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*Original Article*

# Cardiovascular diseases in children and adolescents from 1990 to 2021: global burden and predictions

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**Abstract:** Background: Cardiovascular diseases (CVDs) in children and adolescents are a growing global health concern. Methods: Using the Global Burden of Disease database (1990-2021), we analyzed six indicators: incidence, prevalence, mortality, Disability-Adjusted Life Years (DALYs), years lived with disability (YLDs), and years of life lost (YLLs), and predicted it using Nordpred prediction model. Findings: Results showed that age-standardized prevalence (ASPR) and incidence rates (ASIR) increased significantly, while Age standardized DALYs rate (ASDR) and Age standardized mortality/death rate (ASMR) decreased. Among 12 CVDs subtypes, only stroke and pulmonary hypertension had declining ASPR. Age-related trends showed increasing ASPR and ASIR with advancing age, while ASDR and ASMR formed U-shaped curves. Frontier analysis revealed varied healthcare efficiency across regions. Future projections indicated continued increases in ASPR through 2046, accompanied by declining mortality-related indicators. Despite YLDs trends remaining stable, male-specific YLDs may rise post-2035. Interpretation: These findings highlight the dual challenge of managing rising ASPR while maintaining mortality gains, particularly in resource-limited settings, emphasizing the need for targeted interventions and policies to address Sociodemographic Index-related inequalities. The 2000 milestone underscores global health efforts' importance. Male-specific YLDs warrant further research. This study advances understanding of CVDs burden worldwide.

**Keywords:** Children and adolescents, cardiovascular diseases, age structure analysis, Nordpred prediction

## Introduction

Cardiovascular Diseases (CVDs) encompass a large group of conditions affecting the heart and blood vessels, including, but not limited to, coronary artery disease, stroke, heart failure, arrhythmias, and heart valve disease [1, 2]. CVDs are the leading cause of mortality globally, according to the World Health Organization (WHO) [1]. Numerous studies have assessed the occurrence and global burden of CVDs [2, 3, 4]. For example, Gregory et al. noted that CVDs are the leading cause of death worldwide, with a rising burden in nearly all countries, especially outside of high-income countries [2]. Zhuang et al. focused on young adults aged 15 to 39 and found that the highest burden of CVDs in the 35-39 age group, with 72 countries showing an increase in ASIR, while over 80% experienced a decrease in ASMR and ASDR from 1990 to 2019 [3]. Sun et al. found that countries/regions with low and medium-low SDI had a higher burden of CVDs among young adults compared to those with high and medium-high SDI [4]. Overall, these studies suggest a significant and increasing burden of CVDs in young adults, particularly among males.

The trend of younger populations experiencing CVDs is a growing concern, and more children and adolescents are being diagnosed, with a rising ASIR. Childhood and adolescent CVDs include conditions such as rheumatic heart disease, ischemic heart disease and endocarditis [3, 5-7]. Rheumatic heart disease has the highest ASIR in this age group, while ischemic heart disease ranks highest in ASMR and ASDR, with main risk factors being high blood pressure,

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high body mass index, and elevated low density lipoprotein cholesterol [2, 4]. The development of CVDs in children and adolescents is influenced by various innate and acquired factors, including unhealthy lifestyle, age, gender, genetic factors, and environmental exposures [5, 8-11]. Furthermore, adverse intrauterine environmental exposures during pregnancy can negatively impact fetal cardiovascular development, leading to cardiovascular issues after birth [12-14]. Addressing the complex etiology of CVDs in young populations is crucial.

The study assesses the global burden of CVDs specifically among children under 20 years old. Utilizing data from the Global Burden of Disease (GBD) 2021 study, which evaluates a comprehensive range of CVDs subtypes across 204 countries and territories from 1990 to 2021, this research provides updated epidemiological insights into the disease burden in children and adolescents. The analysis incorporates the associations with social determinants of health (SDI) levels. By predicting these indicators up to 2046, the study offers valuable information for clinicians, epidemiologists, and policymakers to optimize healthcare resources and formulate effective public health strategies targeting CVDs prevention and control in this vulnerable population group.

## Methods

### *Data acquisition and download*

The GBD 2021 study offers a comprehensive analysis of health burden using the latest epidemiological data and enhanced standardized methods [15]. For this investigation, we derived six epidemiological indicators attributed to CVDs in children and adolescents from the GBD 2021 data [16]. Additionally, the study incorporates the SDI, which quantifies the sociodemographic development of an area based on income, education, and fertility [17].

### *Calculation of ASR for child and adolescent populations*

Age-standardized rates were directly obtained from the GBD 2021 Results Tool. The age-standardized estimates provided by the GBD study were used for comparisons across years, regions, and countries. Initially, we calculated age-specific mortality rates per 100,000 population. These rates were then adjusted for the proportion of each age group in the standard population, thereby minimizing potential bias in comparing age groups. Finally, the weighted age-specific rates are aggregated to produce an overall ASR for the child and adolescent population.

### *Estimated annual percentage change (EAPC)*

The EAPC was used to quantify the temporal trends in age-standardized rates from 1990 to 2021. A log-linear regression model was fitted as follows: $\ln(ASR) = \alpha + \beta \times year + \varepsilon$, where ASR represents the age-standardized rate and $\beta$ is the regression coefficient. The EAPC was calculated as $100 \times [\exp(\beta) - 1]$. The 95% confidence interval (CI) of the EAPC was estimated based on the standard error of $\beta$. An increasing trend was considered when the lower limit of the 95% CI was greater than 0, whereas a decreasing trend was considered when the upper limit was less than 0. If the 95% CI included 0, the trend was considered stable.

### *Frontier analysis*

Frontier analysis is a statistical method used to assess the relative efficiency of decision-making units in fields such as economics and public health. In this study, we employed Data Envelopment Analysis to assess the relationship between the burden of ASDR, ASMR and SDI. This analysis generated an efficiency frontier curve, representing the theoretical minimum ASDRs or ASMRs achievable at each SDI level. SDI was used as the socioeconomic input variable, whereas ASDR and ASMR were treated as the health outcome indicators. For each country, the frontier represented the lowest theoretically achievable ASDR or ASMR at a given level of SDI. The difference between the observed value and the corresponding frontier value was used to characterize the potential improvement opportunity.

### *Nordpred prediction*

The Nordpred prediction model is a robust statistical framework widely used for projecting disease burden across different populations. The analysis focused on estimating trends of ASRs for the period extending from 2022 to 2046. This projection utilized comprehensive historical data collected from 1990 to 2021,

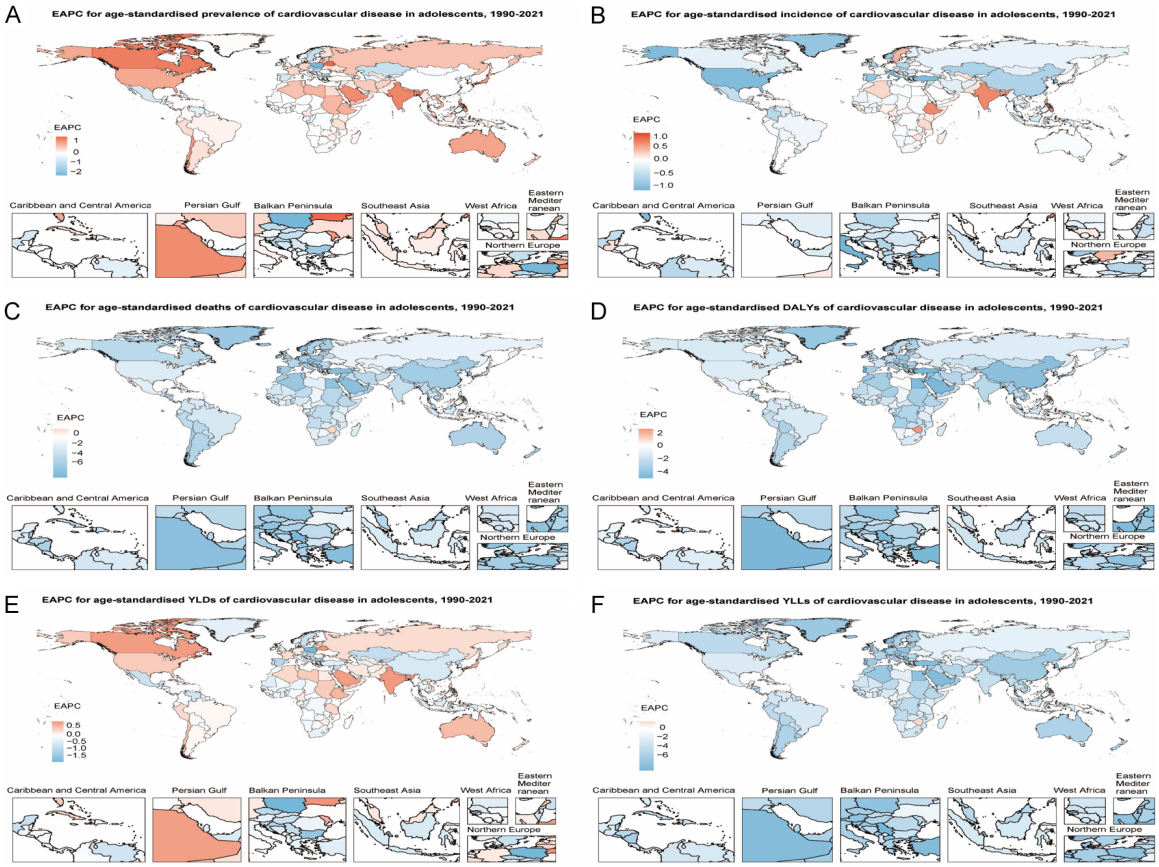



**Figure 1.** EAPCs for six epidemiological indicators for global child and adolescent CVDs from 1990 to 2021. A. EAPC for ASPR; B. EAPC for ASIR; C. EAPC for ASDR; D. EAPC for ASR of DALYs; E. EAPC for ASR of YLDs; F. EAPC for ASR of YLLs.

ensuring a data-driven foundation for the estimates. We also stratified the analysis by sex, allowing for a more nuanced understanding of gender-specific trends in the burden of CVDs. The Nordpred model was applied to the historical data from 1990 to 2021 to project CVD burden from 2022 to 2046. The analysis was stratified by sex and age group. The model settings, including the age and period groupings, extrapolation assumptions, and major model parameters, were specified according to the standard implementation of the Nordpred package.

## Results

### *Global trends in child and adolescent CVDs*

Globally, the number of prevalence cases of CVDs in children and adolescents increased from 15.35 million in 1990 to 20.93 million in 2021. In contrast, the ASMR for CVDs in this population declined from 7.19 in 1990 to 3.12 in 2021 (**Figure 1** and **Table 1**). DALYs for children and adolescents CVDs decreased from 14.79 million in 1990 to 7.99 million in 2021 (**Figure 1** and **Table 1**).

Analysis of trends in six indicators of 12 CVDs subtypes revealed that most exhibited an increasing EAPC in ASPR, while stroke and pulmonary arterial hypertension exhibited a decreasing trend during this period (Supplementary Figure 1A). In terms of ASIR, the rheumatic heart disease, pulmonary arterial hypertension, and peripheral vascular disease increased, while the other nine subtypes decreased (Supplementary Figure 1B). ASMR, ASDR, and ASYLLs for all subtypes showed decreasing trends (Supplementary Figure 1C, 1D, 1F), while most subtypes saw increases in YLDs (Supplementary Figure 1E).

### *Age-specific trends in child and adolescent CVDs*

Our study analyzed six epidemiological indicators related to CVDs in children and adolescents across four age groups: 0-4, 5-9, 10-14,

**Table 1.** The six epidemiological indicators of the globally children and adolescent CVDs in 1990 and 2021 include counts, ASRs, and EAPCs for ASR from 1990 to 2021

| | Number (95% UI) | | ASR (95% UI) | | EAPC for ASR (95% CI) |
|---|---|---|---|---|---|
| | 1990 | 2021 | 1990 | 2021 | |
| Prevalence | 15345812.63 (12390966.03-18569761.07) | 20928983.82 (16652804.85-25860941.24) | 679.45 (548.62-822.19) | 794.02 (631.78-981.13) | 0.64 (0.56-0.73) |
| Incidence | 2134448.33 (1667532.63-2715350.96) | 2738540.04 (2074960.89-3589001.34) | 94.50 (73.83-120.22) | 103.90 (78.72-136.16) | 0.64 (0.56-0.73) |
| Deaths | 163751.28 (147009.50-190128.86) | 81419.72 (71596.20-91661.14) | 7.25 (6.51-8.42) | 3.09 (2.72-3.48) | -2.53 (-2.61--2.45) |
| DALYs | 14791657.73 (13368075.39-16966494.14) | 7990383.38 (7076648.61-9061976.18) | 654.91 (591.88-751.20) | 303.14 (268.48-343.80) | -2.28 (-2.35--2.22) |
| YLDs | 1133510.58 (795222.22-1557997.37) | 1407909.41 (963907.12-1962293.48) | 50.19 (35.21-68.98) | 53.41 (36.57-74.45) | 0.25 (0.19-0.3) |
| YLLs | 13658147.15 (12228047.82-15924522.50) | 6582473.96 (5754595.45-7443538.69) | 604.72 (541.41-705.07) | 249.73 (218.32-282.40) | -2.6 (-2.68--2.52) |

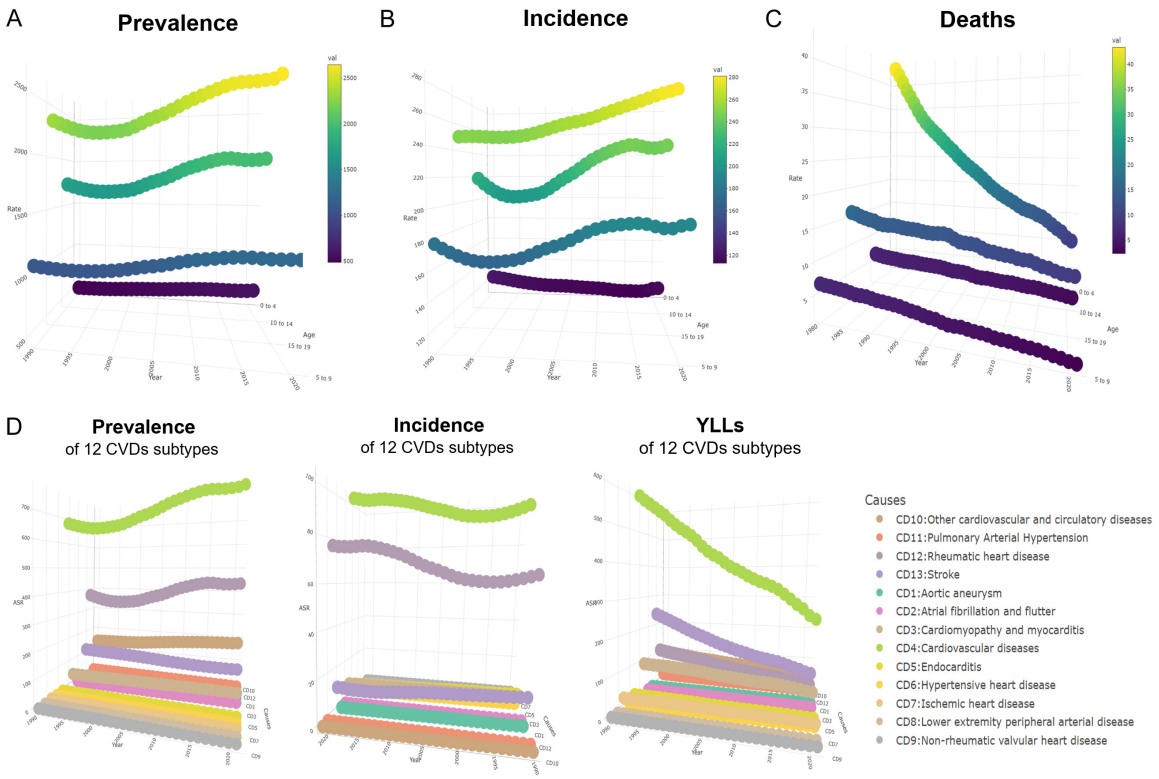



**Figure 2.** Three-dimensional view of trend changes in ASR over time and age for CVDs and 12 subtypes of CVDs from 1990 to 2021. (A-C) Trend changes in ASPR (A), ASIR (B), and ASMR (C) for CVDs; (D) Trend changes in ASPR, ASIR, and ASR for YLLs for individual subtypes of CVDs.

and 15-19 years, examining trends from 1990 to 2021. As shown in the three-dimensional view of age, period, and rate (**Figure 2**; **Table 2**), in 1990 and 2021, the 15-19-year age group had the highest ASIR of CVDs, whereas the 0-4-year age group had the lowest. ASIR increased with age in both years (**Figure 2A**, **2B**), whereas ASMR decreased across all age groups from 1990 to 2021 (**Figure 2C**).

In addition, we analyzed ASRs for 12 CVD subtypes across sex in four age groups (Supplementary Figure 2). Among the subtypes, ASPR of coronary heart disease and myocardial infarction was relatively high in adolescent males, highlighting the important interaction of sex and age. The highest ASMR due to coronary heart disease were found in youth in the 15-19-year age group and were particularly evident in

**Table 2.** Number of cases and ASRs for six epidemiological indicators of the children and adolescent CVDs in 1990 and 2021

| | 1990 | | 2021 | |
|---|---|---|---|---|
| | Number (95% UI) | Rate (95% UI) | Number (95% UI) | Rate (95% UI) |
| Prevalence | | | | |
| 0-4 | 3008597 (2373431-3785416) | 485.31 (382.85-610.61) | 3780323 (2883669-4851434) | 574.37 (438.13-737.11) |
| 5-9 | 6345466 (4830860-8210288) | 1087.43 (827.87-1407) | 8417988 (6256076-11050348) | 1225.23 (910.57-1608.37) |
| 10-14 | 9272104 (6710373-12510066) | 1730.89 (1252.68-2335.35) | 13212762 (9341926-18187174) | 1982.01 (1401.35-2728.2) |
| 15-19 | 12102017 (8728505-16393643) | 2329.89 (1680.42-3156.12) | 16501521 (11561809-22885933) | 2644.56 (1852.91-3667.74) |
| Incidence | | | | |
| 0-4 | 762102 (583337-1000319) | 122.93 (94.1-161.36) | 764663 (569335-1030121) | 116.18 (86.5-156.51) |
| 5-9 | 1039640 (667264-1551894) | 178.16 (114.35-265.95) | 1322581 (823331-2020293) | 192.5 (119.84-294.05) |
| 10-14 | 1170530 (674471-1838820) | 218.51 (125.91-343.27) | 1636142 (911443-2613593) | 245.43 (136.72-392.06) |
| 15-19 | 1296624 (818145-1949399) | 249.63 (157.51-375.3) | 1753694 (1088490-2676383) | 281.05 (174.44-428.92) |
| Deaths | | | | |
| 0-4 | 187443 (147863-248895) | 30.24 (23.85-40.15) | 66325 (51750-82335) | 10.08 (7.86-12.51) |
| 5-9 | 35077 (28731-43430) | 6.01 (4.92-7.44) | 16163 (13959-18524) | 2.35 (2.03-2.7) |
| 10-14 | 30723 (26388-36088) | 5.74 (4.93-6.74) | 20968 (18630-23564) | 3.15 (2.79-3.53) |
| 15-19 | 74259 (67472-81685) | 14.3 (12.99-15.73) | 59384 (53450-65450) | 9.52 (8.57-10.49) |
| DALYs | | | | |
| 0-4 | 16888210 (13406268-22334870) | 2724.18 (2162.52-3602.76) | 6181113 (4907564-7599594) | 939.13 (745.64-1154.65) |
| 5-9 | 3392883 (2818282-4117704) | 581.44 (482.97-705.65) | 1927324 (1634248-2287662) | 280.52 (237.86-332.97) |
| 10-14 | 3047422 (2622980-3558976) | 568.89 (489.65-664.38) | 2491664 (2114340-2968500) | 373.77 (317.17-445.3) |
| 15-19 | 6254801 (5648174-6956989) | 1204.18 (1087.39-1339.37) | 5380667 (4737606-6172300) | 862.31 (759.26-989.18) |
| YLDs | | | | |
| 0-4 | 249243 (163703-354755) | 40.2 (26.41-57.22) | 286721 (185470-417708) | 43.56 (28.18-63.46) |
| 5-9 | 485646 (316589-710318) | 83.23 (54.25-121.73) | 588665 (375011-879225) | 85.68 (54.58-127.97) |
| 10-14 | 664587 (424418-967588) | 124.06 (79.23-180.63) | 866499 (541486-1300598) | 129.98 (81.23-195.1) |
| 15-19 | 867545 (558052-1273236) | 167.02 (107.44-245.12) | 1073934 (662118-1618893) | 172.11 (106.11-259.45) |
| YLLs | | | | |
| 0-4 | 16638967 (13133976-22077873) | 2683.97 (2118.6-3561.3) | 5894391 (4602832-7313510) | 895.57 (699.34-1111.19) |
| 5-9 | 2907236 (2381162-3599697) | 498.21 (408.06-616.88) | 1338659 (1156117-1534244) | 194.84 (168.27-223.31) |
| 10-14 | 2382835 (2046456-2799118) | 444.82 (382.03-522.53) | 1625165 (1443906-1826408) | 243.79 (216.6-273.97) |
| 15-19 | 5387256 (4894751-5926039) | 1037.16 (942.34-1140.89) | 4306733 (3876135-4746833) | 690.2 (621.2-760.73) |

young males. These indicators emphasize the prominent burden of coronary heart disease and hypertension, especially among children and adolescents (**Figure 2D**).

*Global trends by SDI and HDI*

Analyzing the five SDI subregions shows that ASPRs in all subregions exhibited an increasing trend from 1990 to 2021, and the most significant rise was in low and medium SDI regions (**Table 3**; Supplementary Figure 3A). In contrast, the ASIR of the high, medium-high, and medium SDI regions showed decreasing trends during the same period, whereas medium-low and low SDI regions experienced an increase from 1990 to 2021 respectively (**Table 3**; Supplementary Figure 3B). All five SDI regions showed significant decreases in ASMR, particularly notable in the high and medium-high SDI regions (**Table 3**; Supplementary Figure 3C). A negative correlation was observed between the EAPC of ASDR and SDI in the 204 nations (**Figure 3A**, Supplementary Figure 3D). A significant negative correlation was also found between EAPC of ASMR and SDI (**Figure 3B**, Supplementary Figure 3C). For ASYLDs, only medium-high SDI and medium SDI regions declined, while the remaining regions showed increasing trends (**Table 3**, Supplementary Figure 3E). Furthermore, the ASYLLs in all five SDI subregions generally showed decreasing trends (**Table 3**; Supplementary Figure 3F). Specifically, there was a negative correlation between the EAPC for ASIR and HDI, suggesting a progressive decrease in these indicators as HDI increased (Supplementary Figure 4).

In addition, frontier analyses using health production function models suggest a major epide-

**Table 3.** The counts, ASRs, and EAPCs for ASR of the six epidemiological indicators of the children and adolescent CVDs in the five SDI regions in 1990 and 2021

| | Number (95% UI) | | ASR (95% UI) | | EAPC for ASR (95% CI) |
|---|---|---|---|---|---|
| | 1990 | 2021 | 1990 | 2021 | |
| Prevalence | | | | | |
| High SDI | 1197073.99 (982598.94-1494561.44) | 1340450.83 (1029542.28-1784766.59) | 468.72 (384.99-584.55) | 564.4 (434.68-747.97) | 0.69 (0.62-0.76) |
| High-middle SDI | 1922750.83 (1592592.07-2320562.35) | 1542943.76 (1262609.65-1893415.76) | 500.94 (415.21-604.13) | 491.06 (402.17-602.21) | 0.13 (0.05-0.22) |
| Middle SDI | 5852036.38 (4475802.76-7529280.18) | 5698893.3 (4354367.49-7340012.75) | 747.8 (572.83-960.78) | 728.96 (558.17-937.37) | 0.18 (0.07-0.28) |
| Low-middle SDI | 3790642.35 (2860344.96-4945912.91) | 6145121.32 (4583694.89-8121188.56) | 667.63 (502.23-873.68) | 779.53 (582.74-1027.92) | 0.72 (0.62-0.81) |
| Low SDI | 2569700.4 (1878469.04-3401607.98) | 6185156.42 (4483413.43-8294421.36) | 995.57 (724.07-1323.99) | 1078.25 (780.71-1447.56) | 0.35 (0.32-0.39) |
| Incidence | | | | | |
| High SDI | 77842.6 (59723.38-100676.75) | 64338.34 (49603.24-82530.69) | 30.97 (23.83-39.98) | 27.73 (21.48-35.47) | -0.66 (-0.8–0.52) |
| High-middle SDI | 243960.84 (185062.01-319119) | 160639.81 (118430.01-214181.63) | 65.28 (49.69-85.13) | 52.2 (38.68-69.32) | -0.69 (-0.75–0.63) |
| Middle SDI | 830211.1 (571063.8-1175446.67) | 737550.31 (492682.7-1064307.88) | 107.63 (74.15-152.25) | 96.09 (64.5-138.23) | -0.22 (-0.3–0.13) |
| Low-middle SDI | 587600.34 (394317.75-847009.46) | 864588.17 (562509.6-1274021.63) | 101.99 (68.26-147.27) | 110.75 (72.26-162.91) | 0.44 (0.37-0.5) |
| Low SDI | 393204.77 (256378.32-575839.28) | 909378.29 (573793.93-1366573.71) | 147.83 (95.45-217.79) | 157.4 (99.15-236.8) | 0.3 (0.27-0.34) |
| Deaths | | | | | |
| High SDI | 5863.98 (5526.5-6277.85) | 1936.12 (1796.83-2061.31) | 2.35 (2.22-2.52) | 0.84 (0.77-0.89) | -3.36 (-3.44–3.28) |
| High-middle SDI | 18059.04 (16055.46-20700.12) | 4055.55 (3598.41-4573.72) | 4.91 (4.35-5.65) | 1.35 (1.19-1.53) | -4.2 (-4.36–4.04) |
| Middle SDI | 48089.79 (43657.08-54328.66) | 16764.8 (15035.87-18648.24) | 6.29 (5.7-7.12) | 2.23 (1.99-2.49) | -3.1 (-3.22–2.98) |
| Low-middle SDI | 62255.76 (53800.37-73830.79) | 31387.74 (26739.92-36326.35) | 10.29 (8.91-12.17) | 4.12 (3.49-4.78) | -2.69 (-2.77–2.61) |
| Low SDI | 29348.08 (23759.26-37621.41) | 27183.74 (21463.22-32889.85) | 9.74 (7.9-12.39) | 4.62 (3.66-5.58) | -2.36 (-2.45–2.28) |
| DALYs | | | | | |
| High SDI | 588579.24 (539889.75-648941.41) | 265053.46 (225880.3-315044.28) | 236.84 (217.39-261.18) | 114.13 (97.43-135.33) | -2.4 (-2.44–2.35) |
| High-middle SDI | 1659438.41 (1473420.87-1902333.12) | 446246.73 (386466.75-513840.14) | 452.56 (400.98-520.37) | 147.62 (127.71-170.09) | -3.69 (-3.81–3.58) |
| Middle SDI | 4391410.11 (3972104.24-4999349.05) | 1711558.84 (1505366.76-1951958.72) | 575.08 (519.81-655.56) | 227.06 (199.21-259.43) | -2.79 (-2.88–2.69) |
| Low-middle SDI | 5487313.54 (4761253.06-6492586.12) | 2931852.81 (2501498.72-3414836.33) | 904.37 (785.92-1067.28) | 385.14 (327.58-449.59) | -2.5 (-2.57–2.43) |
| Low SDI | 2652703.37 (2165738.83-3366715.66) | 2627061.95 (2096640.35-3191031.65) | 879.29 (720.27-1107.2) | 446.72 (357.39-541.9) | -2.14 (-2.21–2.07) |
| YLDs | | | | | |
| High SDI | 108814.56 (74673.53-149742.38) | 109666.16 (73958.27-158030.11) | 42.44 (29.1-58.51) | 46.05 (31.03-66.43) | 0.3 (0.23-0.37) |
| High-middle SDI | 171664.09 (119907.68-233831.45) | 126174.34 (87945.39-173930.82) | 44.73 (31.22-60.95) | 40.2 (28.01-55.41) | -0.3 (-0.33–0.26) |
| Middle SDI | 425368.69 (287408.62-601796.84) | 389731.21 (261986.53-557647.17) | 54.46 (36.8-76.98) | 50 (33.64-71.48) | -0.14 (-0.21–0.07) |
| Low-middle SDI | 262722.64 (175250.37-377245.6) | 401143.94 (264355.77-583066.44) | 46.08 (30.7-66.24) | 51.03 (33.67-74.1) | 0.47 (0.4-0.54) |
| Low SDI | 163935.68 (106832.17-240490.34) | 380083.04 (247560.56-562658.49) | 63.01 (41-92.69) | 66.15 (43.05-97.97) | 0.22 (0.19-0.24) |
| YLLs | | | | | |
| High SDI | 479764.68 (451789.92-514286.32) | 155387.3 (143831.28-165679.17) | 194.4 (182.9-208.66) | 68.08 (62.77-72.75) | -3.4 (-3.48–3.32) |
| High-middle SDI | 1487774.32 (1319426.81-1712090.68) | 320072.4 (283127.11-361769.73) | 407.83 (360.89-470.86) | 107.42 (94.64-121.81) | -4.34 (-4.5–4.17) |
| Middle SDI | 3966041.43 (3594985.97-4497377.9) | 1321827.63 (1181737.53-1475493.6) | 520.62 (471.45-591.46) | 177.06 (157.65-198.54) | -3.22 (-3.34–3.09) |
| Low-middle SDI | 5224590.9 (4508872.43-6210777.03) | 2530708.87 (2145069.02-2939935.66) | 858.29 (741.8-1017.74) | 334.11 (282.07-389.26) | -2.76 (-2.84–2.68) |
| Low SDI | 2488767.69 (2013396.99-3198095.5) | 2246978.91 (1765258.74-2728594.27) | 816.28 (661.93-1042.14) | 380.57 (299.76-461.25) | -2.41 (-2.49–2.32) |

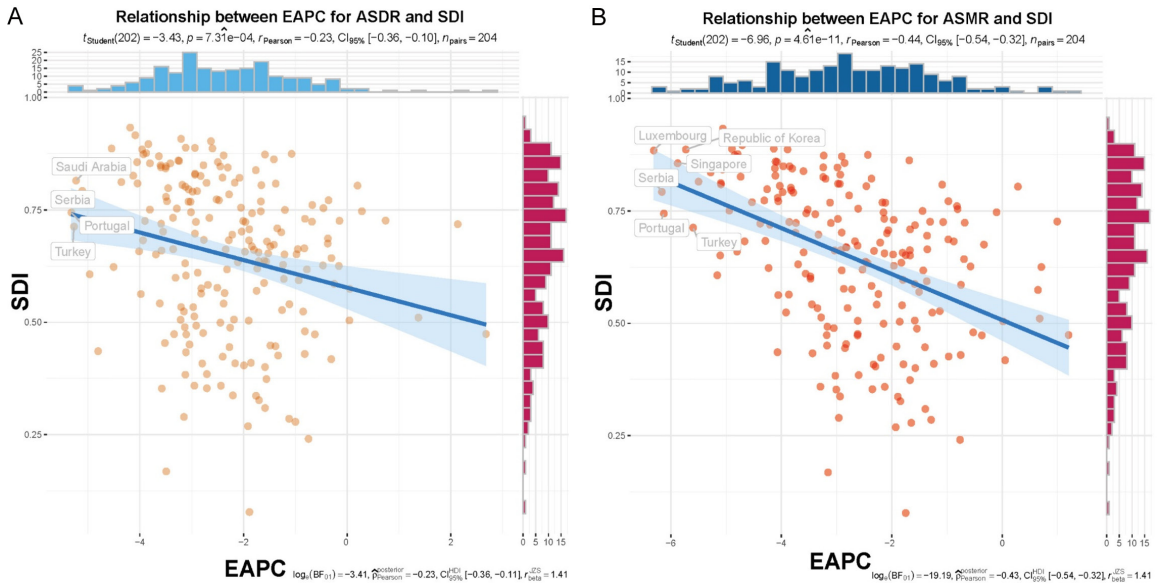



**Figure 3.** Relationship between EAPCs of ASDR (A), ASMR (B), and SDI levels in children and adolescents with CVDs from 1990 to 2021.

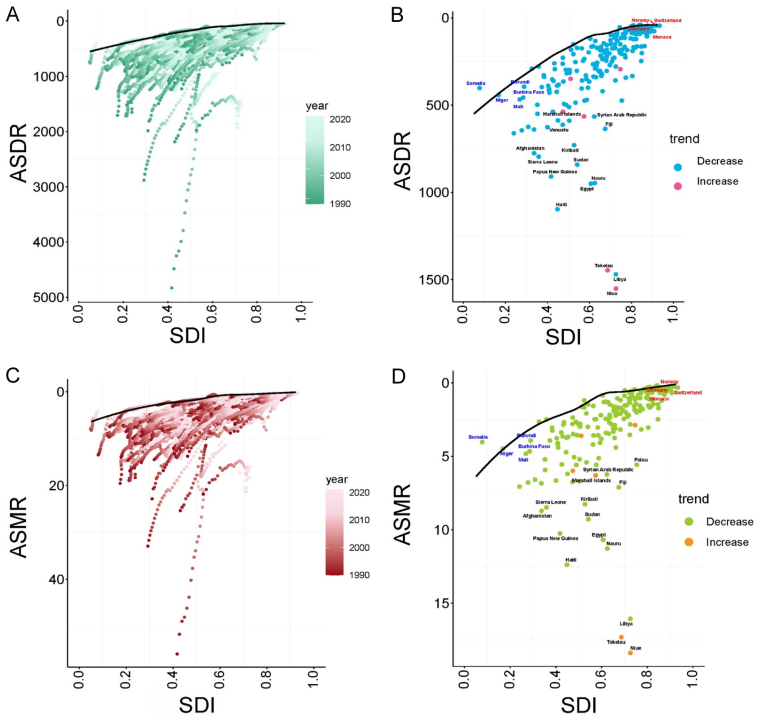



**Figure 4.** Frontier analysis of ASDR and ASMR associated with different SDI countries in children and adolescents with CVDs. (A, B) The trend of ASDR changes from 1990 to 2021 (A), and the ASDR in 2021 (B); (C, D) The trend of ASMR changes from 1990 to 2021 (C), and the ASMR in 2021 (D).

miologic shift in the burden of CVDs in adolescents. **Figure 4A** shows a generalized decrease in ASDR with increasing SDI values, indicating a global trend of decreasing ASDR over time (**Figure 4A**). The spatial-temporal decomposition identifies 83 countries (**Figure 4B**) where ASMR declined faster than the expected trajectory, in contrast to 12 outlier countries (pink markers) that experienced paradoxical increases in mortality despite improvements in SDI. Similarly, ASMR tends to decline as SDI increases (**Figure 4C**, **4D**).

*Regional level*

From 1990 to 2021, rates of ASMR, ASDR, and ASYLLs for CVD in children and adolescents trended downward in all 32 regions (Supplementary Table 1). Notably, East Asia had the most significant decline in ASMR, ASDR, and ASYLLs. From 1990 to 2021, ASPR tends to decline in Central Europe and Central Latin America, etc. On the contrary, ASIRs in regions such as South Asia and low and medium SDIs showed an increasing trend. Regarding

**Table 4.** The prediction of ASR for the six epidemiological indicators of the children and adolescent CVDs from 2020 to 2046

| Year | Prevalence | | | Incidence | | | Deaths | | |
|---|---|---|---|---|---|---|---|---|---|
| | ASR | | | ASR | | | ASR | | |
| | Both | Male | Female | Both | Male | Female | Both | Male | Female |
| 2020 | 14543.47931 | 15659.49871 | 13569.28816 | 1500.290652 | 1666.564328 | 1346.248718 | 459.412799 | 544.076085 | 387.081657 |
| 2025 | 14624.7198 | 15675.91258 | 13709.19874 | 1493.682354 | 1641.770311 | 1356.719773 | 428.593177 | 509.182351 | 359.449199 |
| 2030 | 14740.23748 | 15742.02481 | 13876.29421 | 1496.471472 | 1633.515417 | 1371.526637 | 407.410854 | 484.621872 | 340.741763 |
| 2035 | 14847.66509 | 15818.46291 | 14020.868 | 1503.519774 | 1634.685836 | 1386.548833 | 396.118607 | 470.655661 | 331.091809 |
| 2040 | 14939.19916 | 15897.88498 | 14133.79149 | 1513.963248 | 1644.570652 | 1400.485091 | 394.139935 | 467.002437 | 329.828351 |
| 2046 | 15044.76877 | 15993.47645 | 14261.14789 | 1527.270079 | 1658.493015 | 1416.876571 | 393.966636 | 465.072389 | 330.282347 |
| Year | DALYs | | | YLDs | | | YLLs | | |
| | ASR | | | ASR | | | ASR | | |
| | Both | Male | Female | Both | Male | Female | Both | Male | Female |
| 2020 | 9931.832889 | 12061.76733 | 7984.153429 | 730.15769 | 786.793051 | 684.508049 | 9201.6752 | 11274.9743 | 7299.64538 |
| 2025 | 9310.639082 | 11333.18469 | 7461.106821 | 729.967474 | 783.468405 | 686.887972 | 8579.94462 | 10549.4202 | 6772.91014 |
| 2030 | 8901.432501 | 10834.70653 | 7128.399991 | 731.487536 | 782.859225 | 690.624027 | 8168.44089 | 10052.3274 | 6433.87103 |
| 2035 | 8693.540935 | 10563.41231 | 6968.057141 | 732.642386 | 782.922101 | 693.298807 | 7956.98924 | 9781.21804 | 6265.57912 |
| 2040 | 8666.262687 | 10499.28399 | 6959.90125 | 733.275934 | 783.428785 | 694.791706 | 7923.49686 | 9714.6833 | 6246.59537 |
| 2046 | 8675.945558 | 10471.19291 | 6985.656018 | 733.899797 | 784.125337 | 696.290284 | 7925.03114 | 9683.03291 | 6258.61425 |

ASYLDs, the most significant decrease was observed in Central Europe, while the most significant increase was observed in South Asia. Detailed values are shown in Supplementary Table 1.

*National level*

In 2021, countries such as the Congo have significantly higher ASPRs. About half of the 204 countries show an increasing trend in ASPR between 1990 and 2021, while the other half show a decreasing trend. Larger increases were observed in countries such as Saudi Arabia, and the most significant increase was observed in Belarus. In terms of ASIR in 2021, countries such as Congo have higher ASIR values. Fiji had the most significant increase in ASIR from 1990 to 2021 (Supplementary Table 2). Libya, Tokelau and Niue all have high ASMR values. Most of the other 204 countries studied have a decreasing trend in ASMR (Supplementary Figures 5, 6; Supplementary Table 2).

*Nordpred prediction*

The Nordpred prediction analysis forecasts a global increase in the ASPR from 2021 to 2046. The ASMR is expected to decline over time and changes in the ASIR are projected to be less pronounced. From 2021 to 2046, the ASDR for pediatric and adolescent CVDs is anticipated to decrease primarily driven by the declining trend in ASMR (**Table 4**). The ASIR of male CVDs is projected to decrease by 2030, but is expected to increase by 2046, showing an upward trend. For female pediatric and adolescent CVDs, the ASDR and ASYLLs is projected to decline from 2021 to 2040 (**Figure 5**; **Table 4**).

## Discussion

In this study, we comprehensively evaluated the global burden of CVDs among children and adolescents using GBD 2021 estimates from 1990 to 2021. Several important findings emerged. First, despite an increase in the absolute number of children and adolescents with CVDs worldwide, mortality rates by age, DALYs, and YLLs have decreased significantly, and the prevalence of CVDs has increased, indicating improved survival and disease management. Importantly, the increase in the absolute number of prevalent cases should be distinguished from changes in age-standardized rates, as absolute case counts can be influenced by population growth and changes in population structure. Therefore, the increase in the number of prevalent cases should not be interpreted alone as evidence of an increase in individual-level disease risk. Second, this burden is significantly unequal between SDI regions and countries, with an increasing inci-

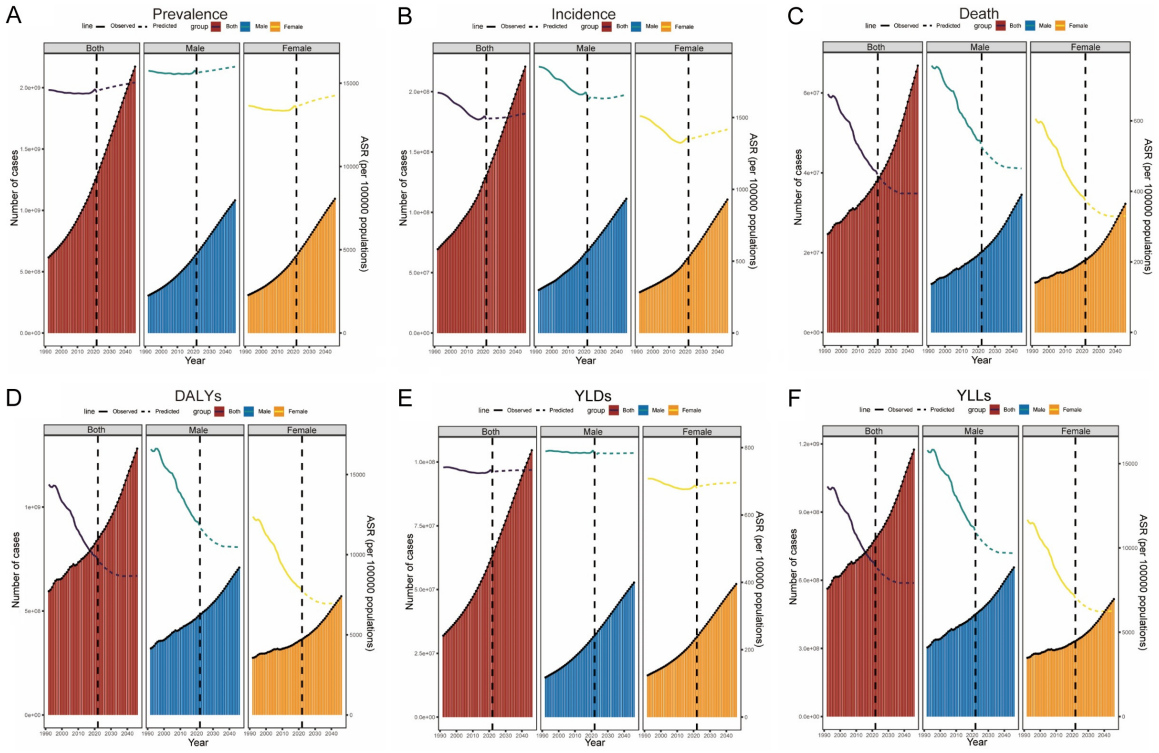



**Figure 5.** Projections of the number of cases and ASR of six epidemiological indicators of the children and adolescents CVDs in different sexes from 2020 to 2046.

dence in regions with low socioeconomic status and limited medical efficiency. Third, future projections suggest that prevalence is likely to continue to rise despite further declines in mortality, highlighting the potential transition from acute and fatal CVDs toward a growing need for long-term disease management among young people.

Globally, increased health awareness, medical breakthroughs, and preventive actions have been associated with declining trends in ASMR, ASDR, and ASYLLs for CVDs. Notably, ASMR, ASDR, and ASYLLs for CVDs decreased the most in East Asia; this may partly reflect improvements in healthcare resources, access to medical care, and changes in health-related behaviors associated with socioeconomic development. The ASPR reduction in Pulmonary Hypertension and stroke in other CVDs subtypes shows advances in early detection, effective treatment, and prevention, resulting in better diagnostics, as well as increased risk of stroke, supported by increased public awareness and improved pharmacologic approaches. But for the other 10 CVDs subtypes, the rising ASPR points to rising risk factors, highlighting the need to better understand their environmental, social, and economic drivers.

According to our analysis, the age group of 0-4 years had the lowest ASPR and ASIR of CVDs, whereas the age group of 15-19 years had the highest. The age group of 0 to 4 years old had the highest ASMR, while the age group of 5 to 9 years old had the lowest rates. These trends may result from an accumulation of physiological and environmental factors with age [18], early diagnosis and treatment, advances in medical technology, and improved health interventions, all of which have effectively reduced ASMR and severe complications [19]. The higher ASMR and DALYs in the youngest age group show their sensitivity and the severity of the disease, emphasizing the importance of age-specific health interventions and preventive actions. The unique age-specific patterns observed in this study can be explained by differences in disease mechanisms at different developmental stages. The higher mortality burden in children aged 0-4 years may reflect the effects of congenital cardiovascular anom-

alies, early complications, and limited physiological reserve. In contrast, the increased incidence and prevalence observed in adolescents may be related to the accumulation of cardiovascular risk factors, including obesity, hypertension, unhealthy dietary patterns, and physical inactivity. These findings highlight that cardiovascular prevention should begin early in life with interventions tailored to the stage of development.

From 1990 to 2021, our analysis shows that the EAPC of ASPR, ASMR, ASDR, and ASYLLs of CVDs was associated with SDI and HDI levels. The SDI is a composite indicator designed for the GBD research that measures a region's overall social development. The United Nations Development Programme proposed the HDI, which analyzes a country's performance across the aspects of health, education, and standard of living collectively. The combination of the SDI and the HDI makes it easier to examine the conditions that support social development and how they translate into health and education outcomes. High SDI areas typically exhibit superior healthcare and health education, leading to reduced ASIR and ASMR [1]. Countries with high and high middle SDI often implement effective preventive measures, advocating for improved diet and physical activity [20]. Moreover, high HDI countries tend to implement robust public health policies and security systems that effectively control the burden of CVDs in children and adolescents [16].

The burden of CVDs in children and adolescents varies significantly by region, impacted not only by SDI levels and economic development, but also by lifestyle, genetic predispositions, and environment. Unhealthy lifestyles, such as physical inactivity, poor dietary habits, and smoking, are key risk factors for CVDs, with their ASPR changing by area, which may contribute to regional variations in disease burden [21]. Additionally, specific regions may exhibit heightened genetic susceptibility and confront environmental exposures may contribute to regional differences in ASIR and ASPR. Climate change and temperature fluctuations further compound these risks, especially in regions experiencing temperature extremes [22].

Nordpred prediction analysis revealed a projected increase in ASIR for CVDs among children and adolescent boys, indicating an increase in new cases between 2035 and 2046. Notably, the increase in YLLs for CVDs among girls between 2040 and 2046 may reflect more severe cardiovascular health difficulties at specific ages, which could be caused by hormonal changes, lifestyle choices, or socioeconomic factors. Several measures might be implemented to address the expected increase in CVDs burden among children and adolescents. First, governments can improve health awareness through educational campaigns that emphasize cardiovascular health and regular exercise [23]. Strengthening public health laws, such as prohibiting the sale of high-sodium and high-sugar foods, is also critical [24].

Several limitations should be acknowledged. First, this study relied on GBD 2021 estimates, which are generated through statistical modeling and may be influenced by the availability and quality of underlying epidemiological data, particularly in regions with limited healthcare resources [25, 26]. Second, although SDI and HDI analyses identified important associations between socioeconomic development and cardiovascular burden, these ecological associations cannot establish causal relationships at the individual level. Third, the Nordpred projections were based on historical trends and may not fully capture future changes in healthcare policies, medical advances, environmental exposures, or emerging cardiovascular risk factors. Finally, differences in disease diagnosis and reporting capacity across countries may have contributed to variations in estimated disease burden.

In conclusion, this study examined changes between 1990 and 2021 using GBD 2021 data to represent the global, regional, and national burden of CVDs among children and adolescents. Our findings show that, while there is still a minor trend towards higher illness incidence, there is a more dramatic trend toward decreasing disease mortality and ASDR, which correlates with SDI levels. These findings provide important epidemiological information for the development of new therapeutics and underscore the need for continuous improvement in policies aimed at preventing, diagnosing, treating, and managing CVDs in children and adolescents.

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## Disclosure of conflict of interest

None.

## Abbreviations

CVDs, Cardiovascular Diseases; GBD, Global Burden of Diseases, Injuries, and Risk Factors Study; SDI, Sociodemographic Index; HDI, Human Development Index; ASR, Age standardized rate; ASPR, Age standardized prevalence rate; ASIR, Age standardized incidence rate; ASDR, Age standardized DALYs rate; ASMR, Age standardized mortality/death rate; ASYLDs, Age-Standardized YLDs Rate; ASYLLs, Age-Standardized YLLs Rate; DALYs, Disability-Adjusted Life Years; YLDs, Years Lived with Disability; YLLs, Years of Life Lost; EAPC, Estimated Annual Percentage Change.

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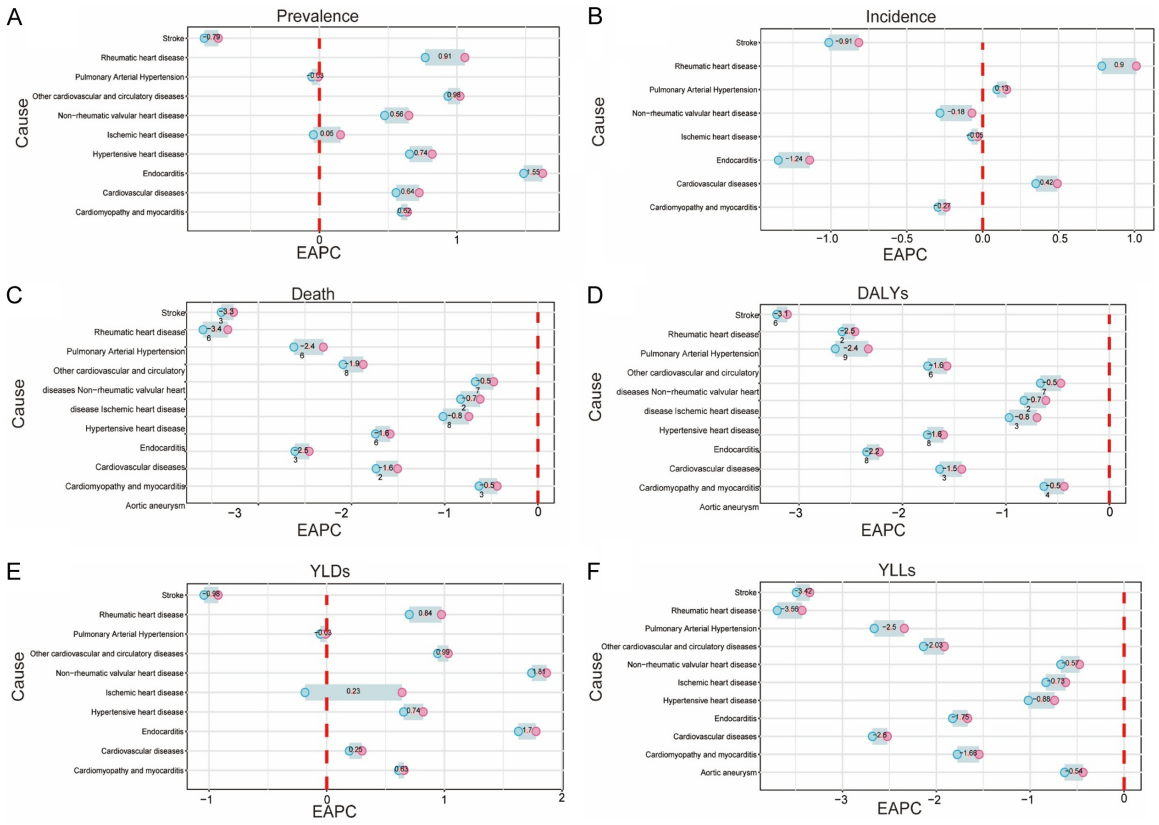
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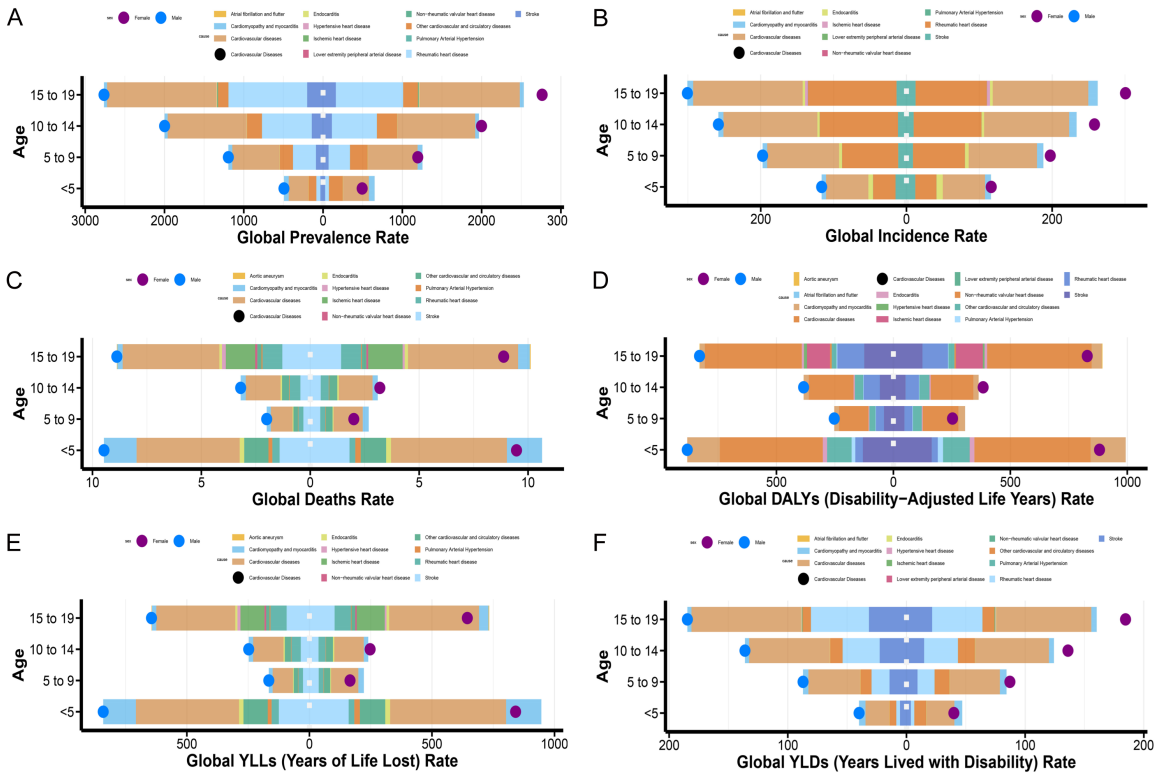
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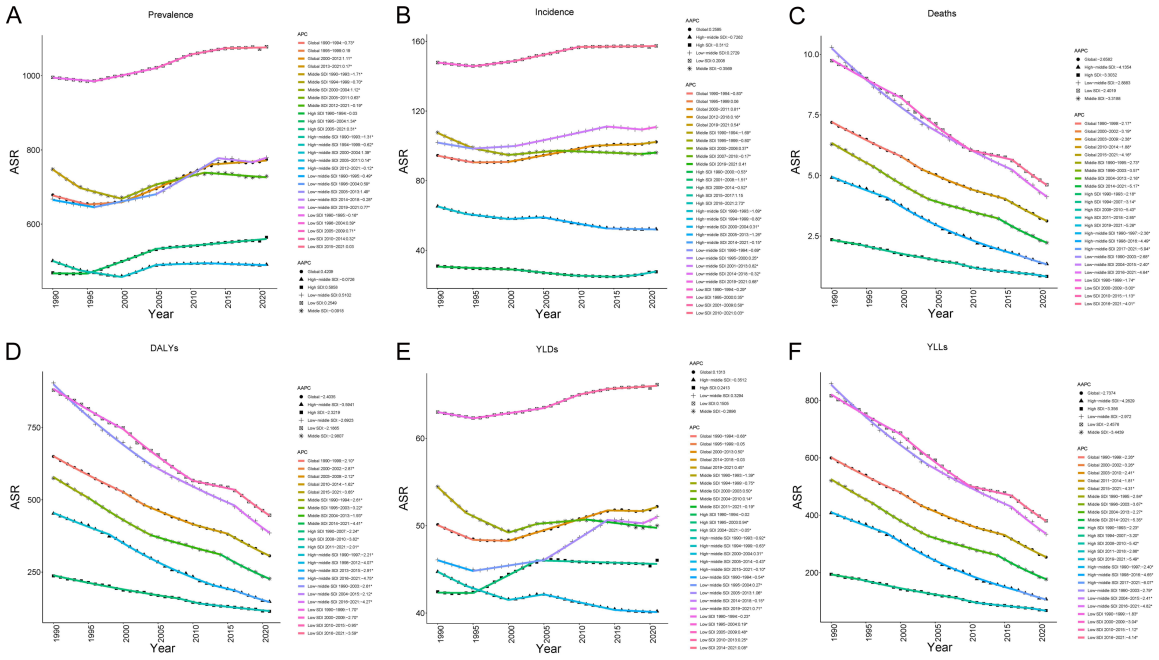
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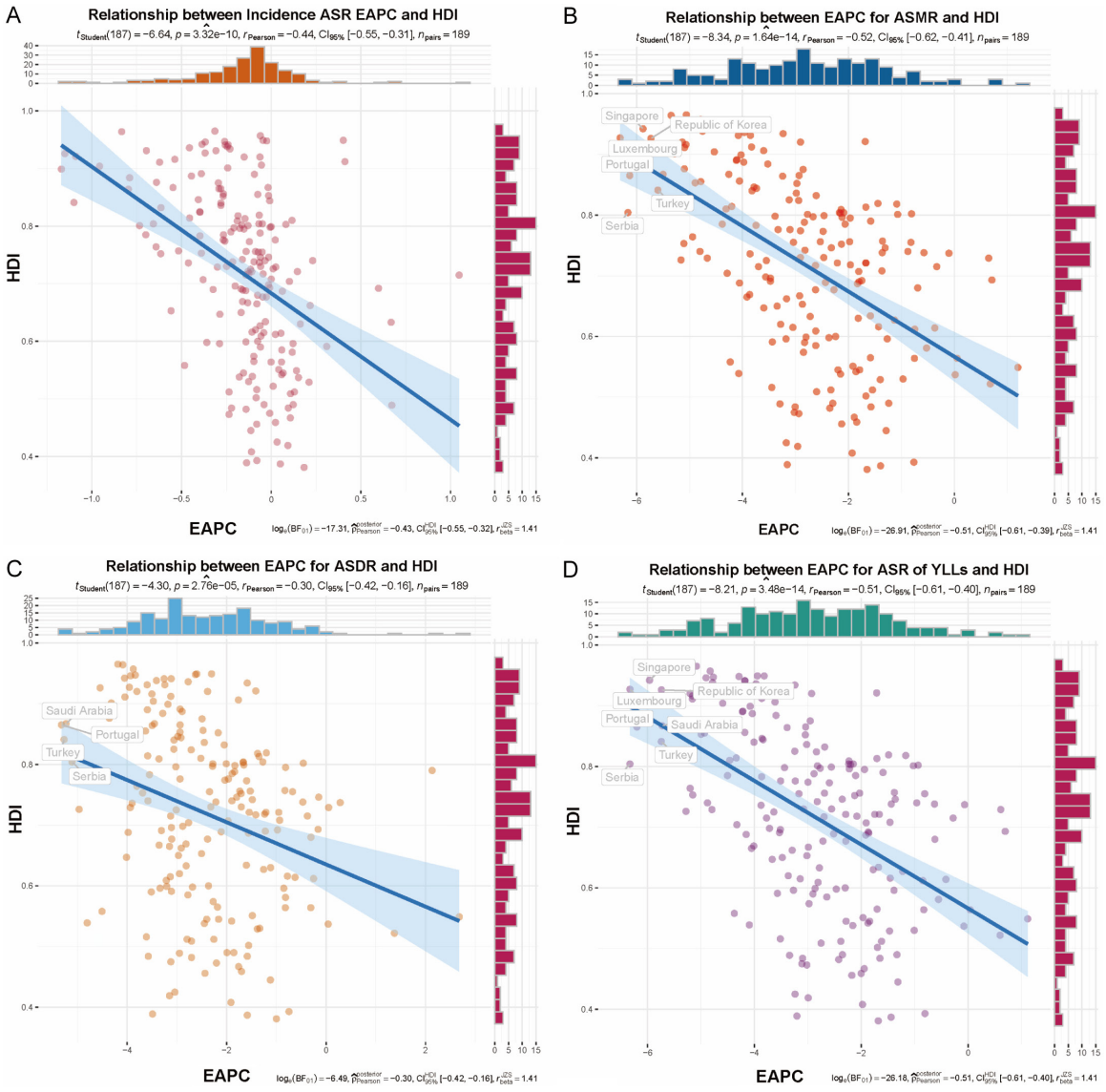

**Supplementary Figure 1.** EAPCs for ASPR (A), ASIR (B), ASMR (C), ASDR (D), ASR of YLDs (E), and ASR of YLLs (F) in children and adolescents with CVDs and 12 subtypes of CVDs from 1990 to 2021.



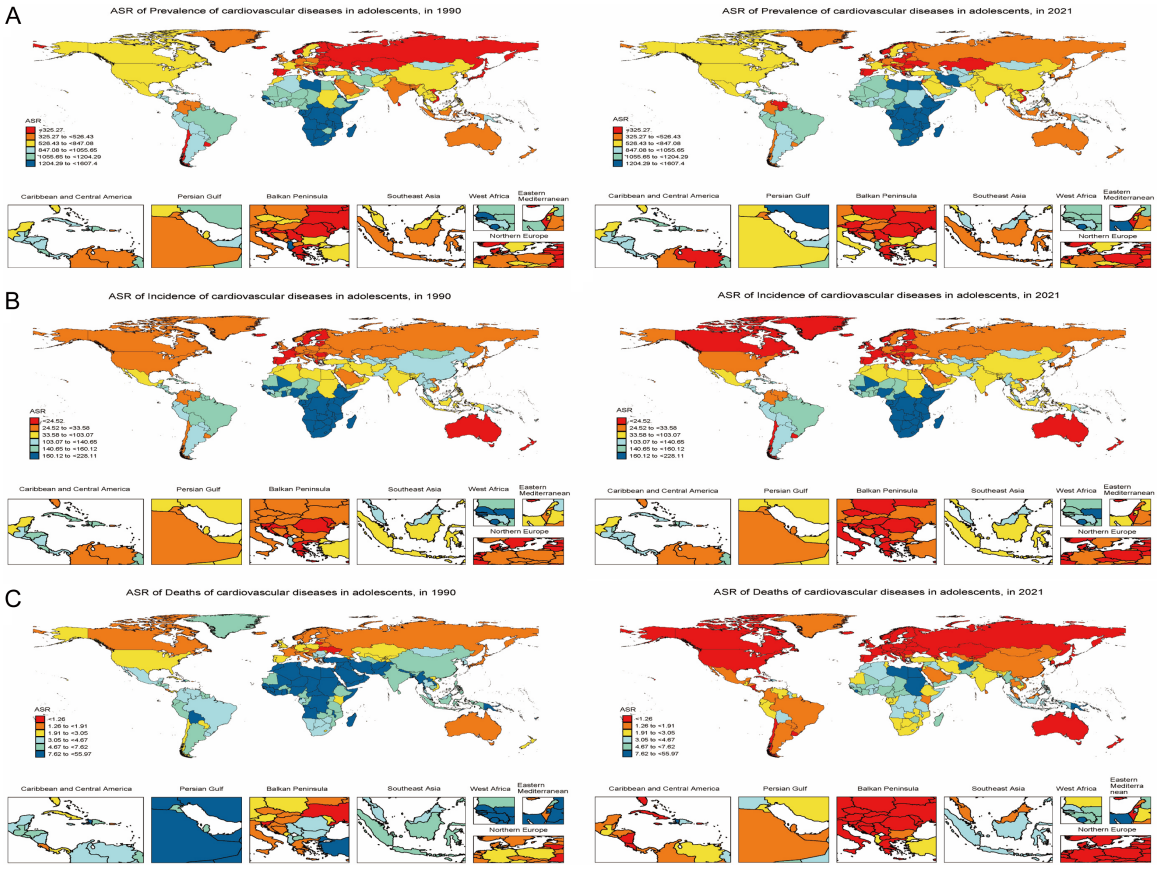
**Supplementary Figure 2.** Comparison of ASPR (A), ASIR (B), ASMR (C), ASDR (D), ASR of YLDs (E), and ASR of YLLs (F) in children and adolescents with CVDs and subclasses of CVDs across four age groups and by gender.



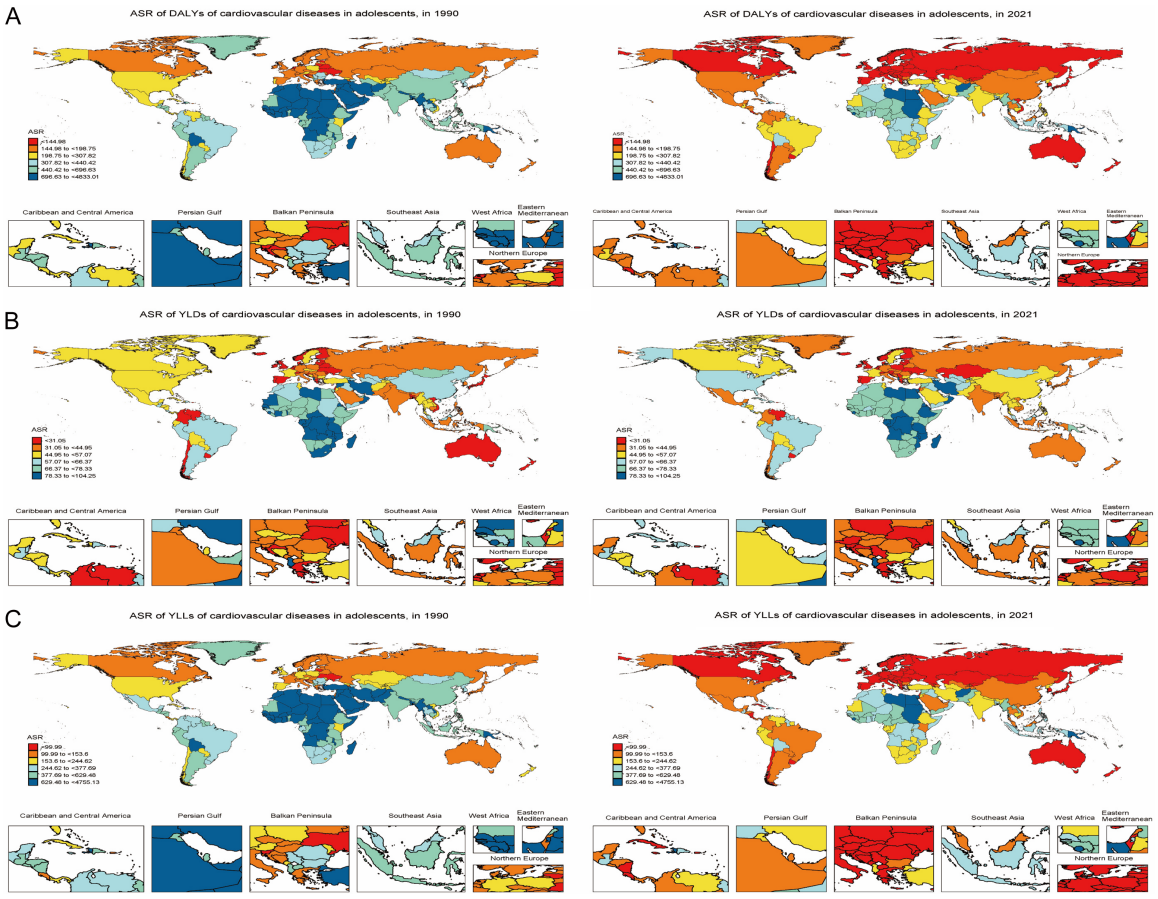

**Supplementary Figure 3.** Temporal trends in six epidemiological indicators of the burden of children and adolescent CVDs in globally and in five SDI regions.




**Supplementary Figure 4.** Relationships between EAPC of ASR and HDI levels for four epidemiological indicators of CVDs in children and adolescents. A. Relationships between EAPC of ASIR and HDI levels; B. Relationships between EAPC of ASMR and HDI levels; C. Relationships between EAPC of ASDR and HDI levels; D. EAPC of ASR of YLLs in relation to HDI levels.




**Supplementary Figure 5.** ASPR (A), ASIR (B), and ASMR (C) of the globally children and adolescent CVDs in 1990 and 2021.




**Supplementary Figure 6.** The ASRs of DALYs (A), YLDs (B) and YLLs (C) of the globally children and adolescent CVDs in 1990 and 2021.