

The Heterogeneous Global Burden of Hemoglobinopathies Among Women of Childbearing Age, 1990-2021, with Projection to 2030

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Objective: To systematically assess the global, regional, and national disease burden of Hemoglobinopathies among women of childbearing age (WCBA) from 1990 to 2021, whilst projecting trends to 2030.

Methods: Data were sourced from the Global Burden of Disease 2021 database, covering 204 countries and five socio-demographic index strata. Analyses focused on thalassemia and SCD among WCBA aged 15–49 years, with indicators including prevalence, deaths, and disability-adjusted life years (DALYs). Joinpoint regression, age–period–cohort model, decomposition analysis, frontier analysis, and Bayesian Age-Period-Cohort models explored the changes, drivers, inequalities, and future trends in disease.

Results: Between 1990 and 2021, the overall burden of thalassemia in the WCBA declined, with age-standardized prevalence rates (ASPR) decreasing from 12.75 to 9.90 per 100,000 population and age-standardized DALY rates falling from 9.69 to 6.56 per 100,000 population. Conversely, SCD showed a marked increase: ASPR rose from 42.99 to 67.17, age-standardized death rates (ASDR) increased from 0.35 to 0.54, and age-standardized DALY rates climbed from 25.88 to 40.76 per 100,000 population. Regional and national disparities were pronounced, with thalassemia bearing the highest burden in East Asia, while SCD predominantly concentrated in sub-Saharan Africa with low SDI. Decomposition analysis indicated that the decline in thalassemia primarily stemmed from epidemiological improvements, whereas the rise in SCD was mainly associated with population growth and inadequate healthcare accessibility. Projections suggest that by 2030, the burden of thalassemia will continue to decrease, while SCD will further intensify.

Conclusion: Thalassemia and SCD exhibit divergent disease burden trends within the WCBA, posing significant challenges to maternal health. Future efforts should focus on expanding tailored premarital and prenatal screening, genetic counselling, and multidisciplinary antenatal management to reduce inequalities and achieve sustained reductions in haemoglobinopathy burden, particularly in low-SDI regions.

Keywords: hemoglobinopathies, women of childbearing age, thalassemia, sickle cell disorders, projection

Introduction

Hemoglobinopathies rank among the most prevalent single-gene hereditary conditions globally, arising from mutations or deletions in hemoglobin genes.¹ It is estimated that approximately 7% of the global population carries disease-causing genes, with 300,000–400,000 children born annually with severe hemoglobinopathies.² In high-burden regions, carrier rates for disease-causing genes can reach 5–30% in Southeast Asia, the Middle East, and sub-Saharan Africa.³ These disorders frequently result in chronic anemia, increased infection risk, and growth restriction, with significant adverse impacts on maternal and child health.^{4,5} Consequently, hemoglobinopathies represent a critical public health challenge requiring urgent global attention.^{2,6}

Women of childbearing age (WCBA) represent a critical population in hemoglobin disorder prevention and control. On the one hand, they face substantially higher risks of anemia, pregnancy complications, and adverse perinatal events compared to the general population.⁷ On the other hand, they present a crucial window for genetic counselling and screening interventions.⁸ Multinational cross-sectional studies confirm that the weighted prevalence of hemoglobinopathies among women of childbearing age is markedly higher than in the general population of the same age group. This indicates that systematic screening and intervention from pre-pregnancy through pregnancy offer clear cost-effectiveness and should be prioritized as a regional public health strategy^{9–11}

Among all hemoglobinopathies, thalassemia and sickle cell disorders (SCD) represent the most prevalent and significant public health concerns.^{3,12} Both conditions are closely associated with reduced life expectancy and diminished quality of life, while substantially increasing the risk of maternal and neonatal complications.^{1,5,13} Although studies have documented their disease burden across the general population, systematic epidemiological analyses targeting women of childbearing age remain limited.^{14,15} Therefore, this study utilizes the Global Burden of Disease (GBD) database to systematically assess the prevalence, deaths, and disability-adjusted life years (DALYs) of thalassemia and SCD in WCBA from 1990 to 2021, aiming to provide evidence-based support for developing targeted prevention and control strategies.

Methods

Data Sources

GBD 2021 constitutes a large-scale clinical cross-sectional study based on anonymized data from integrated databases.¹⁶ This database covers 204 countries and regions, incorporates five-level socio-demographic index (SDI) stratification, and systematically records data on 371 diseases, 88 risk factors, and injuries.¹⁷ All data undergoes unified validation by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, USA, and is openly accessible via the GBD Visualization Tool.¹⁸ GBD 2021 findings assist policymakers, public health professionals, and researchers in revealing population health disparities, tracking long-term trends, evaluating intervention effectiveness, and formulating comprehensive strategies to reduce health inequalities post-pandemic.¹⁹

Study Population and Indicators

The study subjects comprised WCBA combined with thalassemia and WCBA combined with SCD. Data on the rates and numbers for three WCBA indicators—prevalence, deaths, and DALYs—for thalassemia and SCD from 1990 to 2021 were sourced from GBD 2021. WCBA is defined by the WHO as the reproductive stage of women aged 15 to 49 who are capable of reproduction and experience cyclical hormonal changes.²⁰

Data Analysis

To separately estimate age-standardized rates (ASR) for these two conditions within WCBA, this study employed direct standardization. This method assumes incidence distributions as weighted sums of independent Poisson random variables.²¹

Subsequently, Joinpoint models were employed to identify and quantitatively describe significant turning points in the age-standardized rate time series for WCBA combined with thalassemia and SCD at global, continental, and national levels.²² This model facilitated the calculation of annual percentage change (APC) and its 95% confidence interval (CI) to characterize epidemiological trends during the 1990–2021 study period. Furthermore, to provide an overall assessment of the observed trends, the average annual percentage change (AAPC) was calculated, incorporating the aggregated trend data for during the 1990–2021 study period. From a statistical perspective, an APC or AAPC estimate with its 95% CI lower bound exceeding zero indicates an upward trajectory within the specified interval; when the estimate plus the 95% CI upper bound is below zero, it signifies a downward trend; if the 95% CI encompasses zero, this implies a stable trend.

Further analysis incorporates the Age-period-cohort model. This methodology transcends conventional approaches in health and socio-economic development research by discerning overall and time-specific trends through net drift and local drift, while estimating independent effects across three temporal dimensions: age, period, and birth cohort.^{23,24} Within this framework, age intervals typically correspond to five age groups paired with five periods. Consequently, this study extracted data on thalassemia and SCD prevalence, deaths rates, DALYs rates and corresponding populations from

the 1992–2021 GBD database for the WCBA population (aged 15–49) from 1992 to 2021. Seven five-year age cohorts (15–19 to 45–49 years) were paired with six five-year periods (1992–1996 to 2017–2021) to form 12 overlapping 10-year birth cohorts (1942–1951 to 1997–2006). Furthermore, age effects are described using age-specific rates consistent with birth cohorts, whilst period/cohort effects are expressed as relative risks (RR) relative to an arbitrary reference period/cohort, the selection of which does not affect interpretation.

Moreover, decomposition analysis quantifies the independent incremental contributions of each factor to the overall difference in values between two populations, thereby precisely identifying sources of disparity.²⁵ Based on age structure, population growth, and epidemiological shifts, decomposition analysis of thalassemia and SCD prevalence, deaths, and DALYs within the WCBA precisely quantifies the cumulative contributions of each driver to overall disparities.

Furthermore, frontier analysis was employed to investigate the association between the burden of thalassemia and SCD within the WCBA and socio-demographic development. Specifically, a model using ASR as the dependent variable and the Socio-Demographic Index (SDI) as the explanatory variable was constructed. Through 1000 bootstrap samples, the average ASR at each SDI level was calculated, enabling the measurement of improvement potential by the absolute distance between each country's 2021 ASR and the frontier.²⁶

Finally, to forecast future trends, the Bayesian Age-Period-Cohort (BAPC) model was employed to predict the changing patterns of thalassemia and SCD within the WCBA population up to 2030. This model, integrating historical data with probabilistic distributions, simultaneously accounts for age, time, and cohort effects, thereby enabling estimation of the future burden patterns of these two diseases within this specific cohort.^{27,28}

All procedures for analysis and graphic representation were performed utilising the World Health Organization's Health Equity Assessment Toolkit and the statistical computing software, R (Version 4.3.3).

Results

Variation in Hemoglobinopathy Burden of WCBA at Global, Regional, and National Levels

From 1990 to 2021, the overall global burden of thalassemia exhibited a downward trend. The number of prevalence individuals increased from 180,646 cases [95% uncertainty interval (UI): 149,696–217,870] to 189,793 cases (95% UI: 155,920–232,577) ([Figures S1A, S1B](#) and [Table 1](#)). During the same period, the number of deaths decreased from 2,072 (95% UI: 683–3,446) to 1,960 (95% UI: 473–3,760) ([Figures S1C, S1D](#) and [Table 1](#)), while disability-adjusted life years (DALYs) declined from 134,536 (95% UI: 47,205–218,870) to 125,370 (95% UI: 33,107–237,005) ([Figures S1E, S1F](#) and [Table 1](#)). In contrast, age-standardized prevalence rates (ASPR) decreased from 12.75 (95% UI: 10.56–15.38) to 9.90 (95% UI: 8.14–12.14) ([Figures S2A, S2B](#) and [Table 1](#)). Similarly, age-standardized death rates (ASDR) decreased from 0.15 (95% UI: 0.05–0.25) to 0.10 (95% UI: 0.02–0.20) ([Figures S2C, S2D](#) and [Table 1](#)), and the age-standardized DALYs rate decreased from 9.69 (95% UI: 3.45–15.76) to 6.56 (95% UI: 1.71–12.43) ([Figures S2E, S2F](#) and [Table 1](#)). At the regional level, East Asia recorded the highest ASPR for thalassemia in 2021 [28.51, 95% UI: 22.49–36.36]; Southeast Asia had the highest ASDR (0.29, 95% UI: 0.08–0.56); while the highest age-standardized DALYs rate was also observed in Southeast Asia [17.90(95% UI: 5.05–33.31)] ([Table 1](#)). At the SDI level, Middle SDI countries exhibited the highest 2021 ASPR [15.49 (95% UI: 12.73–18.89)], whilst the 2021 ASDR and age-standardized DALYs rates for Low-middle SDI reached 9.22 (95% UI: 1.88–20.71) and 0.15 (95% UI: 0.03–0.32) respectively, the highest among all subdivisions ([Table 1](#)). At the national level, Cambodia reported the highest ASPR at 106.41 (95% UI: 79.21–142.46); whereas Guinea-Bissau recorded the highest ASDR and age-standardized DALYs rates at 1.09 (95% UI: 0.04–8.6) and 68.61 (95% UI: 2.62–538.18), respectively ([Table S1](#)).

In contrast to thalassemia, SCD showed a marked increase during the same period. The global prevalence increased from 622,466 cases (95% UI: 504,139–767,291) to 1,262,532 cases (95% UI: 1,009,699–1,586,529) ([Figures S3A, S3B](#) and [Table 2](#)). During the same period, the number of deaths increased from 4,796 (95% UI: 2,989–7,551) to 10,370 (95% UI: 6,071–16,854) ([Figures S3C, S3D](#) and [Table 2](#)), while DALYs rose from 366,351 (95% UI: 247,339–533,426) to 772,406 (95% UI: 490,291–1,172,642) ([Figures S3E, S3F](#) and [Table 2](#)). In terms of rates, the ASPR increased from 42.99 (95% UI: 34.79–53.02) to 67.17 (95% UI: 53.76–84.37) ([Figures S4A, S4B](#) and [Table 2](#)). Similarly, the ASDR rose from

Table 1 Numbers and ASR of Thalassemia Burden in the WCBA in 1990 and 2021, Categorised by Global, Regions and Nation

Location	Prevalence				Deaths				DALYs			
	1990		2021		1990		2021		1990		2021	
	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR
Global	180646 (149,696,217,870)	12.75 (10.56, 15.38)	189,793 (155,920,232,577)	9.9 (8.14, 12.14)	2072 (683, 3446)	0.15 (0.05, 0.25)	1960 (473, 3760)	0.1 (0.02, 0.2)	134,536 (47,205, 218,870)	9.69 (3.45, 15.76)	125,370 (33,107, 237,005)	6.56 (1.71, 12.43)
High SDI	7632 (6234, 9265)	3.47 (2.83, 4.21)	8259 (6810, 9957)	3.6 (2.97, 4.34)	77 (35, 127)	0.03 (0.02, 0.06)	35 (17, 58)	0.01 (0.01, 0.02)	4841 (2321, 7877)	2.2 (1.05, 3.58)	2250 (1204, 3548)	0.98 (0.52, 1.54)
High-middle SDI	29668 (24,036, 37,102)	10.38 (8.41, 12.97)	29,815 (24,196, 37,230)	10.68 (8.68, 13.3)	389 (133,703)	0.14 (0.05, 0.25)	163 (54,287)	0.05 (0.02, 0.09)	24,629 (8,966, 43,635)	8.77 (3.21, 15.53)	9962 (3725, 16,870)	3.41 (1.25, 5.79)
Middle SDI	110837 (90,721,136,745)	22.89 (18.72, 28.24)	92,200 (75,740, 112,511)	15.49 (12.73, 18.89)	917 (317, 1573)	0.21 (0.07, 0.35)	555 (159, 1040)	0.09 (0.02, 0.17)	59,655 (22,438, 99,757)	12.94 (4.96, 21.63)	34,517 (11,431, 62,311)	5.67 (1.84, 10.24)
Lower-middle SDI	27722 (21,938, 35,248)	9.26 (7.31, 11.77)	47,316 (36,290, 61,691)	9.08 (6.97, 11.84)	521 (139,969)	0.18 (0.05, 0.34)	773 (149, 1653)	0.15 (0.03, 0.32)	34,289 (9,763, 62,794)	11.6 (3.39, 21.23)	50,126 (10,541, 105,839)	9.64 (2.06, 20.31)
Low SDI	4680 (3573, 6168)	3.72 (2.84, 4.9)	12,074 (9166, 15,843)	3.93 (2.99, 5.16)	166 (37, 353)	0.14 (0.03, 0.29)	430 (81,974)	0.14 (0.03, 0.33)	11,007 (2,628, 23,158)	8.74 (2.11, 18.42)	28,371 (5,706, 63,102)	9.22 (1.88, 20.71)
Andean Latin America	456 (344,606)	4.41 (3.32, 5.86)	841 (628, 1112)	4.84 (3.62, 6.4)	8 (1,19)	0.09 (0.01, 0.2)	9 (1, 21)	0.05 (0.01, 0.12)	512 (81, 1146)	5.24 (0.85, 11.82)	530 (79, 1251)	3.04 (0.46, 7.18)
Australasia	545 (410,710)	10.3 (7.75, 13.42)	727 (548,940)	10.69 (8.07, 13.84)	1 (0,1)	0.01 (0.01, 0.02)	0 (0,0)	0 (0, 0.01)	42 (25, 65)	0.8 (0.48, 1.22)	26 (15,40)	0.38 (0.22, 0.59)
Caribbean	480 (362,630)	4.84 (3.65, 6.35)	621 (465,816)	5.25 (3.93, 6.89)	12 (4,27)	0.13 (0.04,0.29)	28 (6,66)	0.23 (0.05,0.54)	768 (249,1651)	8.04 (2.59,17.33)	1659 (374,3861)	13.77 (3.12,32.01)
Central Asia	766 (581, 1005)	4.26 (3.23, 5.59)	1049 (800,1370)	4.48 (3.42, 5.85)	6 (1, 14)	0.04 (0.01, 0.08)	7 (2, 15)	0.03 (0.01, 0.06)	433 (127,886)	2.45 (0.71, 5.06)	469 (153,917)	1.99 (0.66, 3.87)
Central Europe	1415 (1091, 1810)	4.72 (3.64, 6.03)	1152 (885, 1476)	4.96 (3.82, 6.35)	6 (2,11)	0.02 (0.01, 0.04)	2 (1, 4)	0.01 (0, 0.01)	397 (165,690)	1.35 (0.56, 2.33)	138 (62,240)	0.59 (0.27, 1.01)
Central Latin America	2162 (1635, 2840)	4.71 (3.56, 6.18)	3495 (2627, 4581)	5.18 (3.9, 6.79)	8 (2, 16)	0.02 (0, 0.04)	14 (3, 35)	0.02 (0, 0.05)	513 (139, 1075)	1.17 (0.32, 2.46)	893 (239, 2125)	1.31 (0.35, 3.13)
Central Sub-Saharan Africa	537 (391,732)	3.83 (2.78, 5.21)	1451 (1058, 1984)	3.97 (2.89, 5.42)	8 (0, 32)	0.06 (0, 0.25)	20 (2, 77)	0.06 (0, 0.22)	537 (59, 2063)	3.91 (0.43, 15.15)	1365 (160, 4960)	3.77 (0.44, 13.76)
East Asia	106,897 (84,098, 137,013)	30 (23.59, 38.46)	83,268 (65,610, 106,198)	28.51 (22.49, 36.36)	867 (294, 1519)	0.27 (0.09, 0.47)	326 (108,581)	0.1 (0.03, 0.17)	55,219 (20,231, 94,647)	16.42 (6.13, 28.11)	20,215 (7,824, 34,415)	6.31 (2.37, 10.76)
Eastern Europe	2460 (1847, 3219)	4.61 (3.47, 6.04)	2027 (1521, 2663)	4.83 (3.63, 6.36)	1 (1,2)	0 (0,0)	1 (1,2)	0 (0,0)	168 (122, 227)	0.33 (0.24, 0.44)	142 (107,185)	0.36 (0.27, 0.46)
Eastern Sub-Saharan Africa	2030 (1507,2750)	4.05 (3.5,48)	5190 (3851,6999)	4.25 (3.15,5.72)	73 (16,159)	0.15 (0.03,0.33)	141 (27,315)	0.12 (0.02,0.27)	4851 (1120,10,403)	9.65 (2.26,20.99)	9452 (1934,20,716)	7.66 (1.62, 16.9)
High-income Asia Pacific	2451 (1900, 3107)	5.5 (4.26, 6.97)	1830 (1424, 2313)	5.39 (4.2, 6.82)	27 (7, 53)	0.06 (0.02, 0.12)	6 (1, 13)	0.02 (0, 0.04)	1669 (464, 3265)	3.77 (1.04, 7.35)	387 (110,792)	1.09 (0.32, 2.21)
High-income North America	955 (793,1148)	1.33 (1.1, 1.6)	1079 (913,1287)	1.34 (1.13, 1.6)	11 (9, 13)	0.01 (0.01, 0.02)	6 (5,8)	0.01 (0.01, 0.01)	674 (554,793)	0.91 (0.75, 1.07)	392 (294,485)	0.47 (0.36, 0.58)
North Africa and Middle East	3827 (2982, 4911)	4.44 (3.45, 5.7)	7226 (5592, 9292)	4.58 (3.54, 5.89)	105 (24, 212)	0.11 (0.03, 0.23)	103 (22, 221)	0.07 (0.01, 0.14)	7249 (1727, 14,452)	7.69 (1.89, 15.39)	7036 (1606, 14,806)	4.52 (1.02, 9.5)
Oceania	193 (150, 250)	11.3 (8.74, 14.64)	412 (320,533)	11.47 (8.9, 14.83)	5 (1, 10)	0.31 (0.06, 0.69)	9 (1, 21)	0.25 (0.04, 0.61)	292 (61,642)	18.3 (3.89, 40.56)	544 (98, 1277)	15.47 (2.85, 36.37)
South Asia	14,248 (11,182, 18,132)	5.13 (4.02, 6.53)	25,704 (19,730, 33,466)	5.1 (3.91, 6.63)	252 (28,618)	0.09 (0.01, 0.23)	606 (41, 1580)	0.12 (0.01, 0.31)	17,053 (2506,40,647)	6.1 (0.9, 14.62)	39,939 (3,546, 102,060)	7.91 (0.71, 20.21)
Southeast Asia	35,065 (28,012, 43,825)	26.98 (21.51, 33.79)	42,901 (33,375, 55,560)	24.03 (18.7, 31.13)	578 (190,982)	0.48 (0.16, 0.81)	536 (144, 1023)	0.29 (0.08, 0.56)	37,168 (12,939,62,006)	29.55 (10.5, 49.45)	32,471 (9,260, 60,503)	17.9 (5.05, 33.31)
Southern Latin America	226 (172,297)	1.79 (1.36, 2.36)	309 (238,400)	1.83 (1.41, 2.37)	2 (1,3)	0.01 (0.01, 0.02)	1 (1,2)	0.01 (0, 0.01)	102 (50, 188)	0.81 (0.39, 1.49)	83 (44, 147)	0.49 (0.26, 0.87)

Southern Sub-Saharan Africa	705 (525,950)	4.61 (3.42, 6.22)	1049 (777, 1412)	4.81 (3.56, 6.48)	23 (4,49)	0.17 (0.03, 0.36)	38 (6, 88)	0.18 (0.03, 0.41)	1475 (288, 3077)	10.35 (2.06, 21.83)	2341 (397,5350)	10.77 (1.84, 24.62)
Tropical Latin America	1864 (1412, 2440)	4.4 (3.33, 5.76)	2814 (2139, 3693)	4.89 (3.72, 6.42)	3 (2, 4)	0.01 (0.01, 0.01)	5 (3,7)	0.01 (0.01, 0.01)	263 (198, 338)	0.63 (0.48, 0.81)	398 (282,537)	0.68 (0.48, 0.92)
Western Europe	1379 (1062, 1786)	1.51 (1.16, 1.97)	1029 (797, 1320)	1.23 (0.95, 1.58)	44 (39, 49)	0.05 (0.04, 0.05)	13 (11, 15)	0.01 (0.01, 0.02)	2893 (2611, 3214)	3.19 (2.88, 3.54)	808 (682, 935)	0.98 (0.83, 1.14)
Western Sub-Saharan Africa	1986 (1499, 2645)	3.98 (3, 5.3)	5619 (4227, 7464)	4.16 (3.13, 5.52)	33 (14, 72)	0.07 (0.03, 0.15)	88 (35, 190)	0.07 (0.03, 0.14)	2256 (1020, 4853)	4.47 (2.02, 9.58)	6082 (2515, 12,724)	4.39 (1.82, 9.21)

Abbreviations: ASR, age-standardized rates; WCBA, Women of Childbearing Age; DALYs, Disability-Adjusted-Life-Years.

Table 2 Numbers and ASR of the Burden of SCD Among WCBA in 1990 and 2021, Categorised by Global, Regions and Nation

Location	Prevalence				Deaths				DALYs			
	1990		2021		1990		2021		1990		2021	
	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR	Number	ASR
Global	622466 (504,139,767,291)	42.99 (34.79, 53.02)	1,262,532 (1,009,699, 1,586,529)	67.17 (53.76, 84.37)	4796 (2989, 7551)	0.35 (0.22, 0.55)	10,370 (6071, 16,854)	0.54 (0.32, 0.88)	366,351 (247,339, 533,426)	25.88 (17.48, 37.92)	772,406 (490,291, 1,172,642)	40.76 (25.84, 61.85)
High SDI	38103 (33,650,42,912)	17.1 (15.12, 19.25)	37,197 (32,650,42,064)	15.95 (14.02, 18.01)	226 (195, 267)	0.1 (0.08, 0.12)	280 (223, 365)	0.11 (0.09, 0.14)	16,313 (13,944, 19,151)	7.2 (6.12, 8.49)	18,616 (15,054, 23,623)	7.55 (6.04, 9.64)
High-middle SDI	19395 (15,788, 23,270)	6.82 (5.55, 8.18)	26,101 (21,080,31,836)	9.52 (7.68, 11.61)	143 (46,289)	0.05 (0.02, 0.11)	91 (43, 157)	0.03 (0.01, 0.05)	10,224 (4,327, 18,961)	3.66 (1.56, 6.79)	7498 (4485, 11,369)	2.62 (1.56, 3.94)
Middle SDI	120,918 (93,691, 153,887)	24.26 (18.76, 30.89)	207,139 (160,064, 265,090)	36.13 (27.97, 46.23)	690 (270, 1182)	0.15 (0.06, 0.25)	1178 (422, 2279)	0.2 (0.07, 0.39)	55,765 (27,960, 86,825)	11.58 (5.8, 18.02)	92,640 (44,228, 161,687)	15.87 (7.54, 27.83)
Lower-middle SDI	241,497 (191,728, 304,690)	77.76 (61.61, 98.14)	481,061 (378,346, 610,683)	90.95 (71.48, 115.5)	1580 (793, 2533)	0.55 (0.27, 0.88)	3341 (1318, 6032)	0.64 (0.25, 1.16)	126,194 (73,308, 186,120)	42.09 (24.26, 62.47)	256,468 (126,802, 432,041)	48.96 (24.17, 82.45)
Low SDI	202,361 (164,207, 250,225)	155.74 (125.64, 193.31)	510,706 (409,065,647,820)	161.3 (128.29, 205.28)	2152 (1174, 4984)	1.84 (0.99, 4.36)	5474 (2834, 12,041)	1.9 (0.98, 4.24)	157,563 (95,321, 330,708)	129.04 (76.92, 277.31)	396,751 (230,147, 802,876)	132.04 (75.81, 272.17)
Andean Latin America	210 (154,279)	2.05 (1.51, 2.73)	371 (277,485)	2.14 (1.6, 2.8)	4 (1,9)	0.04 (0.01, 0.09)	4 (1, 9)	0.02 (0.01, 0.05)	250 (56, 563)	2.41 (0.55, 5.5)	257 (81,570)	1.5 (0.47, 3.33)
Australasia	15 (11, 21)	0.29 (0.21, 0.39)	20 (15, 27)	0.29 (0.22, 0.39)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	3 (2,4)	0.05 (0.04, 0.07)	8 (5,11)	0.11 (0.07, 0.16)
Caribbean	2641 (1947, 3432)	26.75 (19.7, 34.76)	2453 (1823, 3280)	20.86 (15.51, 27.89)	114 (61, 186)	1.19 (0.64, 1.96)	159 (72, 286)	1.33 (0.6, 2.4)	7312 (4043,11,772)	74.8 (41.31, 120.48)	9858 (4501, 17,563)	83.2 (38.01, 148.03)
Central Asia	1 (0,2)	0 (0,0.01)	1 (0,2)	0 (0, 0.01)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,1)	0 (0,0.01)	1 (0,2)	0 (0,0.01)
Central Europe	52 (39,70)	0.18 (0.13, 0.24)	33 (26,42)	0.15 (0.12, 0.19)	2 (2, 3)	0.01 (0.01, 0.01)	1 (1,1)	0 (0,0)	135 (117, 157)	0.44 (0.38, 0.51)	48 (38, 58)	0.19 (0.15, 0.23)
Central Latin America	156 (112,215)	0.34 (0.24, 0.47)	122 (83,177)	0.18 (0.12, 0.26)	17 (14, 20)	0.04 (0.03, 0.05)	36 (28, 45)	0.05 (0.04, 0.07)	1053 (876, 1247)	2.45 (2.04, 2.91)	2097 (1635, 2647)	3.08 (2.4, 3.89)
Central Sub-Saharan Africa	52,132 (39,695, 66,964)	365.48 (275.9, 471.9)	136,585 (104,069, 178,762)	368.19 (278.76, 483.2)	626 (42, 2334)	5.15 (0.35, 19.41)	1574 (125, 5543)	4.83 (0.38, 17.09)	43,552 (7,328, 146,645)	337.85 (53.61, 1159.38)	109,032 (19,176, 349,324)	318.21 (53.6, 1032.83)
East Asia	10396 (7771,13,454)	2.97 (2.22, 3.85)	8393 (6279, 10,840)	2.74 (2.06, 3.54)	127 (21,310)	0.04 (0.01, 0.1)	49 (9, 119)	0.01 (0, 0.03)	8311 (2054, 18,954)	2.53 (0.63, 5.77)	3408 (1168, 7211)	1.02 (0.35, 2.17)
Eastern Europe	23 (14, 34)	0.04 (0.03, 0.06)	18 (12, 27)	0.04 (0.03, 0.06)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	13 (11,16)	0.03 (0.02, 0.03)	6 (5,8)	0.02 (0.01, 0.02)
Eastern Sub-Saharan Africa	41,055 (30,783, 54,280)	77.19 (57.42, 102.47)	94,407 (71,426, 124,917)	74.17 (55.6, 98.52)	334 (102,931)	0.72 (0.22, 2.05)	772 (246, 2167)	0.67 (0.21, 1.92)	25,570 (10,393, 63,074)	51.99 (20.62, 132.49)	57,658 (24,166, 145,219)	48.22 (19.83, 123.39)
High- -income Asia Pacific	16 (10, 26)	0.04 (0.02,0.06)	12 (8,18)	0.03 (0.02, 0.05)	4 (3,4)	0.01 (0.01,0.01)	1 (0,1)	0 (0,0)	220 (199,247)	0.48 (0.43,0.54)	30 (26,35)	0.08 (0.07,0.1)
High-income North America	21,246 (18,142, 24,825)	28.81 (24.62, 33.66)	19,455 (17,559, 21,791)	23.54 (21.27, 26.35)	160 (152, 168)	0.21 (0.2, 0.22)	161 (150, 171)	0.18 (0.17, 0.19)	10,883 (10,133, 11,756)	14.37 (13.36, 15.55)	10,426 (9622,11,319)	12.12 (11.17, 13.19)
North Africa and Middle East	107,698 (90,304, 126,309)	131.47 (110.22, 154.5)	162,132 (132,007, 196,645)	102.06 (83.11, 123.77)	342 (138,596)	0.43 (0.19, 0.75)	496 (208,874)	0.31 (0.13, 0.55)	31,164 (16,932, 47,434)	37.94 (21.29, 57.48)	44,332 (25,141, 68,248)	27.99 (15.82, 43.16)
Oceania	0 (0,1)	0.01 (0, 0.04)	0 (0,1)	0.01 (0, 0.04)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,1)	0.02 (0,0.08)	1 (0,2)	0.02 (0,0.06)
South Asia	131,864 (91,625, 184,971)	45.3 (31.38, 63.65)	179,016 (125,057, 251,802)	35.12 (24.52, 49.39)	369 (155,567)	0.13 (0.06, 0.21)	363 (130,572)	0.07 (0.03, 0.11)	39,607 (23,861, 54,706)	13.94 (8.31, 19.36)	41,810 (24,448, 59,476)	8.26 (4.82, 11.76)

Southeast Asia	26 (8, 60)	0.02 (0.01, 0.05)	34 (10, 79)	0.02 (0.01, 0.04)	1 (1,3)	0 (0,0)	1 (0,3)	0 (0,0)	90 (34, 198)	0.07 (0.03, 0.16)	76 (19,194)	0.04 (0.01, 0.11)
Southern Latin America	14 (9, 20)	0.11 (0.07, 0.16)	30 (22, 41)	0.18 (0.13, 0.24)	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)	8 (6,12)	0.07 (0.05, 0.1)	12 (8,17)	0.07 (0.04, 0.1)
Southern Sub-Saharan Africa	108 (86, 134)	0.68 (0.53, 0.85)	154 (124, 189)	0.71 (0.57, 0.86)	3 (1, 7)	0.02 (0, 0.05)	6 (1, 15)	0.03 (0, 0.07)	216 (50, 469)	1.45 (0.34, 3.17)	385 (70,937)	1.77 (0.32, 4.31)
Tropical Latin America	2942 (2481,3443)	7.12 (6,8.34)	4808 (4006, 5722)	8.2 (6.83, 9.76)	61 (55, 68)	0.15 (0.13, 0.17)	185 (167, 203)	0.3 (0.28, 0.33)	4017 (3604, 4458)	9.72 (8.71, 10.8)	11,111 (10,113, 12,179)	18.63 (16.96, 20.42)
Western Europe	5155 (4288, 6244)	5.53 (4.61, 6.7)	5008 (4191, 5985)	5.76 (4.83, 6.86)	13 (11, 16)	0.01 (0.01, 0.02)	19 (17, 22)	0.02 (0.02, 0.02)	1201 (1010, 1436)	1.28 (1.07, 1.53)	1485 (1285, 1710)	1.64 (1.41, 1.89)
Western Sub-Saharan Africa	246,717 (201,358,3,021,39)	470.46 (381.61, 5, 79.1)	649,478 (519,908, 81, 3,819)	464.74 (369.11, 5 85.54)	2617 (1672,4134)	5.64 (3.59, 8. 98)	6543 (3850,1 0800)	5.15 (3.03, 8. 51)	192,745 (132,235, 2, 88,017)	395.15 (269.2, 59. 6.59)	480,365 (307,253,75 7919)	362.77 (231.17, 5 73.71)

Abbreviations: SCD, Sickle cell disorders; ASR, age-standardized rates; WCBA, Women of Childbearing Age; DALYs, Disability-Adjusted Life-Years.

0.35 (95% UI: 0.22–0.55) to 0.54 (95% UI: 0.32–0.88) (Figures S4C, S4D and Table 2), and the age-standardized DALYs rate increased from 25.88 (95% UI: 17.48–37.92) to 40.76 (95% UI: 25.84–61.85) (Figures S4E, S4F and Table 2). At the regional level, Western sub-Saharan Africa recorded the highest ASPR, ASDR, and age-standardized DALY rates for SCD in 2021, at 464.74 [95% UI: 369.11–585.54], 5.15 [95% UI: 3.03–8.51] and 362.77 [95% UI: 231.17–573.71] respectively (Table 2). At the SDI level, ASR in low-SDI regions was significantly higher than in other regions. In 2021, ASPR reached 161.30 (95% UI: 128.29–205.28), with ASPR of 161.30 (95% UI: 128.29–205.28), ASDR of 1.90 (95% UI: 0.98–4.24), and age-standardized DALYs rate of 132.04 (95% UI: 75.81–272.17), all ranking highest (Table 2). At the national level, Bahrain recorded the highest ASPR at 975.17 [95% UI: 748.30–1246.94]; whereas Togo led in both ASDR and age-standardized DALYs rates, at 11.74 [95% UI: 4.14–37.11] and 784.41 [95% UI: 319.06–2331.01] respectively (Table S1).

Temporal Trends in Hemoglobinopathies Burden of WCBA

From 1990 to 2021, the overall ASR for thalassemia exhibited a downward trend [AAPC for ASPR: -0.78 (95% CI: $-0.88, -0.67$); AAPC for ASDR: -1.34 (95% CI: $-1.38, -1.30$); AAPC for age-standardized DALYs rates: -1.24 (95% CI: $-1.31, -1.18$)] (Figure 1 and Table S2). Joinpoint regression analysis indicated that the most pronounced decline in global Thalassemia trends occurred between 1993 and 2019 [APC: -0.76 (95% CI: $-0.82, -0.70$)] (Figure 1). Trends in ASDR and age-standardized DALYs rates were broadly consistent, with the most pronounced decline occurring between 2004 and 2007 [APC for ASDR: -2.63 (95% CI: $-2.96, -1.78$); APC for ASDR: -2.55 (95% CI: $-2.84, -0.98$)] (Figure 1 and Table S2). In contrast, from 1990 to 2021, SCD exhibited a significant global increase across all ASRs [AAPC for ASR: 1.47 (95% CI: $1.45, 1.48$); AAPC for ASDR: 1.44 (95% CI: $1.41, 1.47$); AAPC for age-standardized DALYs rates: 1.46 (95% CI: $1.43, 1.49$)] (Figure 1 and Table S2). Notably, in contrast to the sustained increase in ASPR, global SCD trends exhibited a slow upward trajectory in both ASDR and age-standardized DALY rates between 2000 and 2009 [APC for ASDR: 0.25 (95% CI: $0.14, 0.35$); APC for age-standardized DALY rates: 0.03 (95% CI: $-0.12, 0.16$)] (Figure 1 and Table S2).

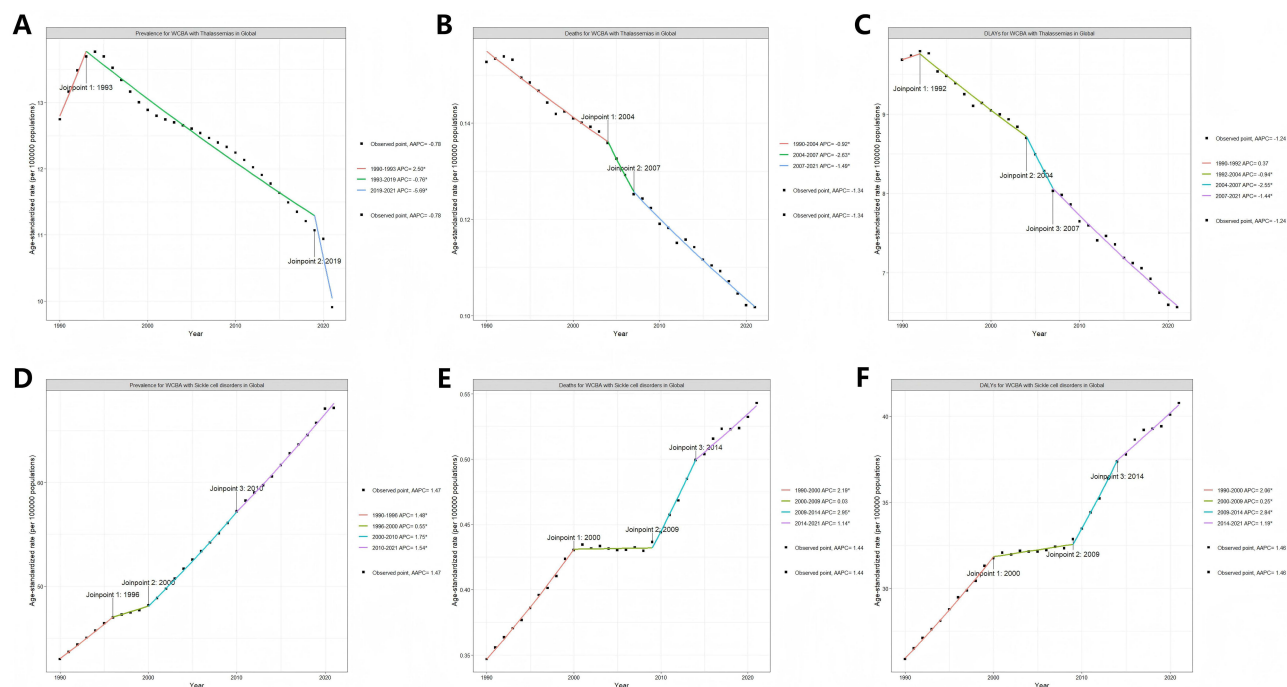


Figure 1 The APC and AAPC for the burden of hemoglobinopathies in WCBA at the global level based on the joinpoint regression analysis model. (A) ASPR of thalassemia; (B) ASDR of thalassemia; (C) age-standardized DALYs rates of thalassemia; (D) ASPR of SCD; (E) ASDR of SCD; (F) age-standardized DALYs rates of SCD. APC, annual percent change. AAPC, average annual percent change. * $p < 0.05$.

Abbreviations: WCBA, Women of Childbearing Age; ASPR, age-standardized prevalence rates; ASDR, age-standardized deaths rates; DALYs, Disability-Adjusted Life-Years; SCD, Sickle cell disorders.

Age, Period and Birth Cohort Effects on Hemoglobinopathies of WCBA

The effects of age, period, and birth cohort on hemoglobinopathies among WCBA, derived from the age-period-cohort model, are illustrated in Figure 2. Globally, the age effect exhibits an overall decreasing pattern, with the highest risk observed in the 15–19 age group for both thalassemia and SCD. Regarding period effects, thalassemia prevalence, deaths, and DALYs rates show a consistent downward trend, whereas SCD prevalence, deaths, and DALYs rates demonstrate

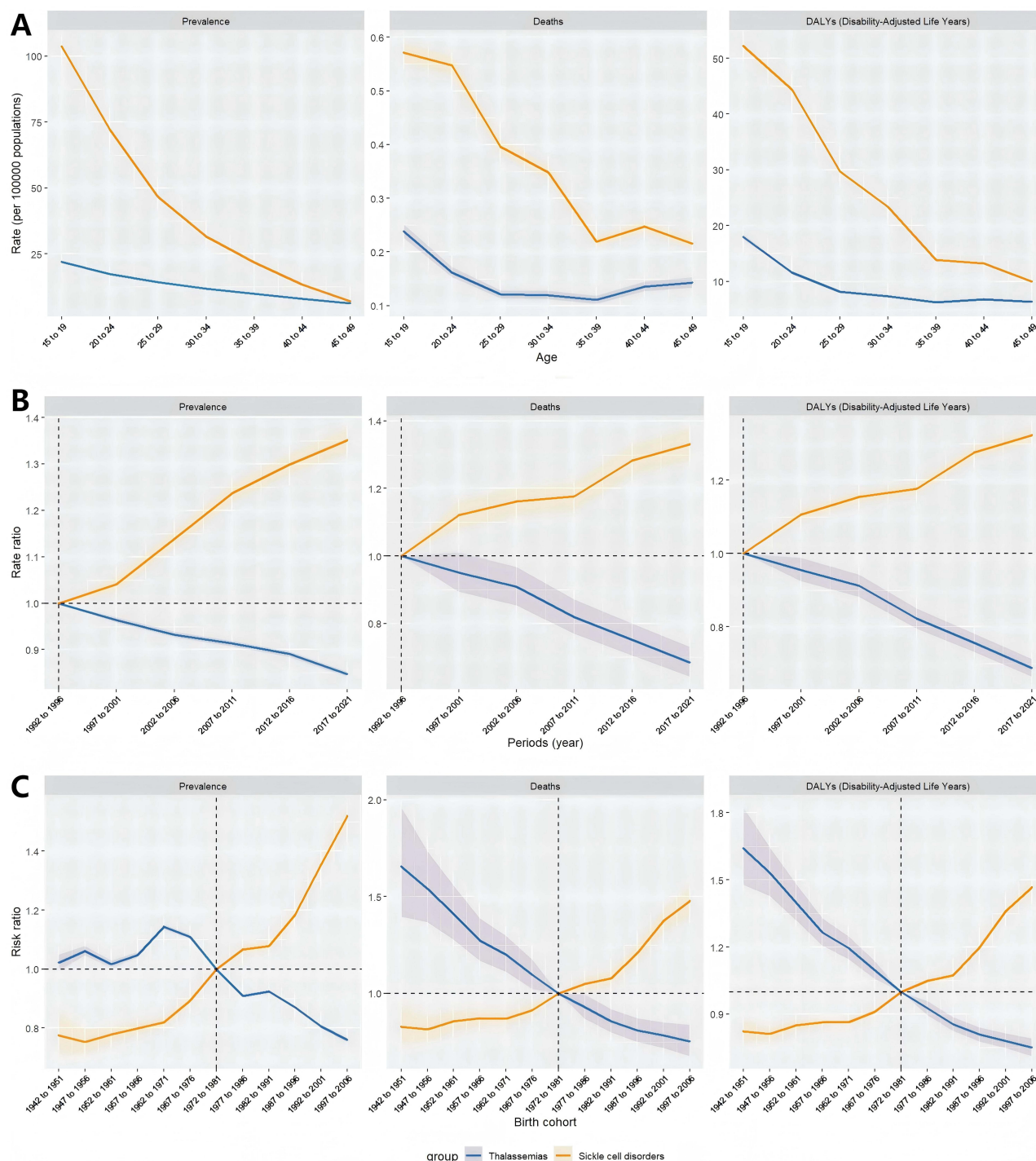


Figure 2 Age, period and birth cohort effects on the burden of thalassemia in WCBA by Age-period-cohort models. **(A)** Age effect; **(B)** Period effect; **(C)** Cohort effect. **Abbreviation:** WCBA, Women of Childbearing Age.

a consistent upward trend, presenting diametrically opposed patterns. Regarding cohort effects, the three indicators for thalassemia reached their highest relative risks in early birth cohorts, subsequently declining to the lowest levels in cohorts born at the end of the 20th century. Conversely, the relative risk for SCD was lowest in mid-period birth cohorts, rising steadily thereafter to peak in cohorts born at the end of the 20th century.

Decomposition Analysis of Hemoglobinopathy Burden Among WCBA

As illustrated in Figure 3 and Table S3, decomposition analysis revealed distinct patterns of burden drivers for thalassemia and SCD within the WCBA framework. Between 1990 and 2021, the global prevalence of thalassemia showed no significant overall change, though demographic factors contributed in differing directions. Population growth increased prevalence by approximately 772.16%, while ageing (−146.77%) and epidemiological improvements (− 525.39%) largely offset this increase (Table S3). Conversely, deaths and DALYs declined overall, primarily driven by epidemiological improvements, contributing 746.54% and 562.14% respectively (Table S3). However, in Low-middle SDI and Low SDI regions, deaths and DALYs exhibited an increase, presenting a trend contrary to the global overall pattern. Unlike thalassemia, the global prevalence of SCD increased by 53.75% and 63.79% due to population growth and epidemiological changes respectively between 1990 and 2021. The rise in deaths was similarly driven primarily by population growth (+49.28%) and epidemiological factors (+59.15%), while the rise in DALYs was attributable to population growth (+50.98%) and epidemiological

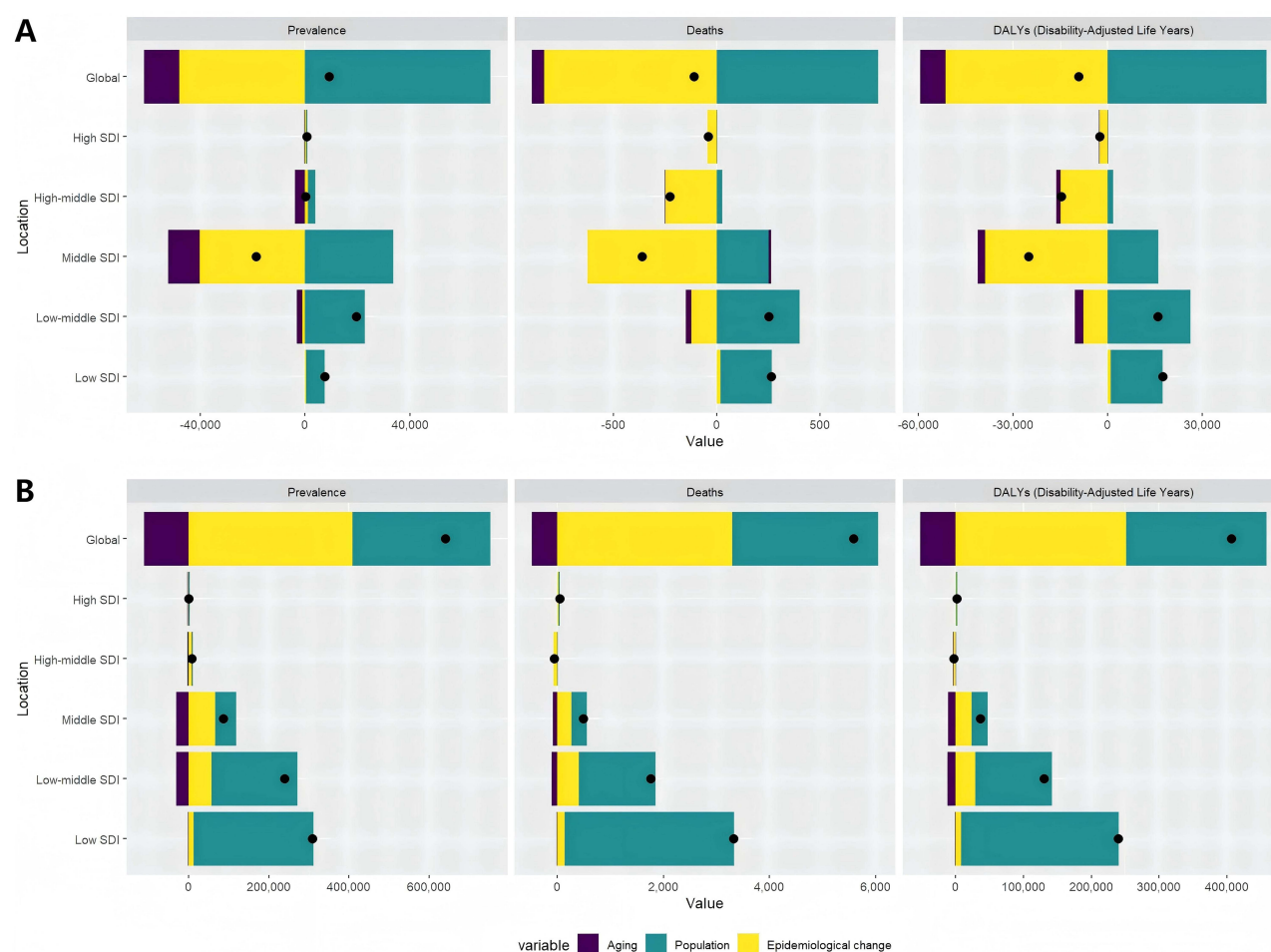


Figure 3 Analysis of burden changes for hemoglobinopathies among WCBA from 1990 to 2021, based on population-level factors including shifts in population size, ageing, and epidemiological transitions. (A) thalassemia; (B) SCD.

Abbreviations: WCBA, Women of Childbearing Age; SCD, Sickle cell disorders.

shifts (+61.82%) ([Table S3](#)). Among different SDI regions, the Low SDI region exhibited the most pronounced increase, with prevalence and DALYs rising by nearly 96.88% and 97.14% respectively ([Table S3](#)).

Frontier Analysis of Hemoglobinopathies Burden Among Women of Childbearing Age

Using 2021 data, a frontier analysis was conducted based on the relationship between SDI and the ASPR, ASDR, and age-standardized DALYs rates for hemoglobinopathies ([Figures 3, 4](#), and [Table S4](#)). For thalassemia, countries with SDI values between 0.2 and 0.5 tended to lie closer to the frontier fit line, exhibiting relatively smaller effect differences. However, when SDI rose above 0.5, the differences progressively increased ([Table S4](#)). In frontier analyses based on ASPR and SDI, the five countries with the greatest effective differences (49.95–104.36) exhibited SDI levels concentrated between 0.47 and 0.68, including Cambodia, Laos, Thailand, Maldives, and Myanmar ([Figure 4](#) and [Table S4](#)). In frontier analyses based on ASDR and SDI, the top five countries (0.70–1.09) exhibited SDI levels ranging from 0.35 to 0.73, including Guinea-Bissau, Pakistan, Kiribati, Seychelles, and Cambodia ([Figure 3](#) and [Table S4](#)). In the frontier analysis based on age-standardized DALYs rates and SDI, the top five countries (43.31–68.33) exhibited SDI levels ranging from 0.35 to 0.53, including Guinea-Bissau, Pakistan, Kiribati, Cambodia, and Laos ([Figure 3](#) and [Table S4](#)).

Conversely, for SCD, countries with SDI between 0.2 and 0.5 were generally distant from the frontier fit line, with the most pronounced divergence observed in those with SDI between 0.3 and 0.4 ([Figure 5](#) and [Table S4](#)). In frontier analysis based on ASPR and SDI, the five countries with the greatest effective variation (618.00–975.17) exhibited SDI levels between 0.29 and 0.75, including Bahrain, Sierra Leone, Benin, Burkina Faso, and Togo ([Figure 4](#) and [Table S4](#)). In the frontier analysis based on ASDR and SDI, the top five countries (6.66–11.74) exhibited SDI levels ranging from 0.29 to 0.41, comprising Togo, Benin, Guinea, Burkina Faso, and The Gambia ([Figure 4](#) and [Table S4](#)). In the frontier analysis based on age-standardized DALY rates and SDI, the top five countries (432.73–784.39) exhibited SDI levels ranging from 0.29 to 0.41, comprising Togo, Benin, Guinea, Burkina Faso, and Sierra Leone ([Figure 4](#) and [Table S4](#)).

Predictive Analysis of the Global Burden of Hemoglobinopathies Among Women of Childbearing Age

From 2021 to 2030, the global burden of thalassemia among WCBA is projected to continue declining ([Figure 6](#) and [Table S5](#)). By 2030, the number of cases is estimated at approximately 99,615, with an ASPR of 4.70 per 100,000; deaths will remain around 1,853 cases, yielding an ASDR of 0.09 per 100,000, with total DALYs reaching 116,598 (ASR: 5.66 per 100,000 population), all showing a downward trend compared to 2022. In contrast, the global burden of SCD in the WCBA continues to rise ([Figure 6](#) and [Table S5](#)). Projections for 2030 indicate a prevalence of 1,481,259 cases, with an ASR of 73.97 per 100,000; approximately 12,128 deaths, yielding an ASDR of 0.59 per 100,000; and total DALYs projected at 910,141, corresponding to an ASR of 44.92 per 100,000 ([Figure 6](#) and [Table S5](#)).

Discussion

This study utilised the latest GBD 2021 data to explore for the first time the epidemiological trends, regional, aetiological, and socioeconomic disparities of hemoglobinopathies among WCBA, while assessing the gap between the current situation and the Sustainable Development Goals. Findings indicate that between 1990 and 2021, the global burden of thalassemia in WCBA showed an overall downward trend, whilst SCD exhibited a significant increase. The patterns of change for both conditions differed markedly across regions and socio-demographic levels. These results suggest that although hemoglobinopathies have been partially controlled globally, the burden of SCD continues to intensify, particularly in countries with low socio-demographic levels. This poses a significant challenge to the health of WCBA worldwide that must not be overlooked.

The global decline in thalassemia burden among WCBA provides robust evidence-based support for preventive systems encompassing premarital/prenatal screening, genetic counselling, and newborn testing, signifying the precision and continuous optimisation of regional public health strategies.^{15,29,30} These interventions not only reduce the probability of severe cases being born but also assist WCBA in making more informed reproductive decisions during the preconception phase.³¹ Moreover, regular blood transfusions, iron chelation therapy, and haematopoietic stem cell

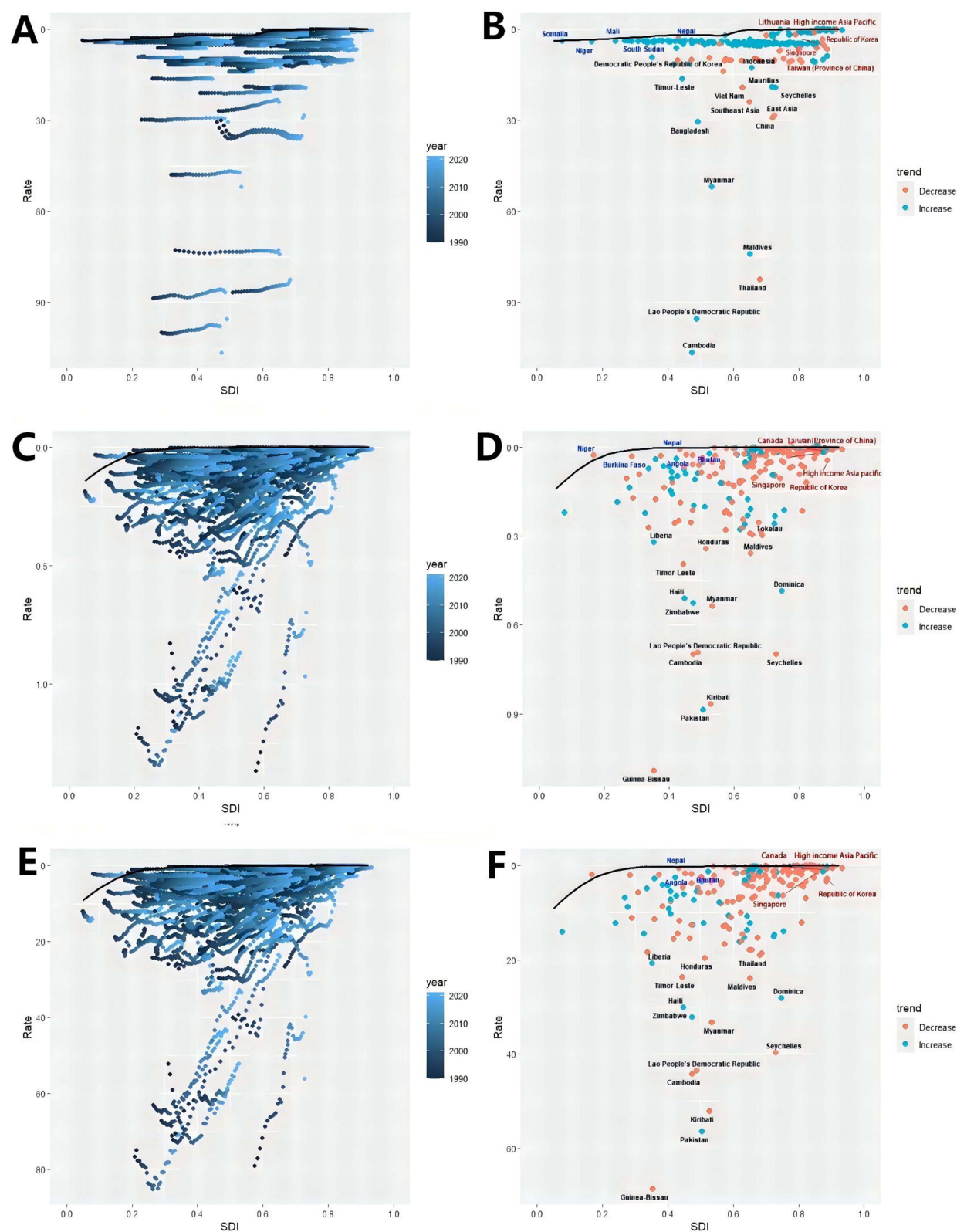


Figure 4 Frontier analysis of the relationship between SDI and the burden of thalassemia in WCBA in 2021. (A) and (B) Frontier analysis of ASPR; (C) and (D) Frontier analysis of ASDR; (E) and (F) Frontier analysis of age-standardized DALYs rates.

Abbreviations: WCBA, Women of Childbearing Age; ASPR, age-standardized prevalence rates; ASDR, age-standardized death rates; DALYs, disability-adjusted life-years.

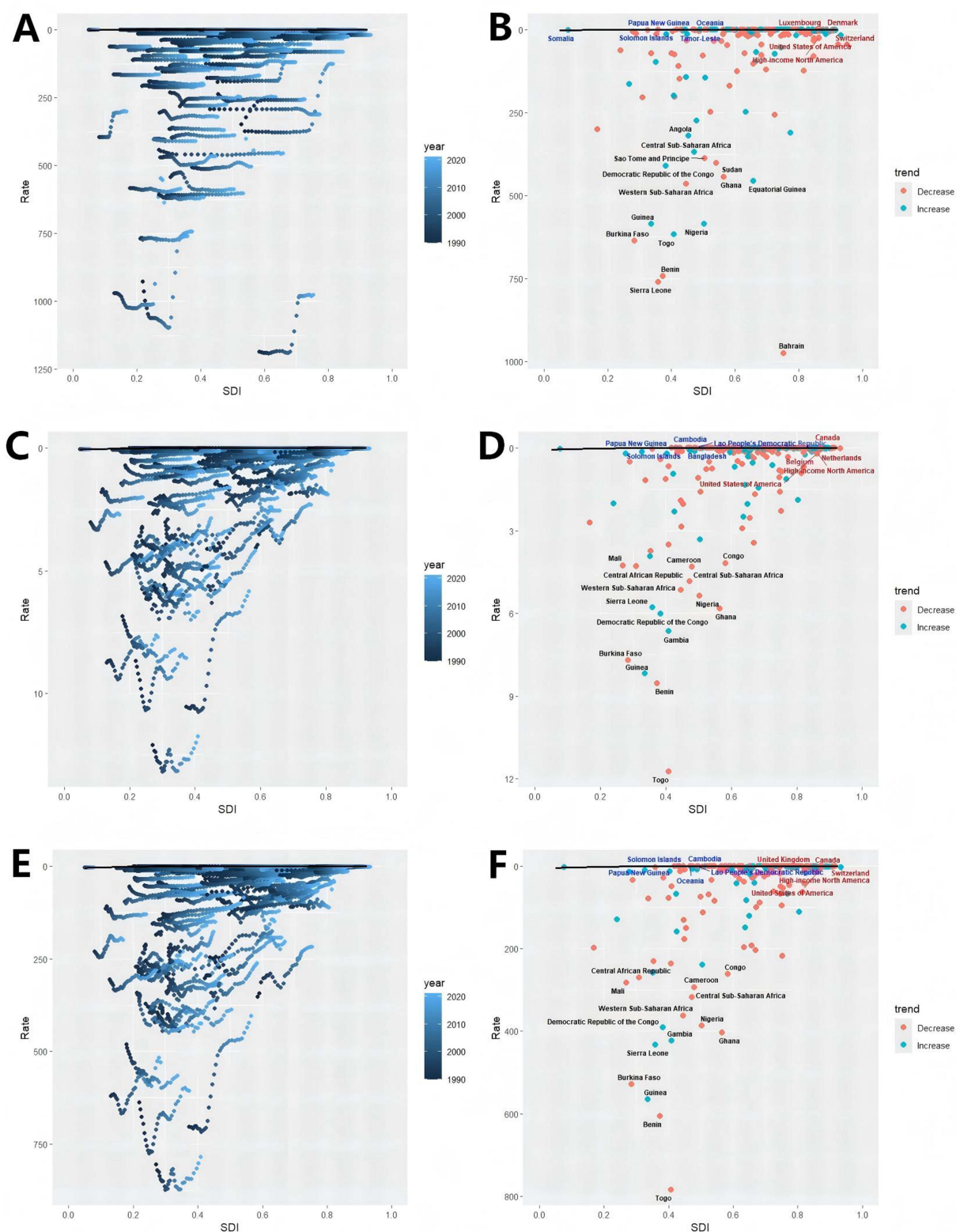


Figure 5 Frontier analysis of the relationship between SDI and the burden of SCD in WCBA in 2021. (A) and (B) Frontier analysis of ASPR; (C) and (D) Frontier analysis of ASDR; (E) and (F) Frontier analysis of age-standardized DALY rates.

Abbreviations: SCD, Sickle cell disorders; WCBA, Women of Childbearing Age; ASPR, age-standardized prevalence rates; ASDR, age-standardized death rates; DALYs, Disability-Adjusted Life-Years.

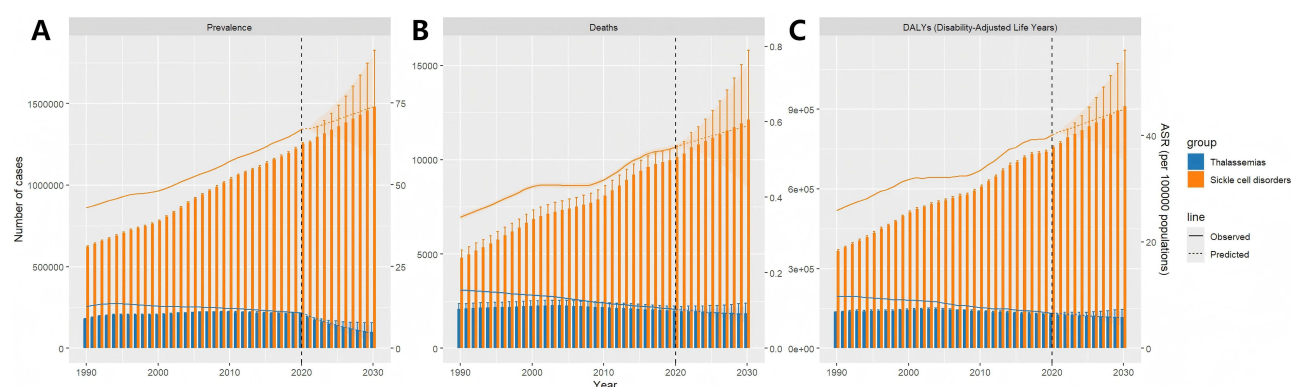


Figure 6 Projected burden of hemoglobinopathies in women of childbearing age (WCBA) from 1990 to 2030 based on the Bayesian Age-Period-Cohort (BAPC) model. **(A)** Prevalence; **(B)** Deaths; **(C)** DALYs.

Abbreviations: ASR, denotes age-standardized rates; BAPC, refers to the Bayesian Age-Period-Cohort model.

transplantation have markedly improved patient quality of life, enabling some women with thalassemia to successfully enter the childbearing stage.³² Notably, some middle- and high-SDI countries have made considerable progress in reducing disease birth rates. Conversely, in low-SDI nations, limited screening coverage leaves many pregnant women exposed to risks including severe anemia, gestational hypertension, and foetal growth restriction.³³ Collectively, these findings demonstrate that the decline in thalassemia reflects not only a population-wide trend but also the direct impact of preconception and antenatal healthcare safeguards for WCBA.

In contrast, the rising global burden of SCD in WCBA regions presents a distinct challenge. This phenomenon primarily stems from population growth and improved childhood survival rates, which have increased the number of women entering childbearing age. However, preconception screening and antenatal care standards have failed to keep pace, creating a significant gap.^{14,34,35} Furthermore, the hypercoagulable state and haemodynamic alterations during pregnancy exacerbate the vascular obstruction and haemolytic pathology associated with SCD, markedly increasing the risks of pre-eclampsia, preterm birth, and stillbirth.³⁶ Consequently, improvements in childhood survival have not translated into reduced maternal health burdens, instead concentrating risks within the WCBA. We also note that SCD burdens remain particularly severe in some low SDI regions, primarily attributable to inadequate carrier screening and genetic counselling coverage, limited access to critical treatments such as blood transfusions and hydroxyurea, and the absence of multidisciplinary antenatal management systems.^{37,38} Therefore, for women of childbearing age, there is an urgent need to implement a synchronised intervention system during both preconception and pregnancy. This system should centre on genetic counselling, standardized blood transfusion support, and comprehensive multidisciplinary follow-up throughout pregnancy, thereby systematically reducing the risk of adverse maternal and infant outcomes associated with SCD.³⁹

This study's age-period-cohort analysis reveals generational patterns in the burden of hemoglobinopathies among WCBA women. Age effects indicate the highest risk among 15–19-year-old WCBA, primarily attributable to physiological inflection points during adolescence and early pregnancy (rapidly increasing iron demand, haemodynamic and haemostatic state remodelling). This aligns with mechanisms amplifying anemia and related complications during gestation, and is highly consistent with the additional burden of eclampsia, infection, and preterm birth inherent in adolescent pregnancies in resource-constrained settings.^{40,41} Period effects reveal a divergent trajectory: WCBA thalassemia rates continue to decline due to carrier screening, preconception/prenatal testing, and expanded standardized treatment, whereas SCD rates persistently rise due to inadequate prevention and control. This contrast directly reflects disparities in public health investment and accessibility between the two conditions.^{14,42} Cohort effects further reveal: Thalassemia risk declines in newer birth cohorts, reflecting intergenerational gains from screening and genetic counselling, whereas SCD risk increases in more recent cohorts. This indicates that improved childhood survival has not translated into reduced perinatal burden, instead manifesting concentrated during pregnancy.^{30,37} Recently, the WHO's inaugural global guidelines elevated the maternal deaths risk in SCD pregnancies to 4–11 times that of the general

population, underscoring the imperative for multidisciplinary management and preventive interventions.³⁴ Consequently, prevention strategies must be advanced to adolescence and the preconception period, complemented by reinforced standardized pathway management during pregnancy, to genuinely alleviate the hemoglobin disorder burden among women of childbearing age.

Decomposition analysis indicates that the decline in thalassemia burden in WCBA regions primarily stems from epidemiological improvements rather than demographic factors, underscoring the importance of differentiated public health governance and sustained capacity enhancement.^{10,43} Conversely, the increase in SCD burden is chiefly attributable to population expansion and epidemiological factors, demonstrating that relying solely on single-dimensional interventions during women's reproductive years proves insufficient to alleviate the burden.^{14,44} Combining SDI stratification results reveals that women in low and low-to-medium SDI regions bear the heaviest burden, reflecting the concentrated manifestation of health inequalities in pre-pregnancy screening coverage and antenatal care management.⁴⁵ Thus, decomposition analysis not only uncovers sources of disparity but also guides policy formulation: prioritising expansion of pre-pregnancy screening and genetic counselling in regions with rapid population growth, while strengthening antenatal care management and treatment accessibility in areas with inadequate healthcare improvements.⁴⁶

Frontier analysis further reveals a mismatch between socio-demographic levels and the hemoglobinopathy burden among WCBA. Regarding thalassemia, some low-to-medium SDI countries approach the theoretical frontier, demonstrating that even with limited resources, rational screening and genetic counselling can significantly improve health outcomes for WCBA.¹⁵ Conversely, in certain medium-to-high SDI countries, the disease burden remains higher than expected, potentially indicating deficiencies in policy implementation and resource utilisation efficiency. In contrast, SCD in low-SDI countries lies far from the frontier fit line, indicating that socioeconomic development has not translated into health gains for women of reproductive age.^{36,47,48} This divergence thus not only highlights interregional inequalities but also reflects gendered health disparities: women's reproductive health needs are frequently neglected in low-resource settings.

Finally, predictive analyses further underscore future challenges. The thalassemia burden in the WCBA is projected to continue declining until 2030, indicating that sustained implementation of existing interventions will further improve women's reproductive health.¹⁵ However, the SCD burden in the WCBA is expected to persistently rise, signifying that unless SCD is prioritised in maternal and child health agendas, its threat to women's reproductive health will intensify. Consequently, policymakers may need to promote preconception screening and genetic counselling in low-SDI regions, while expanding antenatal follow-up and multidisciplinary management to reduce the future SCD burden among WCBA women.³⁷ Given the multifactorial aetiology of hemoglobinopathies, intersectoral collaboration tailored to local contexts is essential. This requires integrated approaches addressing quality nutrition, maternal healthcare, genetic disease management, and potential social barriers to accelerate sustainable development goals for reducing hemoglobinopathy burdens among women of reproductive age.

It should be noted that this study retains certain limitations. Firstly, the hemoglobinopathies examined here encompass only thalassemia and SCD, with other subtypes excluded due to missing GBD data. This gap constrains our ability to explore these nuances; future research should integrate clinical registry data with GBD estimates to elucidate the burden of all hemoglobinopathies within the WCBA. Secondly, healthcare capacity and diagnostic systems in resource-poor regions are comparatively weak, potentially leading to underdiagnosis or misdiagnosis of hemoglobinopathies and consequently underestimating the disease burden. Thirdly, the GBD database relies on data modelling without processing raw data. Fourthly, the GBD database cannot fully account for genetic diversity and genotypic variations across different ethnicities and populations, which are critical for understanding the disease spectrum of thalassemia and SCD, as well as maternal risks. Consequently, this study requires further field research covering extensive clinical cohorts to calibrate and expand upon the conclusions drawn from this analysis.

Conclusion

In summary, hemoglobinopathies remain a major challenge for development and health in the WCBA. This study demonstrates that the burden of thalassemia in the WCBA declined overall between 1990 and 2021, while SCD increased significantly, with marked variations across regions and socio-demographic strata. The reduction in thalassemia primarily resulted from the expansion of screening, genetic counselling, and standardized treatment, whereas the rise in SCD was

closely linked to population growth and inadequate healthcare resources. Projections indicate that by 2030, the burden of thalassemia will continue to decrease, whereas SCD will intensify further, particularly in regions with low SDI. Future strategies should focus on expanding preconception screening and genetic counselling tailored to local contexts, alongside strengthening multidisciplinary antenatal management and treatment accessibility. This approach aims to achieve a sustained reduction in the burden of hemoglobinopathies and enhance global women's reproductive health.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

The data used in this study was obtained from the GBD database, which is publicly available and does not require additional ethical approval. The GBD database has undergone ethical review, and the original data collectors obtained informed consent from the patients. Therefore, this study was granted an exemption by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University. We confirm that this study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest regarding this manuscript.

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