106.49 (93.04,121.41)	519098 (455272, 591175)	121.01 (106.13,136.31)	0.6(0.53,0.67)
Oceania	2173(1770,2661)	92.33(75.7,111.07)	5929 (4970,7141)	98.19(83.83,116.3)	0.1(0.07,0.13)
South Asia	262377 (235514, 291801)	52(47.01,57.54)	840979 (758183, 933001)	60.53(54.91,66.94)	0.56(0.53,0.6)
Southeast Asia	193062 (169940, 222357)	88.66(78.4,101.14)	643459 (571256, 735608)	109.15 (97.49,123.78)	0.67(0.63,0.71)
Southern Latin America	132724 (115958, 151335)	290.44 (253.85,330.16)	355694 (317024, 397343)	397.25 (354.19,443.98)	1.01(0.89,1.14)
Southern Sub-Saharan Africa	9161 (7983, 10443)	33.04(28.67,37.4)	21066 (18091, 24377)	36.37(31.26,41.78)	0.21(0.17,0.25)
Tropical Latin America	134083 (116819, 155092)	150.78 (131.19,174.83)	467064 (395032, 545262)	183.3 (154.71,213.99)	0.76(0.68,0.84)
Western Europe	3269178 (3006826, 3552997)	536.5 (493.25,583.87)	7302185 (6758120, 7894775)	722.96 (667.59,783.86)	1.14(0.99,1.29)
Western Sub-Saharan Africa	20719 (18218, 23475)	22.43(19.7,25.35)	52114 (45387, 59034)	24.26(21.2,27.37)	0.23(0.21,0.24)
Deaths					
Global	82630 (76087, 88392)	2.66(2.4,2.84)	181078 (155364, 195717)	2.31(1.96,2.5)	-0.37(-0.46, -0.27)
	54409		109347	4.1(3.38,4.49)	-0.53(-0.68, -

High SDI	(49327, 57137)	4.98(4.48,5.25)	(88332, 120502)		0.39)
High-middle SDI	12236 (11477, 12976)	1.49(1.37,1.58)	30985 (26604, 33613)	1.66(1.42,1.8)	0.44(0.26,0.61)
Middle SDI	7124 (6392,7889)	0.8(0.71,0.89)	17980 (16022, 20283)	0.75(0.66,0.85)	-0.19(-0.29, -0.09)
Low-middle SDI	5895 (4483,7706)	1.11(0.83,1.41)	16010 (13469, 18624)	1.27(1.06,1.48)	0.49(0.42,0.57)
Low SDI	2884 (1912,3934)	1.5(0.99,2.02)	6527 (4884,8368)	1.51(1.12,1.97)	0.07(-0.08,0.22)
Andean Latin America	194 (164,221)	0.91(0.78,1.04)	480(398,575)	0.82(0.68,0.98)	-0.32(-0.6, -0.05)
Australasia	1060 (958,1130)	4.76(4.26,5.08)	2368 (1969,2631)	3.68(3.1,4.08)	-0.82(-1.08, -0.55)
Caribbean	382 (345,420)	1.49(1.34,1.63)	796(697, 905)	1.48(1.29,1.69)	0.1(-0.16,0.36)
Central Asia	77(67,89)	0.17(0.14,0.2)	478(422,537)	0.68(0.6,0.76)	5.72(5.09,6.35)
Central Europe	2311(2176,2519)	1.65(1.54,1.81)	9072 (8158,9789)	3.85(3.47,4.14)	3.25(2.98,3.51)
Central Latin America	1076(1038, 1102)	1.34(1.28,1.37)	3305 (2930,3722)	1.35(1.2,1.52)	0.22(-0.27,0.7)
Central Sub-Saharan Africa	378 (252,515)	2.12(1.41,2.92)	931 (650,1336)	2.2(1.5,3.34)	0.05(-0.07,0.16)
East Asia	1853(1483,2189)	0.28(0.22,0.33)	3058 (2508,3810)	0.16(0.14,0.2)	-2.19(-2.7, -1.68)
Eastern Europe	528 (506,546)	0.21(0.2,0.21)	3092 (2857,3305)	0.9(0.83,0.96)	5.06(4.7,5.42)
Eastern Sub-Saharan Africa	1120 (750,1498)	1.71(1.13,2.3)	2255 (1696,3031)	1.54(1.14,2.17)	-0.47(-0.57, -0.37)
High-income Asia Pacific	8974 (8037,9484)	5.26(4.64,5.61)	23254 (16867, 26839)	3(2.27,3.42)	-1.2(-1.79, -0.61)
High-income North America	17711 (15647, 18764)	4.84(4.27,5.12)	31558 (25811, 34476)	4.2(3.49,4.57)	-0.73(-0.96, -0.49)
North Africa and	3569 (2877,445	2.18(1.72,2.69)	7130 (5757,8442)	1.71(1.39,2.06)	-0.74(-0.81, -

Middle East	7)				0.68)
Oceania	29(21,44)	1.2(0.92,1.68)	62(45,90)	0.91(0.7,1.31)	-1.01(-1.15, -0.87)
South Asia	5049 (3528,6996)	1.07(0.74,1.45)	16201 (12987,19111)	1.29(1.03,1.53)	0.64(0.55,0.73)
Southeast Asia	614 (477,1128)	0.29(0.22,0.56)	1874 (1469, 3086)	0.36(0.28,0.6)	0.44(0.21,0.67)
Southern Latin America	1905 (1740,2076)	4.58(4.13,5)	3097 (2744,3360)	3.38(3,3.66)	-0.55(-0.75, -0.34)
Southern Sub-Saharan Africa	374 (285,428)	1.44(1.08,1.71)	768(631,884)	1.64(1.3,1.91)	0.39(0.12,0.65)
Tropical Latin America	2397 (2301,2461)	2.72(2.57,2.82)	5611 (5067,5961)	2.26(2.03,2.4)	-0.41(-0.56, -0.27)
Western Europe	31666 (29021, 33274)	5.35(4.89,5.63)	63091 (51814, 69025)	5.03(4.21,5.48)	-0.06(-0.14,0.03)
Western Sub-Saharan Africa	1362 (915,1850)	1.85(1.23,2.59)	2597 (1846,4032)	1.62(1.15,2.5)	-0.65(-0.74, -0.55)
DALYs					
Global	1791844 (1646002, 1967041)	49.31(45.31,54.17)	3238185 (2934104, 3594474)	39.72(35.79,44.14)	-0.66(-0.75, -0.57)
High SDI	992953 (922590, 1066856)	90.18(83.81,96.51)	1566190 (1356045, 1740983)	65.9(58.18,72.74)	-0.95(-1.1, -0.8)
High-middle SDI	306057 (279303, 342548)	32.97(30.08,36.91)	589769 (524143, 666279)	31.38(27.93,35.35)	-0.14(-0.25, -0.03)
Middle SDI	226926 (204599, 254470)	20.02(17.99,22.43)	470011 (422021, 531312)	18.21(16.31,20.63)	-0.33(-0.42, -0.24)
Low-middle SDI	177039 (136039, 235606)	26.17(20.27,34.14)	420843 (359340, 485904)	28.46(24.05,32.91)	0.29(0.24,0.33)
Low SDI	86836 (56942, 122335)	34.2(23.03,46.51)	186946 (140850, 237357)	32.63(24.72,41.82)	-0.2(-0.32, -0.09)
Andean Latin America	6296 (5305,7157)	25.44(21.56,29.08)	13759 (11459, 16450)	22.44(18.72,26.79)	-0.4(-0.65, -0.14)
	19288		33763		

Australasia	(17872, 20806)	83.68(77.5,90.01)	(29087, 37406)	57.21(50.16,63.17)	-1.21(-1.47, -0.95)
Caribbean	11479 (10244, 12946)	40.51(36.31,45.36)	21045 (18191, 24277)	39.86(34.4,45.99)	0.05(-0.2,0.3)
Central Asia	5088 (3767,7174)	11.22(8.04,16.17)	17789 (14690, 21940)	23.94(19.42,29.98)	3.22(2.81,3.63)
Central Europe	60906 (55828, 68119)	41.78(38.28,46.61)	171411 (156633, 190505)	77.17(70.75,85.2)	2.33(2.08,2.57)
Central Latin America	32076 (31014, 33363)	33.91(32.57,35.61)	85824 (76442, 96679)	33.96(30.26,38.22)	0.14(-0.31,0.59)
Central Sub-Saharan Africa	11206(7349,15403)	46.22(31.05,62.33)	26419(18660,37393)	45.21(31.71,65.23)	-0.15(-0.26, -0.03)
East Asia	66841 (52593, 80610)	8.02(6.43,9.9)	106883 (84366, 139200)	5.42(4.3,6.96)	-1.53(-1.79, -1.26)
Eastern Europe	26743 (20660, 36775)	10.28(7.99,14.11)	93889 (81691, 112816)	28.51(25.01,33.63)	3.45(3.22,3.69)
Eastern Sub-Saharan Africa	36086 (22834, 49310)	39.28(26.46,52.36)	69083 (52409, 90257)	33.16(25.05,44.47)	-0.72(-0.83, -0.61)
High-income Asia Pacific	167836 (155053, 180306)	90.45(82.83,97.03)	291175 (232539, 336889)	44.84(37.27,51.5)	-1.78(-2.32, -1.23)
High-income North America	337224 (309172, 369494)	94.22(86.77,102.67)	500146 (436361, 563374)	72.09(63.77,80.77)	-1.11(-1.37, -0.85)
North Africa and Middle East	119752 (93407, 151706)	57.51(46.2,71.65)	211663 (174900, 248112)	42.23(34.86,49.67)	-1.01(-1.06, -0.97)
Oceania	1169 (761,1866)	29.77(21.6,43.01)	2489 (1733,3751)	25(18.68,35.65)	-0.69(-0.82, -0.56)
South Asia	142573 (101736, 203043)	23.65(16.9,32.74)	394196 (322735, 465627)	26.89(21.94,31.66)	0.4(0.35,0.45)
Southeast Asia	19630 (15528, 33133)	7.54(5.94,12.46)	51059 (40139, 77682)	8.52(6.72,12.96)	0.23(0.05,0.4)
Southern Latin America	38680 (36035, 41517)	86.93(80.49,93.48)	54916 (50004, 60075)	61.8(56.45,67.5)	-0.77(-0.95, -0.6)

Southern Sub-Saharan Africa	12264 (9519, 13792)	35.1(27.14,39.69)	21035 (17777, 24556)	34.39(28.59,39.51)	-0.07(-0.39,0.26)
Tropical Latin America	74415 (72409, 76242)	70.33(67.83,72.38)	131283 (122866, 138171)	51.62(48.19,54.39)	-0.88(-1.05, -0.72)
Western Europe	566358 (530177, 603169)	97.61(91.6,103.36)	870164 (755136, 960381)	78.94(69.92,86.3)	-0.62(-0.71, -0.52)
Western Sub-Saharan Africa	35935 (23837, 47992)	38.23(25.45,51.73)	70194 (48871, 106780)	32.28(22.91,49.92)	-0.76(-0.87, -0.65)

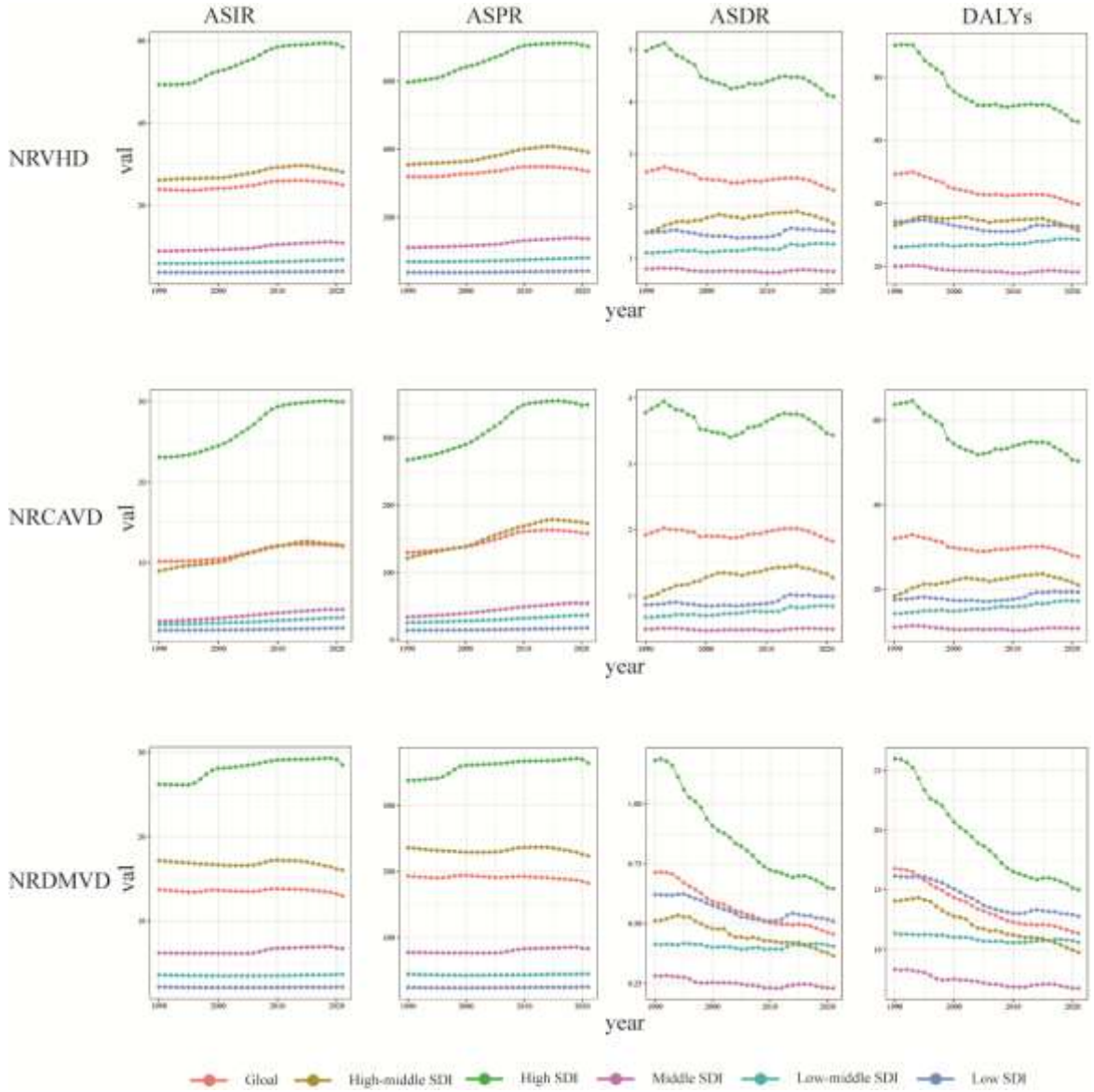

Figure 1: Trends in ASIR, ASPR, ASDR and age-standardized rates of DALYs for NRVHD (including CAVD and DMVD) in global and SDI regions, 1990-2021. NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease; ASIR: age-standardized incidence rate; ASPR: age-standardized prevalence rate; ASDR age-standardized deaths rate; DALYs: disability-adjusted life years; SDI: sociodemographic Index.

Among NRVHD subtypes, the incidence of CAVD in 2021 accounted for 1,044,370 cases (95% UI: 906,615–1,179,672), representing 47.32% % of NRVHD incidence, the ASIR were 12.03 per 100,000 (95% UI: 10.43–13.56), 48.1% of NRVHD ASIR (Table 2, Figure 1).

Table 2: The incidence, prevalence, deaths, disability-adjusted life years and their age-standardized rate of calcific aortic valve disease in global and reginal from1990 to 2021

Location	1990		2021		EAPC_95%CI
	Number	ASR	Number	ASR	
Incidence					
Global	396981 (329260, 464090)	10.17(8.48,11.86)	1044370 (906615, 1179672)	12.03(10.43,13.56)	0.79(0.7,0.89)
High SDI	258052 (214120, 299952)	23.1(19.39,26.78)	625946(542702, 701340)	29.98(26.09,33.53)	1.1(1,1.2)
High-middle SDI	91389 (74605, 109185)	8.98(7.4,10.68)	244578 (208641, 280897)	12.13(10.38,13.88)	1.2(1.08,1.31)
Middle SDI	29076 (23738, 34814)	2.71(2.21,3.22)	116303 (94896, 139288)	4.21(3.43,5.01)	1.59(1.53,1.65)
Low-middle SDI	14289 (11768, 17023)	2.33(1.93,2.73)	46364 (38524, 54557)	3.19(2.68,3.73)	1.08(1.04,1.12)
Low SDI	3648 (3054, 4283)	1.61(1.36,1.84)	9847 (8381, 11323)	1.89(1.61,2.16)	0.55(0.51,0.6)
Andean Latin America	1143 (951,1374)	5.29(4.35,6.36)	5711 (4857,6602)	9.43(8.03,10.96)	1.85(1.8,1.89)
Australasia	5096 (4272, 5916)	21.06(17.81,24.26)	17028 (14712, 19550)	30.99(26.61,35.51)	1.46(1.39,1.53)
Caribbean	1836 (1546,2135)	6.92(5.8,8.06)	5238 (4478,6013)	9.7(8.3,11.13)	1.28(1.18,1.39)
Central Asia	2832 (2271, 3500)	5.77(4.6,7.08)	8951 (7346, 10729)	10.06(8.23,11.76)	2.08(1.91,2.26)
Central Europe	21272 (17502, 25692)	13.81(11.43,16.68)	56157 (48783, 64843)	26.87(23.56,30.71)	2.65(2.31,2.99)
Central Latin America	6905 (5676, 8296)	7.88(6.4,9.49)	30192 (24805, 35812)	11.71(9.64,13.86)	1.6(1.42,1.78)
Central Sub-Saharan Africa	367 (312,426)	1.68(1.47,1.91)	1031 (886,1173)	1.88(1.66,2.12)	0.36(0.26,0.46)
East Asia	12741 (9886,	1.45(1.12,1.76	57704 (44901,	2.57(2,3.12)	2.03(1.97,2.1)

	15724)	)	70370)		
Eastern Europe	29352 (22642, 36517)	10.3(8,12.66)	67601 (52991, 83055)	19.38(15.36,23.74)	2.37(2.21,2.54)
Eastern Sub-Saharan Africa	1129 (962,1288)	1.53(1.32,1.73)	2958 (2558,3360)	1.73(1.51,1.95)	0.37(0.31,0.42)
High-income Asia Pacific	39490 (31462, 48098)	19.33(15.54,2 3.36)	97912 (79649, 115467)	22.73(18.8,26.51)	0.66(0.53,0.79)
High-income North America	104717 (82968, 127208)	29.26(23.5,35. 12)	246667 (210369, 283631)	36.68(31.54,41.73)	0.97(0.8,1.13)
North Africa and Middle East	5999 (5066,695 5)	3.28(2.77,3.81)	21849 (18679, 25206)	4.47(3.79,5.14)	1.08(1.05,1.1)
Oceania	55 (45,66)	1.89(1.57,2.2)	176 (142,211)	2.39(1.95,2.85)	0.5(0.39,0.61)
South Asia	10819 (8789, 13096)	1.94(1.6,2.29)	36024 (29494, 42470)	2.46(2.04,2.91)	0.82(0.78,0.86)
Southeast Asia	3460 (2751, 4164)	1.39(1.1,1.65)	14478 (11611, 17131)	2.22(1.8,2.62)	1.59(1.55,1.64)
Southern Latin America	6923 (5918, 7923)	15.01(12.88,1 7.12)	20017 (17374, 23351)	22.85(19.94,26.48)	1.31(1.1,1.53)
Southern Sub-Saharan Africa	563 (478,650)	2.02(1.72,2.33)	1422 (1194,1652)	2.48(2.11,2.87)	0.59(0.55,0.63)
Tropical Latin America	8407 (6877, 10076)	8.68(7.09,10.4 3)	29005 (23277, 34914)	11.11(8.97,13.36)	0.87(0.78,0.95)
Western Europe	132872 (113971, 150704)	23.01(20.04,2 6.11)	321517 (285402, 354961)	36.45(32.41,40.39)	1.73(1.52,1.94)
Western Sub-Saharan Africa	1003 (858,1160)	1.01(0.87,1.16)	2732 (2367,3117)	1.16(1.01,1.32)	0.37(0.35,0.39)
Prevalence					
Global	4686910 (3874992, 5539483)	129.75 (106.01,152.9 8)	13320896 (11422539, 15249411)	158.35(135.92,181)	0.88(0.78,0.99)
High SDI	3032967 (2503939, 3578606)	267.39 (221.28,314.2 4)	7860601 (6819445, 8892889)	349.64 (303.58,395.77)	1.11(1,1.23)
High-	1153181	121.46	3440879	172.89	

middle SDI	(949563, 1377066)	(99.65,145.53)	(2962649, 3931537)	(149.52,197.05)	1.38(1.25,1.5)
Middle SDI	321384 (259295, 390498)	33.93(27.06,40.86)	1417739 (1134289, 1688924)	54.49(43.43,64.98)	1.75(1.67,1.82)
Low-middle SDI	141850 (113800, 172848)	25.36(20.48,30.85)	496397 (404012, 589829)	36.62(29.46,43.57)	1.26(1.22,1.29)
Low SDI	30542 (24426, 37928)	14.16(11.28,17.3)	85816 (68868, 104074)	17.64(14.26,21.19)	0.75(0.69,0.8)
Andean Latin America	14076 (11665, 17291)	71.52(58.7,88)	77588 (66210, 89728)	133.19 (113.31,154.29)	1.97(1.91,2.03)
Australasia	51083 (42841, 59260)	214.44 (179.76,247.44)	192488 (165456, 223130)	332.99 (286.39,384.01)	1.62(1.54,1.69)
Caribbean	23569 (19826, 27882)	91.96(77.05,108.8)	72781 (62508, 84939)	134.62 (115.73,157.17)	1.43(1.31,1.55)
Central Asia	37213 (29704, 45742)	82.14 (65.58,100.76)	113426 (93422, 135264)	146.37 (119.97,173.94)	2.16(1.98,2.34)
Central Europe	295016 (242496, 353470)	197.53 (163.07,236.16)	866860 (755597, 995397)	379.57 (330.44,437.56)	2.57(2.25,2.91)
Central Latin America	82894 (67918, 99369)	105.4 (85.42,127.23)	395445 (324616, 470756)	160.32 (131.28,191.12)	1.69(1.5,1.87)
Central Sub-Saharan Africa	2665 (2106,3335)	12.49(9.93,15.42)	7684 (6109,9324)	14.67(11.85,17.89)	0.5(0.36,0.64)
East Asia	137958 (104340, 174296)	17.53(13.34,21.9)	719161 (554740, 884832)	33.15(25.5,40.55)	2.31(2.21,2.41)
Eastern Europe	377605 (300012, 463742)	136.91 (109.03,167.66)	949895 (761766, 1153178)	264.72(213.79,319.46)	2.46(2.3,2.63)
Eastern Sub-Saharan Africa	8446 (6751, 10487)	11.63(9.22,14.28)	22929 (18357, 27771)	13.96(11.03,17.01)	0.53(0.46,0.6)
High-income Asia Pacific	482345 (385465, 591335)	244.46 (194.31,297.3)	1447553 (1198037, 1699765)	284.22 (238.29,333.61)	0.62(0.51,0.73)
High-income North America	1196674 (943508, 1460580)	325.59 (256.18,394.83)	2772454 (2360163, 3202756)	403.07 (344.88,462.72)	0.9(0.73,1.06)
North	63862		246280		

Africa and Middle East	(52184, 76626)	38.28(31.34,45.7)	(205247, 291455)	55.12(46.06,64.89)	1.27(1.24,1.29)
Oceania	495 (390,614)	20.1(15.94,24.23)	1671 (1322,2032)	27.09(21.54,32.45)	0.68(0.57,0.79)
South Asia	96318 (75479, 120424)	18.31(14.4,22.93)	349853 (276806, 429247)	24.88(19.64,30.42)	1.07(1.03,1.11)
Southeast Asia	33922 (25960, 42235)	15.06(11.64,18.35)	150953 (115914, 183274)	25.31(19.72,30.59)	1.73(1.69,1.78)
Southern Latin America	72336 (60573, 83631)	159.61 (133.14,184.61)	234828 (202977, 273602)	262.02 (226.21,304.68)	1.53(1.29,1.78)
Southern Sub-Saharan Africa	5112 (4073, 6266)	18.87(14.96,23.03)	13442 (10821, 16420)	23.77(19.01,28.8)	0.69(0.62,0.75)
Tropical Latin America	93906 (76978, 113892)	105.97 (86.08,129.68)	355804 (284981, 430930)	139.74 (111.9,169.21)	0.98(0.89,1.08)
Western Europe	1602828 (1382936, 1854394)	264.82 (228.72,306.36)	4306128 (3789649, 4809887)	425.32 (375.41,477.97)	1.76(1.53,2)
Western Sub-Saharan Africa	8588 (6868, 10576)	9.18 (7.36,11.19)	23674 (19212, 28589)	11.08(8.99,13.41)	0.53(0.5,0.55)
Deaths					
Global	57932 (52886, 61950)	1.92(1.73,2.06)	142205 (120675, 155575)	1.83(1.54,2)	-0.05(-0.16,0.05)
High SDI	41209 (37109, 43310)	3.78(3.37,3.99)	92579 (74404, 102071)	3.43(2.81,3.76)	-0.19(-0.33, -0.04)
High-middle SDI	7642 (7067, 8132)	0.96(0.88,1.03)	23646 (20186, 25781)	1.27(1.08,1.39)	1.01(0.77,1.25)
Middle SDI	4178 (3664, 4807)	0.49(0.42,0.57)	11640 (10228, 13303)	0.49(0.43,0.57)	0(-0.09,0.1)
Low-middle SDI	3346 (2384, 4456)	0.67(0.47,0.89)	10223 (8152, 12209)	0.84(0.67,1.01)	0.78(0.7,0.85)
Low SDI	1508 (895, 2161)	0.86(0.5,1.21)	3951 (2656, 5097)	0.98(0.64,1.31)	0.54(0.37,0.7)
Andean Latin America	131 (106,151)	0.64(0.52,0.74)	356 (293,436)	0.61(0.5,0.74)	-0.19(-0.42,0.05)
	807		2002		

Australasia	(730,861)	3.63(3.25,3.87)	(1662,2221)	3.09(2.59,3.42)	-0.48(-0.75, -0.21)
Caribbean	248 (221,271)	0.99(0.89,1.08)	545 (476,614)	1.01(0.88,1.14)	0.1(-0.15,0.36)
Central Asia	33 (29,39)	0.07(0.06 ,0.09)	205 (179,231)	0.3(0.26,0.34)	5.85(5.07,6.63)
Central Europe	1040(956, 1179)	0.75(0.69,0.86)	6366 (5693,6900)	2.68(2.4,2.91)	4.84(4.47,5.21)
Central Latin America	700 (674,718)	0.88(0.84,0.9)	2226 (1985,2480)	0.91(0.82,1.02)	0(-0.35,0.35)
Central Sub-Saharan Africa	207 (130,294)	1.27(0.77,1.79)	569 (352,857)	1.45(0.88,2.27)	0.39(0.26,0.53)
East Asia	813 (551, 1178)	0.13(0.09,0.18)	1757 (1422,2248)	0.1(0.08,0.12)	-1.33(-1.88, -0.77)
Eastern Europe	352 (338,364)	0.14(0.13,0.14)	2230 (2063,2391)	0.64(0.59,0.69)	5.36(4.98,5.74)
Eastern Sub-Saharan Africa	572 (351,804)	0.98(0.57,1.34)	1379 (899,1885)	1.02(0.66,1.44)	0.06(-0.02,0.15)
High-income Asia Pacific	6321 (5645, 6687)	3.74(3.28,4)	19320 (13988, 22319)	2.46(1.84,2.8)	-0.63(-1.28,0.02)
High-income North America	14039 (12327, 14904)	3.83(3.36,4.07)	27282 (22212, 29883)	3.6(2.97,3.93)	-0.41(-0.65, -0.17)
North Africa and Middle East	1418 (962, 1874)	0.92(0.6,1.2)	3276 (2414,4032)	0.81(0.61,0.99)	-0.3(-0.37, -0.23)
Oceania	24(18,36)	1.08(0.83,1.48)	54(40,77)	0.84(0.64,1.2)	-0.89(-1.04, -0.74)
South Asia	3176 (2106, 4454)	0.72(0.47,1)	11192 (8668, 13804)	0.92(0.7,1.13)	0.83(0.74,0.93)
Southeast Asia	363 (235,666)	0.19(0.12,0.36)	1243 (942,1951)	0.25(0.19,0.39)	0.73(0.47,0.98)
Southern Latin America	1654 (1497, 1797)	4.01(3.61,4.37)	2765 (2449,3011)	3.01(2.67,3.27)	-0.5(-0.72, -0.28)
Southern Sub-Saharan Africa	227 (178,276)	0.99(0.75,1.2)	525 (426,626)	1.23(0.98,1.45)	0.69(0.49,0.89)

Tropical Latin America	1596 (1524, 1643)	1.88(1.76,1.96)	3837 (3444,4097)	1.55(1.39,1.66)	-0.42(-0.57, -0.27)
Western Europe	23490 (21550, 24746)	3.97(3.62,4.18)	53518 (43825, 58592)	4.23(3.53,4.6)	0.37(0.28,0.46)
Western Sub-Saharan Africa	721 (447,961)	1.06(0.64,1.48)	1557 (966,2404)	1.04(0.65,1.63)	-0.22(-0.3, -0.14)
DALYs					
Global	1121945 (1040350, 1218803)	31.99(29.43,34.67)	2243000 (2004168, 2459248)	27.74(24.67,30.48)	-0.38(-0.48, -0.28)
High SDI	701692 (652121, 742299)	63.76(59.17,67.34)	1222299 (1042435, 1341836)	50.38(44.16,54.83)	-0.65(-0.82, -0.48)
High-middle SDI	167508 (154364, 182918)	18.44(16.89,20.18)	394694 (352937, 434424)	21(18.75,23.06)	0.46(0.29,0.62)
Middle SDI	121171 (108424, 138543)	11.04(9.76,12.67)	276278 (242967, 316116)	10.76(9.48,12.35)	-0.14(-0.24, -0.05)
Low-middle SDI	90040 (66249, 120132)	14.26(10.4,18.82)	245090 (199020, 292247)	17.2(13.85,20.5)	0.63(0.58,0.67)
Low SDI	40446 (24961, 58433)	17.55(10.49,25.08)	101674 (68878, 130980)	19.33(13.08,24.89)	0.33(0.2,0.45)
Andean Latin America	3978 (3136, 4630)	16.85(13.59,19.56)	9992 (8267, 12214)	16.44(13.57,19.98)	-0.16(-0.37,0.06)
Australasia	13984 (12964, 14938)	60.68(56,64.74)	27116 (23306, 29987)	45.22(39.49,49.74)	-0.89(-1.15, -0.62)
Caribbean	6816 (6042, 7540)	24.7(21.96,27.21)	13275 (11395, 15250)	24.98(21.44,28.74)	0.07(-0.18,0.31)
Central Asia	1378 (1125, 1769)	2.92(2.36,3.84)	5878 (5034, 6995)	7.85(6.66,9.47)	4.1(3.51,4.7)
Central Europe	26066 (23666, 29655)	17.99(16.31,20.61)	112642 (102498, 123896)	50.1(45.8,54.99)	3.86(3.51,4.21)
Central Latin America	20567 (19867, 21501)	22.15(21.23,23.42)	58212 (52221, 65462)	23.08(20.68,26.05)	-0.04(-0.35,0.28)
Central Sub-Saharan Africa	5637 (3645, 8151)	25.47(15.92,35.95)	14883 (9600, 21789)	27.84(17.2,41.81)	0.24(0.1,0.37)

East Asia	24527 (16591, 34881)	2.86(2.01,3.94)	43823 (35366, 55392)	2.25(1.83,2.82)	-1.13(-1.49, -0.76)
Eastern Europe	13293 (10863, 17264)	5.1(4.17,6.62)	60663 (53910, 70346)	18.23(16.32,20.87)	4.27(3.97,4.57)
Eastern Sub-Saharan Africa	16115 (10579, 23148)	19.98(12.43,27.82)	37760 (24921, 50626)	20.2(13.21,27.55)	-0.07(-0.16,0.01)
High-income Asia Pacific	110145 (101917, 116508)	59.9(54.65,63.71)	220492 (172646, 252863)	32.75(27.02,37.01)	-1.33(-1.95, -0.7)
High-income North America	243224 (224191, 258843)	68.01(62.9,72.2)	382828 (333801, 419029)	54.41(48.14,59.3)	-0.92(-1.21, -0.62)
North Africa and Middle East	45795 (31939, 61038)	22.45(15.51,29.65)	93596 (68114, 115367)	19.01(14.14,23.21)	-0.53(-0.57, -0.48)
Oceania	873 (582, 1367)	23.84(17.62,34.71)	2016 (1395,2977)	20.77(15.34,29.45)	-0.53(-0.67, -0.39)
South Asia	81213 (55083, 115202)	14.42(9.7,20.13)	251747 (197292, 310183)	17.69(13.81,21.73)	0.65(0.6,0.71)
Southeast Asia	9518 (6438, 15903)	3.76(2.53,6.61)	27996 (21601, 41440)	4.73(3.64,7.14)	0.58(0.37,0.8)
Southern Latin America	31879 (29710, 34231)	72.13(66.93,77.55)	46480 (42450, 50689)	52.09(47.68,56.73)	-0.73(-0.93, -0.54)
Southern Sub-Saharan Africa	6055 (4983, 7615)	19.65(16.01,23.95)	12228 (10014, 14946)	21.98(17.85,26.4)	0.34(0.13,0.56)
Tropical Latin America	46545 (45131, 47807)	45.66(43.88,47.08)	83552 (77538, 88493)	33(30.52,35.02)	-0.93(-1.1, -0.75)
Western Europe	397544 (372068, 418278)	68.28(63.96,71.5)	700284 (600116, 766678)	62.44(54.95,67.78)	-0.19(-0.27, -0.1)
Western Sub-Saharan Africa	16795 (10732, 22500)	19.61(12.26,26.12)	37536 (23078, 57538)	19.11(11.83,29.47)	-0.27(-0.36, -0.17)

DMVD contributed 1,162,558 cases (95% UI: 1,084,358-1,244,874), accounting for 52.68% of NRVHD incidence, with ASIR of 12.98 (95% UI: 12.11–13.89) per 100,000, 51.9% of NRVHD ASIR (Table 3, Figure 1).

The global prevalence of NRVHD in 2021 was 28,389,034 cases (95% UI: 26,323,458–30,585,670), marking a 143.26% increase from

1990. The age-standardized prevalence rate (ASPR) increased from 318.94 per 100,000 (95% UI: 294.11–345.46) in 1990 to 335.29 per 100,000 (95% UI: 311.34–361.05) in 2021, with an EAPC of 0.31(95% CI: 0.25-0.38) (Table 1, Figure 1). While the global prevalence of CAVD in 2021 was 13,320,896 cases (95% UI: 11,422,539–15,249,411), representing 46.92% of NRVHD prevalence, with ASPR of 158.35 per 100,000 (95% UI: 135.92–181.00), representing 47.23% of the NRVHD ASPR (Table 2, Figure 1). The prevalence of DMVD reached 15,494,647 cases (95% UI: 14,457,324–16,702,738), comprising 54.58% of NRVDH prevalence, with ASPR of 182.13 per 100,000 (95% UI: 169.95–196.07), accounting for 54.32% of NRVHD ASPR (Table 3, Figure 1).

The global deaths of NRVHD in 2021 was 181,078 (95% UI: 155,364–195,717), with age-standardized deaths rate (ASDR) of 2.31 per 100,000 (95% UI: 1.96–2.50), with an EAPC of -0.37 (95% CI: -0.46 to -0.27) (Table 1, Figure 1). Among that, the CAVD accounted for 142,205 (95% UI: 120,675–155,575), 78.53% of total NRVHD deaths. The ASDR of CAVD was 1.83 per 100,000 (95% UI: 1.54–2.00), 79.15% of total NRVHD ASDR (Table 2, Figure 1). While DMVD contributed 36,844(95% UI: 31,883–41,572), 20.35% of total NRVHD deaths, with ASDR of 0.46 per 100,000 (95% UI: 0.39–0.51), 19.78% of NRVHD ASDR (Table 3, Figure 1).

Table 3: The incidence, prevalence, deaths, disability-adjusted life years and their age-standardized rate of degenerative mitral valve disease in global and reginal from 1990 to 2021

Location	1990		2021		EAPC_95%CI
	Number	ASR	Number	ASR	
Incidence					
Global	566261 (523330, 609607)	13.73(12.69,14.76)	1162558 (1084358, 1244874)	12.98(12.11,13.89)	-0.02(0.07,0.02)
High SDI	289042 (268397, 311012)	26.2(24.31,28.18)	569743 (532337, 610609)	28.49(26.66,30.52)	0.41(0.34,0.48)
High-middle SDI	180837 (166880, 195319)	17.16(15.85,18.51)	333052 (311758, 356305)	16.01(14.99,17.11)	-0.06(-0.13,0)
Middle SDI	67453 (61686, 73335)	6.21(5.7,6.74)	191670(178708,207179)	6.75(6.29,7.29)	0.47(0.38,0.56)
Low-middle SDI	22978 (20516, 25650)	3.61(3.22,4.05)	55269 (49821, 61569)	3.68(3.32,4.09)	0.07(0.02,0.11)
Low SDI	5294 (4731, 5856)	2.18(1.97,2.42)	11811 (10737, 13005)	2.16(1.97,2.37)	0.01(-0.02,0.05)
Andean Latin America	451 (368, 550)	2.07(1.69,2.54)	1277 (1057, 1535)	2.11(1.75,2.55)	0.22(0.13,0.31)
Australasia	4112 (3563, 4874)	16.85(14.58,19.79)	8398 (7111, 10037)	16.1(13.67,19.31)	-0.14(-0.18, -0.11)
Caribbean	742 (621, 885)	2.75(2.28,3.31)	1478 (1253, 1772)	2.75(2.33,3.29)	0.14(0.06,0.22)
Central	13807 (10953,	28.42(22.48,35.8	32828 (27652,	36.89(30.98,43.6	1.13(0.96,1.29)

Asia	17345)	)	39343)	8)	
Central Europe	30331 (25817, 35544)	19.21(16.39,22.43)	45803 (40058, 52920)	21.44(18.85,24.57)	0.64(0.47,0.8)
Central Latin America	2451 (2163, 2758)	2.78(2.47,3.15)	7405 (6628, 8313)	2.87(2.57,3.21)	0.26(0.1,0.42)
Central Sub-Saharan Africa	406 (340, 477)	1.63(1.39,1.89)	907 (766, 1061)	1.45(1.25,1.66)	-0.38(-0.43, -0.33)
East Asia	82888 (77242, 88272)	8.92(8.33,9.5)	245901 (232653, 259885)	10.24(9.7,10.81)	0.67(0.58,0.77)
Eastern Europe	51875 (47690, 56227)	17.82(16.46,19.25)	69201 (64350, 74457)	19.16(17.84,20.66)	0.37(0.3,0.45)
Eastern Sub-Saharan Africa	1276 (1124, 1439)	1.53(1.35,1.7)	2557 (2253, 2862)	1.32(1.18,1.47)	-0.54(-0.59, -0.48)
High-income Asia Pacific	58665 (54354, 63363)	28.07(26.01,30.29)	108750 (101158, 116721)	28.4(26.52,30.46)	0.1(0.05,0.14)
High-income North America	139678 (131581, 148363)	39.89(37.64,42.28)	293501(276789,310493)	43.57(41.2,45.99)	0.39(0.24,0.55)
North Africa and Middle East	10118 (8687, 11759)	5.57(4.79,6.54)	25612 (22313, 29578)	5.32(4.64,6.22)	0.05(-0.06,0.16)
Oceania	172 (137, 215)	5.49(4.35,6.94)	420 (337, 519)	5.39(4.32,6.78)	-0.11(-0.13, -0.09)
South Asia	16822 (15477, 18254)	2.85(2.63,3.09)	44916 (41667, 48223)	2.93(2.72,3.14)	0.15(0.12,0.18)
Southeast Asia	14965 (13021, 17180)	5.72(4.95,6.61)	45435 (39950, 51704)	6.5(5.73,7.42)	0.42(0.39,0.46)
Southern Latin America	4767 (3932, 5855)	9.94(8.21,12.25)	8882 (7380, 10815)	10.38(8.62,12.64)	0.26(0.19,0.33)
Southern Sub-Saharan Africa	387 (356, 418)	1.21(1.12,1.31)	696 (641, 758)	1.06(0.99,1.15)	-0.6(-0.75, -0.44)
Tropical Latin America	3536 (3278, 3790)	3.5(3.25,3.76)	8977 (8427, 9588)	3.4(3.2,3.63)	0.18(0.08,0.27)

Western Europe	127521 (117187, 139155)	22.66(20.88,24.69)	206533 (190290, 223467)	24.79(22.86,26.81)	0.35(0.28,0.41)
Western Sub-Saharan Africa	1292 (1166, 1435)	1.28(1.16,1.41)	3079 (2775, 3428)	1.22(1.11,1.35)	-0.17(-0.19, -0.15)
Prevalence					
Global	7111757 (6572737,7719089)	193.04 (178.74,208.37)	15494647(14457324, 16702738)	182.13 (169.95,196.07)	-0.1(-0.13, -0.06)
High SDI	3870206 (3585779,4185413)	337.89 (313.22,365.83)	8149325 (7632524, 8750587)	364.24 (341.57,390.64)	0.31(0.25,0.36)
High-middle SDI	2248063 (2073439,2447323)	235.91(218.2,256.06)	4486461 (4187532, 4821465)	223.55 (208.8,240.01)	-0.02(-0.07,0.04)
Middle SDI	699387 (632990, 774419)	77.36(70.34,85.01)	2131567 (1978434, 2317641)	83.14(77.41,89.93)	0.4(0.32,0.48)
Low-middle SDI	236184 (206976, 267733)	44.25(38.82,49.94)	597241 (530959, 673732)	44.67(39.91,50.05)	0.07(0.03,0.12)
Low SDI	49418 (42745, 56717)	24.13(21.03,27.41)	115513 (101726, 130949)	24.77(21.96,27.95)	0.14(0.1,0.18)
Andean Latin America	5382 (4251, 6683)	27.28(21.58,33.78)	16250 (13104, 19888)	27.86(22.48,34.06)	0.22(0.14,0.3)
Australasia	49743 (43137, 58430)	202.34 (175.25,237.57)	115502 (98356, 139123)	200.85 (171.78,241.19)	0(-0.03,0.04)
Caribbean	9532 (7702, 11614)	36.71(29.68,45)	19885 (16459, 23915)	36.94(30.61,44.37)	0.16(0.08,0.23)
Central Asia	164483 (131623, 206939)	376.9(302.35,471.55)	360193 (302400, 433574)	496.93 (420.36,589.81)	1.25(1.06,1.45)
Central Europe	395349 (336868, 461279)	264.61 (226.75,306.17)	678553 (594742, 782443)	291.32 (254.9,334.97)	0.56(0.42,0.7)
Central Latin America	28266 (24458, 32552)	35.81(31.18,41.25)	91700 (80539, 104481)	37.25(32.81,42.38)	0.27(0.12,0.41)
Central Sub-Saharan Africa	3373 (2633, 4211)	15.76(12.53,19.43)	7308 (5802, 8967)	13.73(10.91,16.74)	-0.44(-0.53, -0.36)
East Asia	835228 (778575, 897822)	111.55 (104.35,119.29)	2697966 (2558787, 2843604)	124.23 (117.69,130.92)	0.56(0.48,0.65)

Eastern Europe	653909 (597345, 719723)	236.32 (216.72,258.11)	936899 (862626, 1026287)	258.75 (238.93,282.71)	0.46(0.38,0.54)
Eastern Sub-Saharan Africa	10727 (8952, 12602)	14.49(12.22,16.99)	21886 (18404, 25729)	13(11.04,15.16)	-0.41(-0.46, -0.35)
High-income Asia Pacific	757805 (701584, 824389)	380.35 (352.86,411.72)	1938173 (1818157, 2065322)	390.61 (366.97,418.01)	0.12(0.1,0.14)
High-income North America	1942737 (1829074,2071000)	521.74 (490.58,556.92)	3932341 (3732847, 4161755)	562.8 (535.23,594.69)	0.33(0.23,0.44)
North Africa and Middle East	102905 (85688, 121454)	68.01(56.75,80.59)	270184 (230370, 317865)	65.49(56.18,76.56)	0.13(0,0.26)
Oceania	1678 (1308, 2126)	72.25(57.31,90.61)	4262 (3407, 5357)	71.21(57.8,88.53)	-0.08(-0.11, -0.06)
South Asia	166082 (150544, 182992)	33.71(30.84,36.73)	491176 (447265, 539291)	35.67(32.66,38.8)	0.25(0.22,0.28)
Southeast Asia	159232 (137821, 184629)	73.67(63.83,84.87)	493226 (428684, 566120)	83.99(73.57,96.39)	0.41(0.37,0.45)
Southern Latin America	61105 (50073, 74682)	132.44 (108.73,161.93)	123475 (102958, 152017)	138.06 (114.77,169.69)	0.24(0.17,0.3)
Southern Sub-Saharan Africa	4034 (3615, 4494)	14.14(12.73,15.8)	7598 (6779, 8536)	12.57(11.31,14.07)	-0.5(-0.63, -0.37)
Tropical Latin America	40304 (37047, 43713)	45.02(41.41,48.83)	111746 (103635, 120984)	43.75(40.64,47.26)	0.13(0.05,0.22)
Western Europe	1707798 (1578748,1854639)	278.09 (257.08,302.18)	3148081 (2910257, 3407229)	311.3 (287.65,337.34)	0.45(0.39,0.51)
Western Sub-Saharan Africa	12087 (10446, 13993)	13.22(11.49,15.35)	28243 (24381, 32739)	13.14(11.34,15.33)	-0.01(-0.03,0.02)
Deaths					
Global	23954 (21032, 26296)	0.71(0.63,0.78)	36844 (31883, 41572)	0.46(0.39,0.51)	-1.49(-1.6, -1.38)
High SDI	13007 (11846,	1.18(1.07,1.25)	16264 (13478,	0.65(0.55,0.7)	-2.06(-2.2, -

	13785)		17843)		1.91)
High-middle SDI	4443 (3962, 4833)	0.51(0.45,0.56)	6887 (6041, 7711)	0.37(0.32,0.41)	-1.13(-1.22, -1.03)
Middle SDI	2706 (2210, 3196)	0.28(0.23,0.34)	5692 (4775, 7097)	0.23(0.19,0.29)	-0.61(-0.74, -0.49)
Low-middle SDI	2430 (1707, 3236)	0.41(0.29,0.55)	5465 (4214, 6975)	0.4(0.31,0.53)	-0.04(-0.12,0.03)
Low SDI	1336 (776, 1875)	0.62(0.38,0.91)	2479 (1698, 3446)	0.51(0.34,0.73)	-0.69(-0.82, -0.56)
Andean Latin America	62(48,73)	0.27(0.21,0.32)	120(89,148)	0.2(0.15,0.25)	-0.69(-1.24, -0.13)
Australasia	251 (226,269)	1.13(1.01,1.21)	361 (302,408)	0.59(0.5,0.66)	-2.23(-2.5, -1.96)
Caribbean	130 (109,155)	0.48(0.41,0.56)	244 (206,285)	0.46(0.38,0.54)	0.06(-0.28,0.4)
Central Asia	35(29,41)	0.08(0.06,0.09)	214 (189,239)	0.29(0.26,0.33)	5.52(4.86,6.19)
Central Europe	1221 (1121, 1351)	0.86(0.79,0.96)	2432(2165,2649)	1.05(0.93,1.14)	0.76(0.53,1)
Central Latin America	361 (347,374)	0.44(0.42,0.46)	1032 (896,1184)	0.42(0.37,0.48)	0.69(-0.15,1.53)
Central Sub-Saharan Africa	168 (90,246)	0.84(0.46,1.3)	354 (207,547)	0.73(0.44,1.21)	-0.53(-0.61, -0.44)
East Asia	956 (559, 1205)	0.14(0.08,0.18)	1101 (821,1450)	0.06(0.04,0.08)	-3.5(-4.03, -2.97)
Eastern Europe	153 (146,160)	0.06(0.06,0.06)	758 (699,815)	0.22(0.21,0.24)	4.43(4.09,4.78)
Eastern Sub-Saharan Africa	535 (282,751)	0.71(0.39,1.07)	858 (557,1245)	0.5(0.31,0.79)	-1.33(-1.45, -1.2)
High-income Asia Pacific	2621 (2363, 2768)	1.5(1.33,1.6)	3908 (2905,4493)	0.54(0.42,0.61)	-3.03(-3.42, -2.64)
High-income North America	3651 (3289, 3844)	1(0.9,1.05)	4204 (3540,4558)	0.59(0.51,0.64)	-2.35(-2.69, -2.01)

North Africa and Middle East	1924 (1459, 2579)	1.14(0.86,1.52)	3243 (2548,4606)	0.75(0.59,1.08)	-1.33(-1.39, -1.27)
Oceania	4(2,7)	0.07(0.04,0.11)	6(3,10)	0.04(0.03,0.08)	-1.56(-1.71, -1.42)
South Asia	1824 (1031, 2629)	0.34(0.2,0.5)	4845 (3212,6326)	0.36(0.24,0.47)	0.17(0.09,0.25)
Southeast Asia	219 (142,535)	0.1(0.06,0.26)	575 (399,1222)	0.1(0.07,0.23)	0.02(-0.19,0.24)
Southern Latin America	249 (221,273)	0.57(0.5,0.62)	329 (296,355)	0.37(0.33,0.4)	-0.88(-1.19, -0.58)
Southern Sub-Saharan Africa	142 (87,169)	0.44(0.26,0.54)	236 (167,300)	0.4(0.28,0.52)	-0.33(-0.77,0.11)
Tropical Latin America	786 (756,810)	0.83(0.78,0.86)	1702 (1563,1803)	0.67(0.62,0.72)	-0.46(-0.65, -0.28)
Western Europe	8031 (7349, 8561)	1.36(1.24,1.45)	9302 (7674, 10174)	0.78(0.66,0.85)	-1.82(-1.96, -1.68)
Western Sub-Saharan Africa	628 (356,915)	0.78(0.45,1.19)	1021 (623,1558)	0.56(0.35,0.88)	-1.29(-1.41, -1.18)
DALYs					
Global	645877 (553701,749210)	16.79(14.68,19.28)	943258 (818239, 1134001)	11.36(9.87,13.61)	-1.32(-1.41, -1.22)
High SDI	286597 (261114, 323954)	25.98(23.76,29.18)	334695 (286438, 404530)	15.01(13.02,17.98)	-1.87(-2, -1.74)
High-middle SDI	134087 (115261, 158668)	14.09(12.16,16.73)	184649 (156704, 228858)	9.77(8.33,12.01)	-1.24(-1.32, -1.17)
Middle SDI	97118 (81912, 113664)	8.33(6.99,9.75)	175874 (152861, 212348)	6.76(5.85,8.19)	-0.65(-0.75, -0.55)
Low-middle SDI	82288 (57207, 112961)	11.37(8.18,15.04)	165113 (129856, 204532)	10.62(8.41,13.21)	-0.21(-0.26, -0.16)
Low SDI	44878 (23753, 63997)	16.17(9.41,22.69)	81577 (56425, 109180)	12.8(9,17.54)	-0.88(-0.99, -0.77)
Andean Latin America	2302 (1784, 2735)	8.52(6.63,10.13)	3687 (2789, 4541)	5.87(4.45,7.23)	-0.95(-1.47, -0.43)
	5267		6561		

Australasia	(4866, 5791)	22.84(21.1,25)	(5674, 7551)	11.82(10.38,13.45)	-2.25(-2.49, -2.02)
Caribbean	4558 (3716, 5540)	15.47(12.77,18.51)	7557 (6179, 9098)	14.46(11.76,17.45)	0(-0.3,0.3)
Central Asia	3378 (2296, 5095)	7.74(5.12,11.78)	10234 (7974, 13440)	14.09(10.69,18.95)	2.62(2.25,2.99)
Central Europe	33650 (30189, 38167)	22.95(20.59,26.14)	53614 (47716, 61177)	24.51(21.98,27.78)	0.25(0.04,0.47)
Central Latin America	11018 (10612, 11464)	11.32(10.84,11.87)	26377 (23036, 30245)	10.4(9.1,11.92)	0.51(-0.27,1.3)
Central Sub-Saharan Africa	5445 (2782, 7847)	20.34(10.95,29.81)	11291 (6640, 16644)	17.03(10.15,26.5)	-0.67(-0.75, -0.58)
East Asia	39578 (26460, 51543)	4.89(3.4,6.47)	58735 (42657, 85576)	2.94(2.16,4.26)	-1.85(-2.06, -1.64)
Eastern Europe	12718 (8942, 19035)	4.88(3.46,7.27)	30340 (24624, 38511)	9.2(7.59,11.47)	2.18(2.01,2.34)
Eastern Sub-Saharan Africa	19452 (9300, 27713)	18.86(10.03,26.38)	30577 (20704, 42521)	12.7(8.31,18.38)	-1.53(-1.66, -1.4)
High-income Asia Pacific	56708 (51503, 63521)	30.03(27.19,33.63)	70200 (56545, 87586)	11.93(9.77,15.13)	-2.76(-3.13, -2.39)
High-income North America	93395 (81710, 110657)	26.03(22.98,30.5)	115613 (94261, 149324)	17.33(14.31,22.01)	-1.72(-1.94, -1.49)
North Africa and Middle East	65022 (48864, 88288)	31.36(24.08,42.23)	98611 (78336, 139383)	19.51(15.72,27.22)	-1.57(-1.61, -1.52)
Oceania	226 (119,438)	4.39(2.74,7.41)	382 (236,646)	3.44(2.29,5.51)	-0.99(-1.11, -0.88)
South Asia	59659 (34658, 90228)	9(5.36,12.93)	137673 (95986, 174664)	8.9(6.23,11.33)	-0.05(-0.1, -0.01)
Southeast Asia	9107 (6313, 18147)	3.45(2.36,6.71)	21562 (15607, 36749)	3.57(2.57,6)	-0.05(-0.19,0.09)
Southern Latin America	6737 (6027, 7543)	14.67(13.1,16.44)	8346 (7421,9708)	9.6(8.58,11.1)	-0.99(-1.26, -0.71)

Southern Sub-Saharan Africa	6003 (3771, 7057)	14.92(9.35,17.62)	8579 (6268, 10727)	12.08(8.71,15.01)	-0.64(-1.13, -0.15)
Tropical Latin America	27336 (26617, 27999)	24.21(23.4,24.92)	45717 (43132, 47817)	17.82(16.8,18.63)	-0.88(-1.07, -0.68)
Western Europe	165595 (152458, 182826)	28.69(26.49,31.46)	165605 (142786, 193314)	15.99(14.07,18.41)	-1.98(-2.13, -1.82)
Western Sub-Saharan Africa	18725 (10526, 26208)	18.25(10.51,26.3)	31996 (19264, 47153)	12.94(7.95,19.61)	-1.35(-1.48, -1.22)

The DALYs of global attributable to NRVHD in 2021 were 3,238,185 (95% UI: 2,934,104–3,594,474), with an age-standardized DALYs rate of 39.72 (95% UI: 35.79–44.14) per 100,000 and an EAPC of -0.66 (95% CI: -0.75 to -0.57) (Table 1, Figure 1). In which, CAVD contributed 2,243,000 cases (95% UI: 2,004,168–2,459,248), representing 69.27% of NRVHD DALYs, with an age-standardized DALY rate of 27.74 per 100,000 (95% UI: 24.67–30.48), 69.83% of NRVHD age-standardized DALYs rate (Table 2, Figure 1). DMVD were 943,258 (95% UI: 818,239-1134,001) representing 29.13% of NRVHD DALYs, and age-standardized DALYs were 11.36 per 100,000 (95% UI: 9.87-13.61), 28.6% of NRVHD age-standardized DALYs rate (Table 3, Figure 1).

Reginal Level

For different SDI regions, in 2021, the highest ASIR and ASPR for NRVHD (including CAVD and DMVD, were observed in high SDI region, while the lowest rates were found in low SDI regions. The ASIR and ASPR of high SDI region for NRVHD were 58.47 per 100,000 (95% UI: 54.45–62.86) and 701.43 per 100,000 (95% UI: 652.84–754.32), respectively. In contrast, low SDI region reported significantly lower rates, with ASIR of NRVHD was 4.05 per 100,000 (95% UI: 3.73–4.39) and ASPR of 42.44 per 100,000 (95% UI: 38.14–47.25). Trends in ASIR and ASPR for NRVHD (including NRCAVD) exhibited increases across all SDI regions, while for NRDMVD, except for high-middle SDI region, the trend of ASIR and ASPR showed a decline in all SDI regions (Table 1–3, Figure 1). The highest ASDR and age-standard DALYs rate of NRVHD (including CAVD and DMVD) were high SDI region, while the lowest rates were middle SDI region. The NRVHD ASDR and age-standard DALYs rate of High SDI region were 4.10 per 100,000 (95% UI: 3.38–4.49) and 65.90 per 100,000 (95% UI: 58.18–72.74), while for middle SDI, were 0.75 per 100,000 (95% UI: 0.66–0.85) and 18.21 per 100,000 (95% UI: 16.31–20.63). The trend of NRVHD ASDR increased in all SDI regions except high and middle SDI regions, while the trend of age-standard DALY rate decreased in all SDI regions except for low-middle SDI region (Table1, Figure 1). For CAVD, the ASDR exhibited an increasing trend across all SDI regions except for the high SDI region, while the age-standardized DALYs rate demonstrated a declining trend in all regions except for high and middle SDI regions (Table 2, Figure 1). The ASDR and age- standardized DALYs rate of DMVD exhibited declining trends across all SDI regions (Table 3, Figure 1).

For different regions, the ASIR, ASPR, ASDR, and age-standardized DALYs rate for NRVHD (including CAVD and DMVD), were concentrated in High-income North America and Europe, while the lowest were observed in Sub-Saharan regions (Tables 1–3). For NRVHD, the highest ASIR was recorded in High-income North America at 80.25 per 100,000 (95% UI: 74.58–86.04), while the most significant increase in ASIR occurred in Central Europe, with EAPC of 1.63 (95% CI: 1.38–1.87) (Table 1). Andean Latin America exhibited the largest increase in ASPR, with an EAPC of 1.59 (95% CI: 1.55–1.62) (Table 1). In terms of ASDR, Central Asia showed the

greatest rise in ASDR, with an EAPC of 5.72 (95% CI: 5.09–6.35) (Table 1, Figure 1). Regarding DALYs, Western Europe reported the highest age-standardized DALYs rate at 78.94 per 100,000 (95% UI: 69.92–86.30), while Eastern Europe experienced the largest increase, with EAPC of 3.45 (95% CI: 3.22–3.69) (Table 1).

National Level

In 2021, the Republic of Slovenia reported the highest ASIR, ASPR, ASDR and age-standardized DALYs rates for NRVHD (including CAVD), while the highest ASPR and ASIR of DMVD were Georgia, and the highest ASDR and age-standardized DALYs of DMVD were Republic of Serbia (Figure 2).

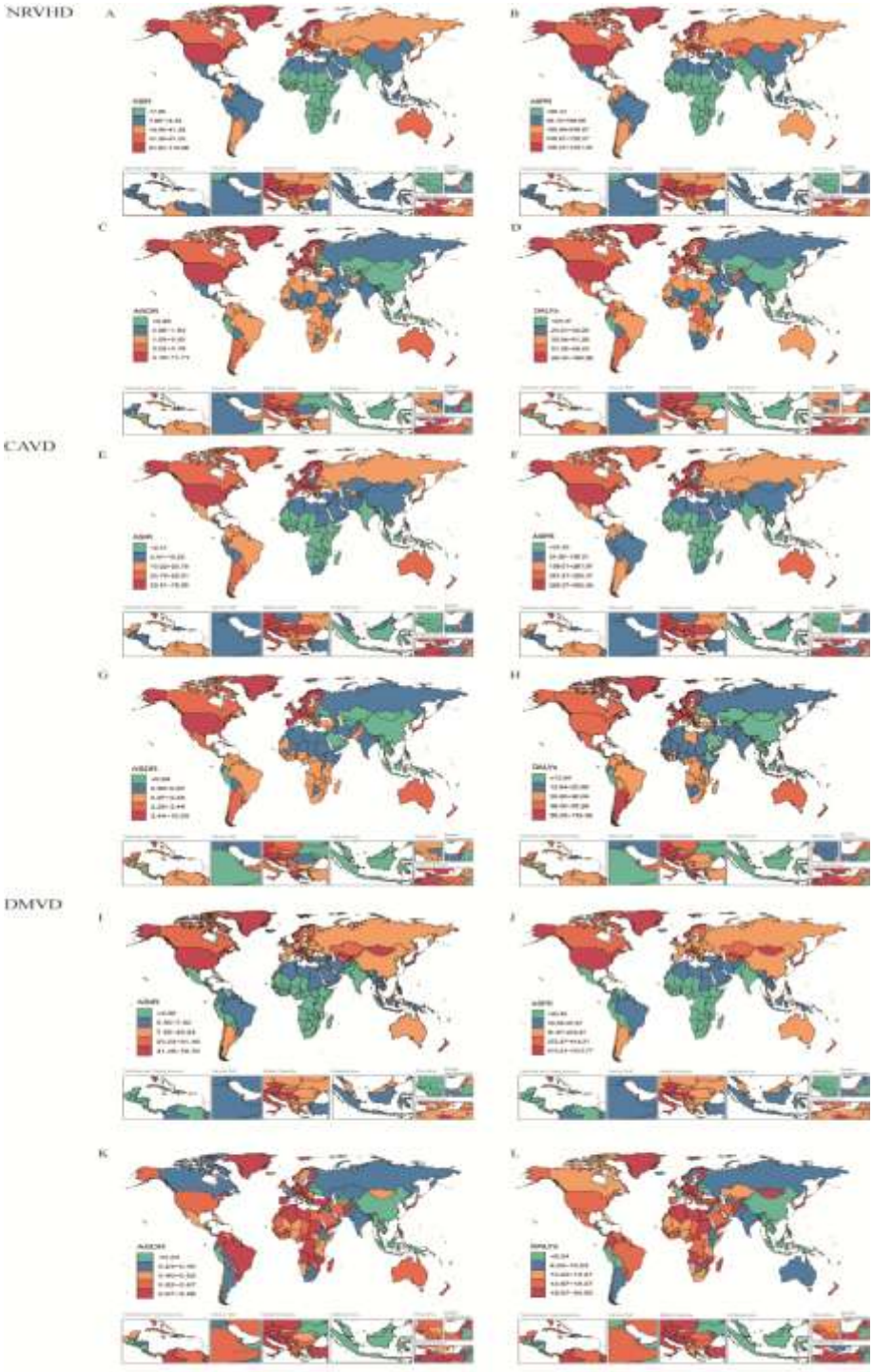

Figure 2

Figure 2: Burden of NRVHD (including CAVD and DMVD) in 204 countries and territories in 2021. ASIR(A), ASPR (B), ASDR (C), and Age standardized rate of DALYs (D) for NRVHD. ASIR(E),

ASPR (F), ASDR (G), and Age standardized rate of DALYs (H)for CAVD. ASIR(I), ASPR (J), ASDR (K), and Age standardized rate of DALYs (L)for DMVD.
NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease; ASIR: age-standardized incidence rate; ASPR: age-standardized prevalence rate; ASDR age-standardized deaths rate; DALYs: disability-adjusted life years.

For NRVHD, since 1990, the Republic of Croatia has experienced the most significant increases in ASIR and ASPR for NRVHD, with estimated 3.02 (95% CI: 2.72–3.31) and EAPC of 2.88 (95% CI: 2.60–3.16), respectively (supplemental Figure1). Similarly, the largest rises in ASDR and age-standardized DALYs rate were Turkmenistan and the Republic of Poland, with EAPC of 7.17 (95% CI: 6.03–8.32) and 4.95 (95% CI: 4.15–5.75), respectively (supplemental Figure1).

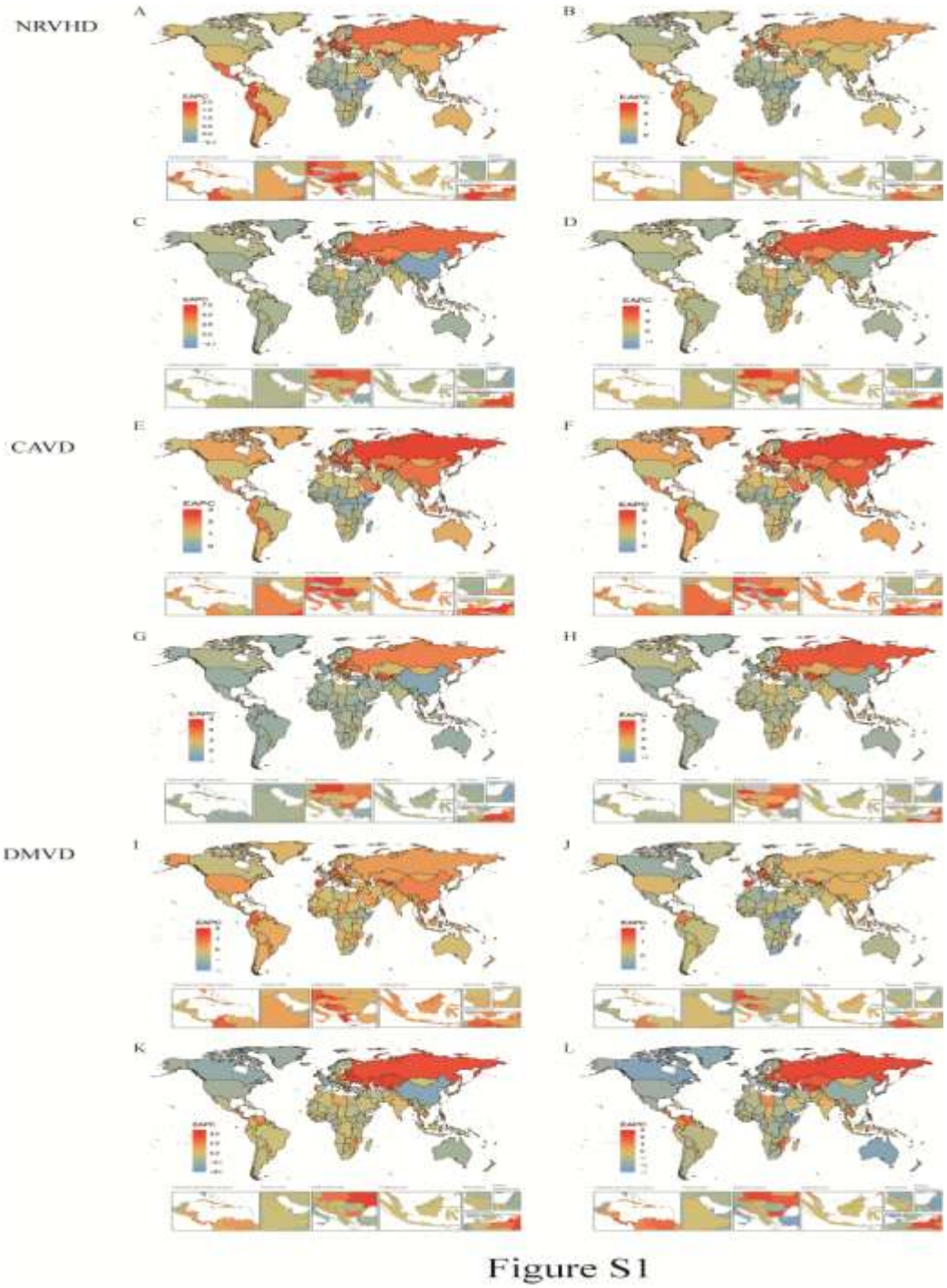

Figure S1

Supplemental Figure 1: EAPC NRVHD (including CAVD and DMVD) in 204 countries and territories from 1990 to 2021.

The EAPC of ASIR(A), ASPR (B), ASDR (C), and Age standardized rate of DALYs (D) for NRVHD. The EAPC of ASIR(E), ASPR (F), ASDR (G), and Age standardized rate of DALYs (H)for CAVD. The EAPC of ASIR(I), ASPR (J), ASDR (K), and Age standardized rate of DALYs (L)for DMVD. EAPC: estimated annual percentage change; NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease; ASIR: age-standardized incidence rate; ASPR: age-standardized prevalence rate; ASDR age-standardized deaths rate; DALYs: disability-adjusted life years.

Age, Period, and Cohort Analysis

We analyzed age, period, and cohort trends of incidence and deaths in NRVHD (including CAVD and DMVD), by calculating the corresponding coefficients to assess their RR.

Age Effects

After controlling for period and birth cohort effects, the RR for incidence of NRVHD increased with age, peaking at 70-74 years, with the value of 246.78 (95% CI: 244.29, 249.29), following a declining trend then re-upward again at 90-94 years. The incidence of CAVD peaked at 80-84 years, with an RR of 114.28(95% CI: 111.95,116.66), and then showed a decline, with an increasing trend again at 95+ years, while the incidence of DMVD peaked at 65-69 years with an RR of 147.94 (95% CI: 146.02,149.88), then showed a continuous decreasing trend (Figure 3A). The deaths for NRVHD (including CAVD and DMVD) showed an increasing trend within age, with the highest RR values of 240.02 (95% CI: 234.21,245.98), 222.51 (95% CI: 217.54,227.59), and 24.8 (95% CI: 23.93,25.7), respectively (Figure 3D).

Period Effects

After controlling for age and birth cohort effects, the RR of NRVHD incidence showed a slight downward trend until 2002-2006, and then showed an increasing trend, with the highest value of RR in 2012-2016 at 1.03 (95% CI1.02,1.05). The RR of CAVD incidence showed a continuous increasing trend, peaking at the highest value in 2012-2016 year with at 1.07 (95% CI: 1.06,1.09), then decline. While the RR for DMVD incidence decreased over time (Figure 3B). The RR for NRVHD, including CAVD deaths showed a decreasing trend until 2012, with a mild increase during 2012-2016, followed by another decreasing trend, while the RR for DMVD deaths showed a continuous decreasing trend (Figure 3E).

Cohort Effects

After controlling the age and period effects, the RR for NRVHD incidence showed a fluctuating trend with birth cohort changes. From the 1945-1949 birth cohort to the 2000-2004 birth cohort, NRVHD, including DMVD showed a decreasing trend, whereas the RR of CAVD incidence was still increasing (Figure 3C). A gradual decline in deaths was observed for NRVHD, including CAVD, from the birth of 1920 to 1924, as well as for DMVD in those born from 1910 to 1914 (Figure 3F).

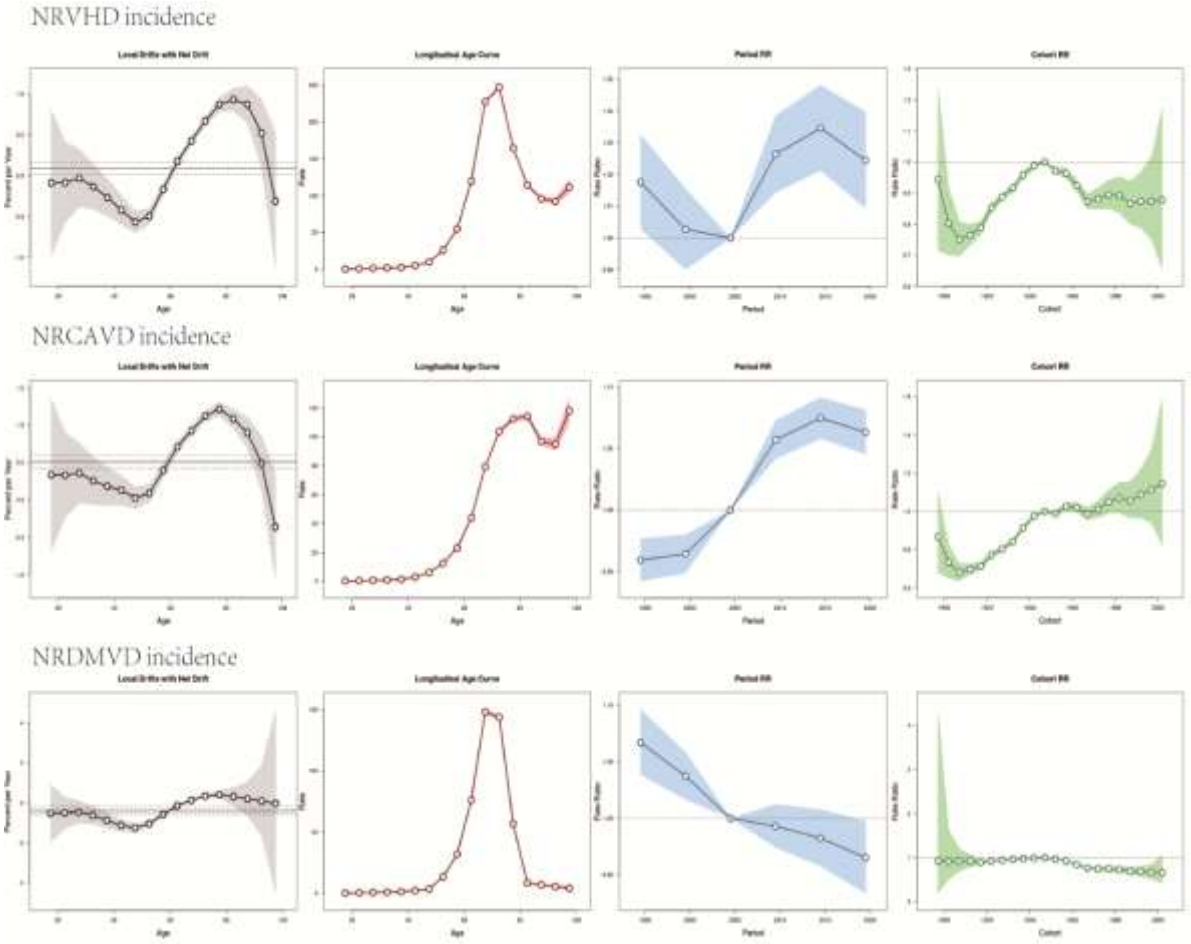

Figure 3: Age, period, and birth cohort effects of NRVHD (including CAVD and DMVD). Age cohort effect on the incidence (A) and deaths (D) of NRVHD (including CAVD and DMVD). Time period effect on the incidence(B) and deaths (E) of NRVHD (including CAVD and DMVD). The effect of birth cohort on the incidence (C) and deaths (F) of NRVHD (including CAVD and DMVD). NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease.

Inequality Analysis

Globally, the disease burden of NRVHD (including CAVD and DMVD) is disproportionately concentrated in high SDI region. Between 1990 and 2021, the SII of age-standardized DALYs rate revealed significant inequality between regions. Specifically, the SII of NRVHD increased from 99.35 (95% CI: 83.71, 114.98) to 135.92 (95% CI: 118.18, 135.66), while its CI declined from 0.22 to 0.11(Figure 4A-B). Similarly, The SII of CAVD rose from 74.82 (95% CI: 63.16, 86.48) to 106.29 (95% CI: 91.97, 120.61), with its CI decreasing from 0.41 to 0.32(Figure 4C-D). The SII of DMVD increased from 22.97 (95% CI: 18.71, 27.24) to 25.67 (95% CI: 21.73, 29.62), accompanied by a decline in its CI from 0.22 to 0.11 (Figure 4E-F).

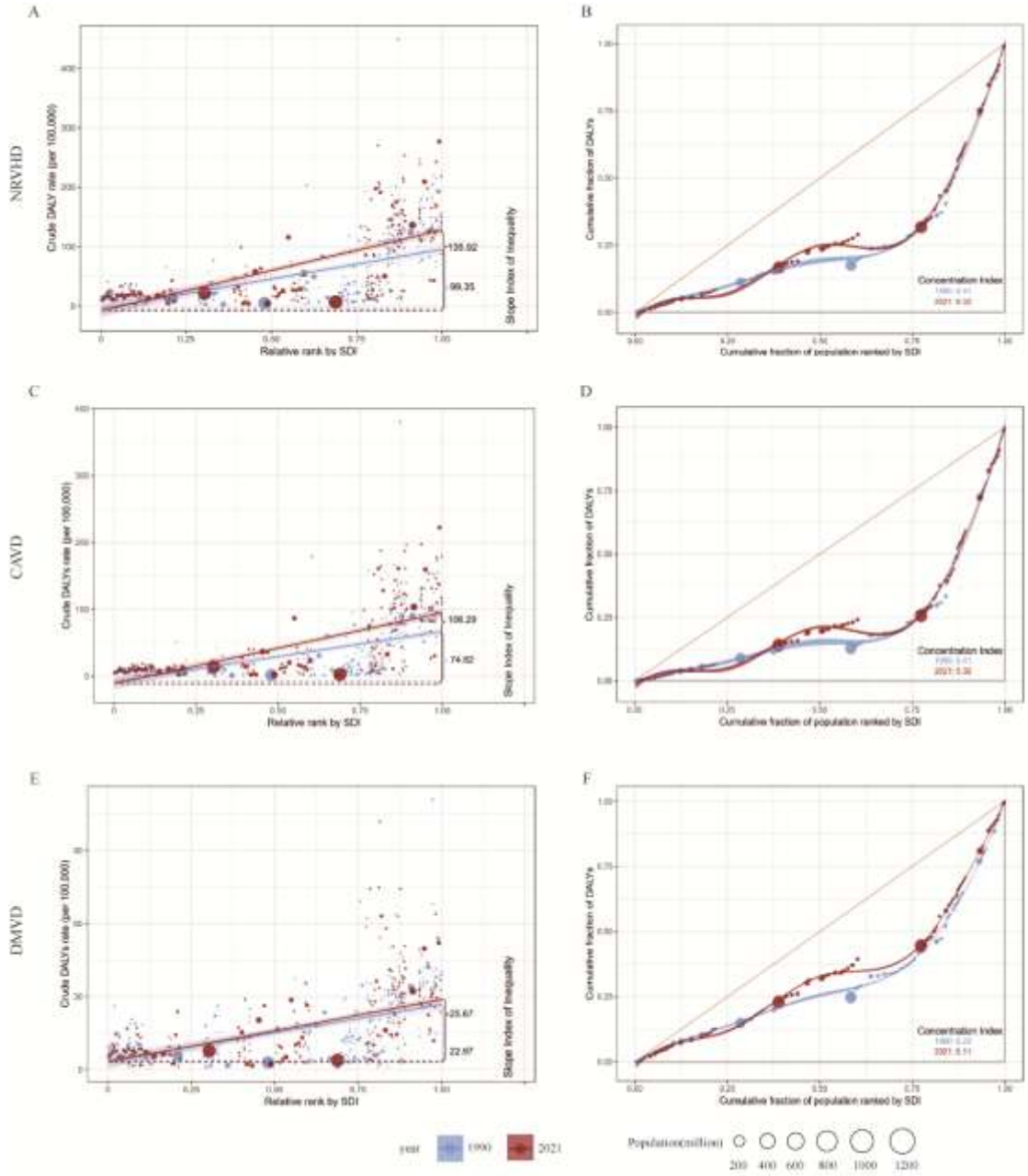

Figure 4

FIGURE 4. global health inequality analysis of NRVHD (including CAVD and DMVD) DALYs in 1990 and 2021.

Health inequality regression (A) and concentration (B) curves of NRVHD. Health inequality regression (C) and concentration (D) curves of CAVD. Health inequality regression (E) and concentration (F) curves of DMVD.

NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease.

Decomposition Analysis

From 1990 to 2021, the global DALYs of NRVHD exhibited an upward trend, with high SDI region bearing the greatest concentration of this burden. Decomposition analysis showed that population growth emerged as the predominant driver to global NRVHD burden (55.95%), followed by aging (52.73%) and epidemiologic changes (-8.69%) (Supplemental Figure2A). The impact of population growth was most pronounced in low SDI region (101.72%), followed by low-middle SDI region (57.18%) and middle SDI region (47.79%). Aging exerted its strongest influence in middle SDI region (57.53%), followed by high SDI region (45.61%)

and high-middle SDI region (44.54%) (Supplemental Figure2A). For CAVD, aging and population growth were the primary contributors, responsible for 47.3% and 48.06% of the global DALYs increase, respectively, while epidemiologic changes played a minor role (4.64%). Regionally, aging had the greatest impact in middle SDI region (53.48%), whereas population growth was most influential in low SDI regions (85.16%) (Supplemental Figure2 B). In the case of DMVD, aging and population growth contributed 86.52% and 102.86%, respectively, to the global DALYs increase, while epidemiologic changes (-89.38%). And aging and population growth were most influential in high SDI regions, account for 154.33%, 148.24% respectively(Supplemental Figure2C).

Predictive Analysis

The global disease burden of NRVHD, including CAVD and DMVD, is projected to decline significantly from 2022 to 2052. The ASIR of NRVHD is expected to decrease to 18.98 per 100,000 by 2052, representing a reduction of 24.35%. Similarly, the ASIR for CAVD and DMVD is projected to decline by 24.98% and 18.38%, respectively (Figure 5). Over the next three decades, the ASPR of NRVHD is anticipated to decrease by 23.52%, with corresponding declines of 21.77% for CAVD and 23.69% for DMVD. Furthermore, the ASDR of NRVHD is projected to decrease by 26%, while reductions of 35.83% and 31.25% are expected for CAVD and DMVD, respectively (Figure 5). Similarly, the age-standardized DALYs rate for NRVHD is forecasted to decline by 26%, with decreases of 26.44% for CAVD and 23.69% for DMVD (Figure 5). These projections indicate a substantial reduction in the global burden of NRVHD and its associated conditions over the next 30 years.

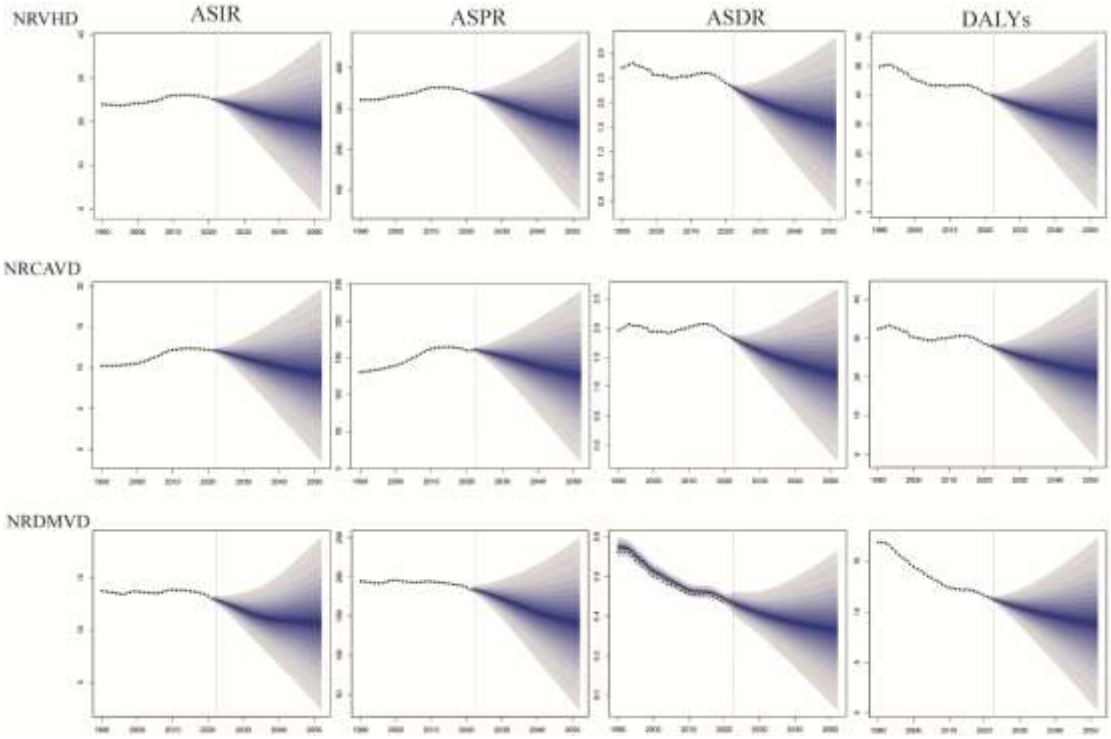

Figure 5: Future burden projection of NRVHD (A), including CAVD (B) and DMVD (C) of global in 2022-2052.
NRVHD: non-rheumatic valvular heart diseases; CAVD: calcific aortic valve disease; DMVD: degenerative mitral valve disease.

Discussion

This study provides the most recent comprehensive data on the incidence, prevalence, deaths, DALYs and corresponding age-standardized metric of NRVHD, including CAVD and DMVD, at global, regional, and national levels from 1990 to 2021. In addition to the trend

analysis, decomposition, inequality, and projection analyses were performed to provide a multifaceted understanding of the disease burden.

From 1990 to 2021, the incidence, prevalence, deaths and DALYs of NRVHD (including CAVD and DMVD) showed an increase trend. The ASIR and ASPR in global of NRVHD (including CAVD) exhibited an upward trend, while the ASDR and age-standardized DALYs rate demonstrated a decline. In contrast, DMVD showed consistent declines across all metrics, including ASIR, ASPR, ASDR, and age-standardized DALYs rate. These findings align with prior GBD studies [3,19,28]. The disease burden of NRVHD, including CAVD and DMVD, was predominantly concentrated in high SDI region, such as High-income North America, Eastern Europe, and Western Europe, where ASIR, ASPR, ASDR and age-standardized DALYs rate consistently ranked highest. Conversely, low SDI region, such as sub-Saharan Africa, ranked the lowest. The decomposition analysis of DALYs for NRVHD (including CAVD and DMVD) revealed that aging and population growth serve as critical drivers of disease burden. Notably, population aging emerged as a predominant factor influencing NRVHD, including CAVD, in middle, high, and high-middle SDI regions [7,29]. Conversely, population growth was identified as the primary contributor in low and low-middle SDI regions. For DMVD, however, both aging and population growth were found to exert significant influence both in high SDI region[19]. Cross-country inequality analyses, which was revealed the absolute and relative disparities of disease burden of NRVHD (including CAVD and DMVD) related to SDI, showed that the disparities were have intensified over time and concentrated in high SDI countries[30,31].

Age, period, and cohort effects represent three fundamental dimensions of individuals and their societies evolve over time[32]. Investigating temporal trends in NRVHD (including CAVD and DMVD) by age, period, and birth cohort effects, can significantly enhance our understanding of the disease's epidemiology. In this study, the incidence was increased with age, with peaking age of NRVHD, CAVD, and DMVD respectively. These findings align with a previous study utilizing GBD 2019 data, in which the peaking age at 50-74 years of NRVDH incidence[3]. The slight peaking age discrepancy may be attributed to differences in analytical methodologies. The APC model employed in this study enables the isolation of age effects by controlling for confounding factors such as period and cohort influences. The deaths of NRVHD (including CAVD and DMVD) were increased with age[5,33].

Several factors may explain the higher burden in high SDI region: (1) Better diagnostic ability, data collection and reporting: high SDI region owns advanced diagnostic capabilities, including cardiac catheterization and echocardiography, better disease surveillance and data collection systems, enable more accurate detection, recording and reporting of NRVHD (including CAVD and DMVD) at early or mild period, leading to higher reported incidence[30,31,34,35]; (2) aging population: People lived in high SDI usually have a longer life expectancy. Aging populations are more likely induce the prevalence of age-related degenerative conditions such as NRVHD (including CAVD and DMVD)[3]. (3) Lifestyle and risk factors: The burden of NRVHD, especially CAVD, in high SDI region may be further exacerbated by lifestyle (e.g. high-fat diet, physical inactivity, obesity, etc.) and the prevalence of risk factors such as hypertension and diabetes[31]. (4) Better data collection and reporting: High SDI areas typically have better disease surveillance and data collection systems that enable more comprehensive recording and reporting of NRVHD incidence and deaths, whereas low SDI areas may suffer from underreporting or delayed diagnosis. Compared with high SDI region, life expectancy in low SDI region is shorter, medical healthcare are relatively poorer, disease surveillance and data collection systems are often inadequate, leading to underreporting, underdiagnosis, or misdiagnosis of NRVHD[3,36]. In low SDI region, infectious diseases (e.g., Acquired Immune Deficiency Syndrome (AIDs), tuberculosis, malaria, etc.) and other acute health problems can take up more healthcare resources and attention, leading to neglect in the diagnosis and treatment of NRVHD[30]. As population growth and the prevalence of diseases such as hypertension and diabetes in low SDI region, which can increase the risk of NRVHD, hence low SDI areas also need further attention[15].

CAVD and DMVD, representing the two

predominant forms of NRVHD, exhibit distinct epidemiological patterns and disease burden profiles. While CAVD demonstrates a strong correlation with overall DVHD trends, characterized by substantial disease burden, DMVD presents a comparatively lower burden with a declining trend[37,38]. The traditional perception of CAVD as a passive, age-related degenerative process marked by leaflet wear and calcium deposition. Emerging histopathological and clinical evidence has redefined CAVD as an active, multifactorial disease process. This complex pathogenesis involves chronic systemic inflammation, oxidative stress, lipoprotein accumulation, and the osteogenic transformation of valvular interstitial cells, culminating in active leaflet calcification, and all the progression are accelerated by aging[39,40]. Furthermore, the modifiable risk factors including urbanization-related lifestyle changes, tobacco use, alcohol consumption, dietary modifications, and the increasing prevalence of hypertension, obesity, and diabetes mellitus play a crucial role in the progress of CAVD[41-43].

Similarly, DMVD also considered to related an age-related degenerative condition manifesting as leaflet fibrosis and myxomatous degeneration. More and more researches have elucidated a sophisticated pathogenic framework of DMVD involving chronic inflammatory pathways, oxidative stress-mediated damage, extracellular matrix dysregulation, and aberrant valvular interstitial cell differentiation[11,44,45]. DMVD shares several risk factors with CAVD, such as aging, hypertension, obesity, and metabolic syndrome[46].

Although the disease burden of DMVD demonstrates a relatively lower than CAVD, its clinical implications remain substantial. The predominant manifestation of mitral regurgitation can precipitate a cascade of hemodynamic consequences, including left ventricular volume overload, left atrial dilation, pulmonary hypertension, and subsequent development of heart failure and arrhythmias[47,48]. The observed decline in DMVD ASIR may reflect improved management of cardiovascular risk factors, particularly enhanced hypertension control and reduced smoking rates[49]. Nevertheless, demographic shifts toward an aging population suggest a potential increase in absolute DMVD cases, underscoring the necessity for intensified research into preventive strategies, early diagnostic modalities, and therapeutic interventions[47].

In summary, over the past three decades, the incidence, prevalence, deaths, DALYs of NRVDH (including CAVD and DMVD) increased, the ASDR and age-standardized DALYs rate of DALYs decreased. Future projection showed that in the next 30 years, the disease burden of NRVHD (including CAVD and DMVD) will be decreased. Significant disparities persist across regions, nations, and SDI categories, necessitating the development of tailored prevention and treatment strategies to address the specific needs of diverse populations, particularly in high-income countries[50-52]. Significant disparities exist between different regions, countries, and SDI categories, and the NRVHD disease burden is predominantly found in high SDI regions, and these disparities appear to be widening over time, and strong correlated with age[53]. Hence in the future, the designation and implementation of NRVHD prevention and management measures should still be paid more to high SDI region, and other factors, such as population aging, lifestyle, environment, and risk factors is also should be considered[54,55].

Limitation

Several limitations inherent in this study warrant careful consideration when interpreting the findings. (1) Potential scarcity of reliable epidemiological data, underreported cases across different countries and regions can infect the precision of the data. (2) We obtained the data from GBD database by numerous assumptions and sophisticated modeling techniques, the results should be interpreted as the most reliable approximations within the constraints of currently available evidence. (3) Emerging evidence suggests that DMVD demonstrates a distinct gender predilection, with several studies indicating a higher prevalence among female populations, while it is not reflected in our article, which can be deeply explored in future research[56,57].

Conclusion

Overall, our study provides new perspectives on the changing trends in the global disease burden of NRVHD, encompassing the two predominant

forms, CAVD and DMVD, with insights in multiple dimensions by using APC model and inequality analysis to elucidates key determinants driving epidemiological transitions. Future projection showed the global disease burden of NRVHD, including CAVD and DMVD, both in men and women, will decline in the next 30 years. These findings carry significant implications for public health policy formulation, particularly in developing targeted prevention strategies and optimizing disease management approaches to mitigate the substantial global impact of NRVHD.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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