Global, regional, and national burden of thalassemia, 1990–2021: a systematic analysis for the global burden of disease study 2021

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Summary

Background Anemia is a significant contributor to the global disease burden, of which thalassemia is the most common hereditary anaemic disease. Previous estimates were based on data that were geographically limited and lacked comprehensive global analysis. This study provides the prevalence, incidence, mortality and disability-adjusted life years (DALYs) of thalassemia in 204 countries and regions of thalassemia between 1990 and 2021, focusing on the age structure and time trends of the disease burden. To provide effective information for health policy, allocation of medical resources and optimization of patient management programs.

Methods Using the standardised Global Burden of Disease (GBD) methodologies, we aimed to derive a more precise representation of the health burden posed by thalassemia by considering four distinct types of epidemiological data, namely the incidence at birth, prevalence, mortality and DALYs. The presented data were meticulously estimated and displayed both as numerical counts and as age-standardised rates per 100,000 persons of the population, accompanied by uncertainty interval (UI) to highlight potential statistical variability. The temporal trends spanning the years 1990–2021 were subjected to a rigorous examination utilizing Joinpoint regression analysis. This methodological approach facilitated the computation of the annual percentage change (APC) and the average annual percentage change (AAPC), along with their corresponding 95% confidence intervals (CIs).

Findings Globally, the age-standardized prevalence rates (ASPR), age-standardized incidence rates (ASIR), age-standardized mortality rates (ASMR), and age-standardized DALYs rates for thalassemia in 2021 were 18.28 per 100,000 persons (95% UI 15.29–22.02), 1.93 per 100,000 persons (95% UI 1.51–2.49), 0.15 per 100,000 persons(95% UI 0.11–0.20), and 11.65 per 100,000 persons (95% UI 8.24–14.94), respectively. Compared to 1990, these rates have decreased by 0.18 (95% UI −0.22 to −0.14), 0.25 (95% UI −0.30 to −0.19), 0.48 (95% UI −0.60 to −0.28), and 0.49 (95% UI −0.62 to −0.29) respectively. In 2021, the ASIR of thalassemia was highest in East Asia at 7.35 per 100,000 persons (95% UI 5.37–10.04), and ASMR was highest in Southeast Asia at 0.37 per 100,000 persons (95% UI 0.29–0.45).Gender comparisons showed negligible differences in disease burden, with the highest prevalence noted in children under five, decreasing with age. The global ASPR and ASMR declined from 1990 to 2021 overall, though an increasing trend in prevalence was found among the elderly. Joinpoint analysis revealed that the global ASPR increased between 2018 and 2021 (APC = 9.2%, 95% CI: 4.8%–13.8%, P < 0.001), ASIR decreased (APC = −7.68%, 95% CI: −10.88% to −4.36%, P < 0.001), and there was a significant rise in ASMR from 2019 to 2021 (APC = 4.8%, 95% CI: 0.1%–9.6%, P < 0.05). Trends in ASPR and ASMR varied across regions, with notable changes in South Asia.

Interpretation The global burden of thalassemia, reflected in its prevalence, incidence, mortality, and DALYs, exhibits significant disparities. Geographic and demographic shifts in disease distribution have been observed from 1990 to 2021, with an overall decrease in burden, yet an increase in cases among the elderly population. Analysis of

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epidemiological trends over time highlights the influence of health policies and significant public health interventions on thalassemia outcomes. There data are crucial for healthcare professionals, policymakers, and researchers to refine and enhance management strategies, aiming to further mitigate thalassemia's global impact.

Keywords: Thalassemia; Epidemiology; Age structure analysis; Joinpoint regression analysis

Research in context

Evidence before this study
Thalassemia, one of the most prevalent hereditary diseases globally, recognized by the World Health Organization (WHO) as a major global health concern included in its global disease burden assessments. Past epidemiological estimates of thalassemia were primarily sourced from published research reviews, national registries, and data from the now-defunct WHO Hemoglobin Disorders Working Group, with the last authoritative report released by the WHO in 2008. These studies highlighted the highest prevalence of thalassemia in the Mediterranean, the Middle East, and Southeast Asia, noting that factors like population migration are altering its global distribution.

Added value of this study
As part of the GBD 2021 study, this research represents the inaugural utilization of GBD data to systematically evaluate the global disease burden of thalassemia in terms of prevalence, incidence, mortality, and disability-adjusted life years (DALYs), while also conducting an analysis of population characteristics and temporal trends. The study unveils the uneven global distribution of thalassemia, its increasing prevalence among elderly patients, and significant gender disparities within specific age groups and over time. Particularly noteworthy is the study's application of Joinpoint regression analysis to assess temporal trends in the burden of thalassemia, pinpointing key moments or pivotal years of substantial changes in disease indicators.

Implications of all the available evidence
These findings provide the latest and most authoritative insights into the disease burden of thalassemia, catering to a global audience of healthcare professionals, including physicians, health policy makers, epidemiologists, and researchers specializing in thalassemia. Highlighting the critical need for continuous improvements in the diagnosis, treatment, and management of thalassemia, this study advocates for the refinement of management strategies and the development of innovative therapeutic approaches.

Introduction

Thalassemia is one of the most common hereditary diseases in the world. It is a heterogeneous hereditary hemoglobin disease characterized by the deficiency of hemoglobin synthesis caused by mutations in the α, β and δ globin genes, resulting in ineffective erythropoiesis.[1,2] with the severity depending on the affected globin chain. Thalassemias are classified into α-thalassemia, β-thalassemia, δβ-thalassemia, and the less common forms such as γδβ-thalassemia.The most prevalent are α- and β-thalassemia.[3] Clinical manifestations range from asymptomatic carriers to severe transfusion-dependent thalassemia(TDT), with β-thalassemia being the most common type requiring regular blood transfusions. Patients with TDT require lifelong blood transfusions and iron chelation therapy to manage iron overload, which can cause serious complications such as impaired growth, delayed sexual maturity, disrupted endocrine homeostasis, and damage to the heart, liver, kidneys, and bones. These complications can severely affect the quality of life and pose significant health risks.

Untreated, severe β-thalassemia can be fatal, often before the age of three.[4–8] The World Health Organization (WHO) has classified thalassemia as a major global health concern and includes it in the assessment of the global burden of disease.

Most previous estimates of thalassemia incidence and mortality are derived from published research reviews, national registries, and data collected by the now-defunct WHO Hemoglobin Disorders Working Group.[9–11] According to a 2008 report by the WHO, over 40,000 babies are born with β-thalassemia annually, with approximately 25,500 of these cases being transfusion-dependent β-thalassemia. For every thousand carriers of the thalassemia gene, outcomes differ starkly between high- and low-income countries. While most carriers in high-income countries may experience chronic disease conditions, in low-income countries, most children with the disease die before the age of five. Hemoglobinopathies, including thalassemia, account for 3.4% of global mortality in children under five and 6.4% in Africa.[12]

Previous studies have found that thalassemia prevalence is highest in the Mediterranean, the Middle East, and Southeast Asia. However, migration has led to a shift in its global distribution. As a result, β-thalassemia has become increasingly common in traditionally non-endemic areas, including Western Europe and North America.[13,14] According to a 39-year follow-up study, the lifetime cost of treating TDT is estimated at $5.4 million. The majority of this cost is attributed to iron chelation therapy (68%, or $3.7 million) and blood transfusions (30%, or $1.6 million). Implementing cost-saving measures in iron chelation therapy could reduce the estimated lifetime cost by about 33%, bringing it down to $4.2 million. Therefore, the lifetime cost of TDT is projected to range from $5 million to $5.7 million.[15]

The Global Burden of Disease (GBD) study is a reliable tool for understanding the current assessment of the prevalence, incidence, mortality, and disability-adjusted life years (DALYs) due to thalassemia. In previous assessments, thalassemia was often discussed as part of the broader disease burden of anemia.[16–18] In this study, we utilize the GBD statistical model to systematically describe the disease burden of thalassemia including prevalence, incidence, mortality, and DALYs, in 2021, with a focus on age and gender distribution and time trends. This analysis is helpful for clinicians, epidemiologists, and health policymakers to further optimize the allocation of medical resources and to formulate more effective public health strategies.

Methods
Data acquisition and download
The 2021 GBD study offers an in-depth assessment of health detriments associated with 369 diseases, injuries, and impairments, as well as 88 risk factors, encompassing 204 nations and territories, utilizing the most recent epidemiological data and enhanced standardized methodologies.[19] In this investigation, the determinations and their 95% uncertainty interval (UI) for prevalence, incidence, mortality and DALYs relating to thalassemia were drawn from the GBD 2021 data. Additionally, the study employed the sociodemographic index (SDI), a measure that quantifies a region's socio-demographic progression based on income, education, and fertility circumstances.[20]

Burden description
In 2021, a comprehensive assessment was conducted to quantify the national burden of thalassemia, encompassing its prevalence, incidence, mortality, and DALYs. Additionally, the investigation delved into the demographic variables influencing thalassemia's impact, examining the distribution of the disease's burden across different age groups and between genders.

Joinpoint regression analysis
In the present study, the Joinpoint regression analysis model was employed—a statistical methodology commonly engaged in epidemiological research to assess temporal trends in disease prevalence or mortality.[21] This model adeptly identifies and quantitatively characterizes significant change points within the time-series data concerning thalassemia prevalence across global, continental, and national scopes. The model facilitated the computation of the annual percent change (APC) and its accompanying 95% confidence interval (CI) to delineate prevalence trends across delineated time frames. Moreover, for a holistic appraisal of the observed trends, the average annual percent change (AAPC) was also calculated, encapsulating aggregated trend data spanning the study period of 1990–2021. From a statistical standpoint, an APC or AAPC estimate, alongside its 95% CI lower bound exceeding zero, denotes an upward trajectory in the specified interval. In contrast, an APC or AAPC estimate coupled with a 95% CI upper bound falling below zero signals a downward trend. When the 95% CI for the APC or AAPC encompasses zero, it implies that the trend has remained stable. The details of the equations and model formulation for the Joinpoint regression analysis were provided in the Supplementary Methods.

Statistics analysis
The prevalence, incidence, mortality, and DALYs was represented as a projection for every 100,000 persons individuals in the populace, inclusive of its 95% UI. All procedures for analysis and graphic representation were performed utilizing the World Health Organization's Health Equity Assessment Toolkit and the statistical computing software, R (Version 3.5.2).

Role of the funding source
The funders of the study did not participate in the design of the study, collection of data, analysis of data, interpretation of the data, or the writing of the report. The first authors had full access to the data in the study, and the corresponding authors final responsibility for the decision to submit for publication.

Results
Global level
In 2021, the worldwide number of thalassemia cases was 1,310,407 (95% UI: 1,099,973–1,572,220), with an age-standardized prevalence rates (ASPR) of 18.28 per 100,000 persons (95% UI: 15.29–22.02) (Table 1). This represents a decrease of 0.18 per 100,000 persons (95% UI: –0.22 to –0.14) from 1990 to 2021 (Table 1). However, the global incidence of thalassemia involved 119,679 cases (95% UI: 93,218–153,985), with an age-standardized incidence rates (ASIR) of 1.93 per 100,000 persons (95% UI: 1.51–2.49) (Table 1). This rate

	Prevalence (95% uncertainty interval)			Incidence (95% uncertainty interval)			Deaths (95% uncertainty interval)			DALYs (95% uncertainty interval)		
	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021
Global	1,310,407 (1,099,973–1,572,220)	18.28 (15.29–22.02)	–0.18 (–0.22 to –0.14)	119,679 (93,218–153,985)	1.93 (1.51–2.49)	–0.25 (–0.30 to –0.19)	11,087 (7882–14,110)	0.15 (0.11–0.20)	–0.48 (–0.60 to –0.28)	817,875 (578,580–1,043,254)	11.65 (8.24–14.94)	–0.49 (–0.62 to –0.29)
Low SDI	139,675 (112,677–177,213)	9.15 (7.38–11.52)	0.09 (0.07–0.11)	19,994 (14,818–26,129)	1.16 (0.86–1.51)	0.09 (0.07–0.12)	3179 (2100–4533)	0.22 (0.14–0.32)	–0.24 (–0.47 to 0.15)	264,392 (178,203–375,943)	17.18 (11.47–24.36)	–0.27 (–0.48 to 0.13)
Low-middle SDI	336,498 (271,989–426,247)	16.72 (13.52–21.10)	–0.01 (–0.10 to 0.10)	34,869 (26,204–45,282)	1.87 (1.40–2.43)	<0.01 (–0.09 to 0.13)	3732 (2438–5037)	0.19 (0.13–0.26)	–0.26 (–0.48 to 0.11)	285,453 (183,662–387,579)	14.47 (9.38–19.49)	–0.28 (–0.50 to 0.10)
Middle SDI	604,765 (500,791–731,047)	29.27 (24.14–35.43)	–0.24 (–0.27 to –0.21)	50,163 (38,363–64,831)	3.28 (2.51–4.24)	–0.31 (–0.34 to –0.27)	3126 (2517–3882)	0.13 (0.11–0.17)	–0.67 (–0.73 to –0.57)	203,519 (164,812–247,186)	9.54 (7.50–11.67)	–0.70 (–0.76 to –0.58)
High-middle SDI	192,022 (158,083–236,899)	21.48 (17.61–26.45)	0.04 (0.01–0.07)	12,833 (9710–17,017)	2.28 (1.73–3.03)	–0.03 (–0.07 to 0.01)	896 (690–1105)	0.08 (0.06–0.10)	–0.74 (–0.80 to –0.65)	55,388 (42,885–66,607)	5.70 (4.42–6.96)	–0.76 (–0.82 to –0.67)
High SDI	36,562 (30,755–43,330)	4.93 (4.14–5.85)	<–0.01 (–0.03 to 0.03)	1733 (1361–2205)	0.35 (0.27–0.44)	–0.14 (–0.22 to –0.07)	145 (112–171)	0.01 (0.01–0.02)	–0.64 (–0.70 to –0.57)	8325 (6681–9782)	0.99 (0.79–1.19)	–0.66 (–0.72 to –0.59)
Central Europe, eastern Europe, and central Asia												
Central Asia	8105 (6554–10,177)	8.36 (6.75–10.51)	0.03 (–0.01 to 0.06)	743 (566–960)	0.76 (0.58–0.98)	–0.04 (–0.10 to 0.01)	55 (40–74)	0.06 (0.04–0.08)	–0.42 (–0.61 to 0.03)	4585 (3356–6180)	4.69 (3.46–6.31)	–0.43 (–0.62 to 0.01)
Central Europe	5477 (4300–6851)	7.22 (5.64–9.09)	0.03 (–0.00 to 0.05)	221 (168–282)	0.44 (0.33–0.56)	–0.04 (–0.10 to 0.01)	9 (7–11)	0.06 (0.04–0.08)	–0.68 (–0.76 to –0.58)	569 (450–706)	0.68 (0.54–0.85)	–0.67 (–0.74 to –0.58)
Eastern Europe	11,270 (8721–14,477)	8.16 (6.26–10.53)	0.05 (0.03–0.07)	485 (357–636)	0.56 (0.41–0.74)	0.07 (0.04–0.09)	7 (5–9)	<0.01 (0.00–0.01)	–0.39 (–0.52 to –0.26)	703 (556–859)	0.54 (0.43–0.65)	–0.36 (–0.46 to –0.26)
High income Australasia	1686 (1299–2127)	7.09 (5.45–9.00)	0.03 (–0.04 to 0.12)	67 (50–86)	0.39 (0.29–0.50)	0.01 (–0.07 to 0.10)	2 (1–3)	<0.01 (<0.01 to 0.01)	–0.58 (–0.68 to –0.46)	126 (97–158)	0.51 (0.40–0.64)	–0.56 (–0.65 to –0.46)
High-income Asia Pacific	4294 (3443–5306)	3.93 (3.13–4.86)	–0.03 (–0.10 to 0.01)	120 (94–152)	0.21 (0.16–0.27)	–0.06 (–0.14 to 0.01)	16 (11–22)	0.01 (0.01–0.01)	–0.76 (–0.83 to –0.65)	891 (632–1176)	0.65 (0.48–0.84)	–0.77 (–0.83 to –0.67)
High-income North America	4163 (3568–4905)	1.53 (1.31–1.81)	–0.18 (–0.29 to –0.09)	196 (161–242)	0.10 (0.08–0.12)	–0.52 (–0.64 to –0.33)	29 (22–33)	0.01 (0.00–0.01)	–0.56 (–0.61 to –0.49)	1379 (1096–1575)	0.45 (0.36–0.51)	–0.57 (–0.63 to –0.52)
Western Europe	14,530 (12,311–17,037)	5.09 (4.27–6.01)	–0.09 (–0.11 to –0.06)	950 (722–1217)	0.48 (0.36–0.62)	0.03 (–0.01 to 0.08)	60 (50–68)	0.01 (0.01–0.01)	–0.73 (–0.76 to –0.72)	2747 (2386–3074)	0.79 (0.69–0.88)	–0.75 (–0.77 to –0.72)
Latin America and Caribbean												
Andean Latin	5421	8.32	0.13	425	0.69	0.12	38	0.06	–0.58	2418	3.67	–0.63

(Table 1 continues on next page)

	Prevalence (95% uncertainty interval)			Incidence (95% uncertainty interval)			Deaths (95% uncertainty interval)			DALYs (95% uncertainty interval)		
	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021	Counts (2021)	Age-standardised rates per 100,000 (2021)	Rate change in age-standardised rates, 1990–2021
(Continued from previous page)												
America	(4199–7153)	(6.43–11.02)	(0.07–0.19)	(303–578)	(0.51–0.92)	(0.03–0.20)	(24–54)	(0.04–0.08)	(−0.70 to −0.39)	(1624–3403)	(2.46–5.18)	(−0.74 to −0.44)
Caribbean	3813 (2957–4937)	20.32 (16.32–25.15)	0.16 (0.11–0.21)	311 (223–415)	0.81 (0.58–1.09)	0.28 (0.21–0.37)	78 (48–123)	0.17 (0.10–0.28)	0.21 (−0.15 to 0.71)	5367 (3168–8511)	12.39 (7.07–20.01)	0.14 (−0.19 to 0.62)
Southern Latin America	1292 (1011–1607)	8.37 (6.43–10.74)	0.01 (−0.06 to 0.06)	60 (46–76)	0.16 (0.12–0.20)	0.08 (0.01–0.15)	5 (4–6)	0.01 (0.00–0.01)	−0.64 (−0.73 to −0.52)	245 (187–303)	0.42 (0.31–0.52)	−0.65 (−0.73 to −0.55)
Tropical Latin America	16,135 (12,545–20,672)	8.32 (6.43–11.02)	0.15 (0.13–0.18)	1091 (797–1444)	0.66 (0.48–0.87)	0.20 (0.17–0.23)	22 (17–26)	0.01 (0.01–0.01)	−0.22 (−0.35 to −0.09)	1557 (1227–1921)	0.76 (0.59–0.94)	−0.25 (−0.35 to −0.14)
North Africa and Middle East												
North Africa and Middle East	77,104 (62,612–93,076)	12.21 (9.91–14.75)	< −0.01 (−0.04 to 0.04)	11,399 (8389–15,045)	1.99 (1.47–2.63)	0.01 (−0.09 to 0.09)	710 (522–934)	0.11 (0.08–0.15)	−0.63 (−0.74 to −0.45)	59,185 (43,874–76,167)	9.59 (7.17–12.33)	−0.64 (−0.74 to −0.43)
South Asia												
South Asia	179,136 (144,502–223,955)	10.00 (8.09–12.47)	−0.04 (−0.13 to 0.06)	18,011 (13,545–23,306)	1.19 (0.89–1.54)	−0.04 (−0.15 to 0.07)	2416 (1218–3602)	0.13 (0.07–0.20)	−0.06 (−0.42 to 0.54)	193,696 (104,093–284,797)	10.96 (5.94–15.93)	−0.09 (−0.44 to 0.48)
Southeast Asia, east Asia, and Oceania												
East Asia	532,033 (422,029–672,468)	54.26 (42.77–69.17)	−0.04 (−0.07 to −0.01)	40,542 (29,651–55,405)	7.35 (5.37–10.04)	−0.06 (−0.11 to −0.01)	1938 (1500–2435)	0.15 (0.12–0.18)	−0.76 (−0.82 to −0.67)	121,303 (96,399–148,023)	11.13 (8.85–13.73)	−0.77 (−0.83 to −0.67)
Oceania	3489 (2787–4320)	20.32 (16.32–25.15)	0.04 (−0.02 to 0.12)	475 (358–604)	2.31 (1.75–2.94)	0.14 (0.03–0.27)	31 (22–43)	0.21 (0.15–0.31)	−0.20 (−0.41 to 0.11)	2136 (1588–2873)	13.51 (9.99–18.52)	−0.21 (−0.41 to 0.06)
Southeast Asia	274,647 (224,462–336,455)	43.38 (35.4–3.19)	−0.08 (−0.17 to 0.02)	24,185 (19,159–30,678)	4.48 (3.56–5.69)	0.02 (−0.07 to 0.14)	2516 (2009–3127)	0.37 (0.29–0.45)	−0.43 (−0.55 to −0.25)	157,961 (125,451–193,257)	24.01 (18.70–29.26)	−0.46 (−0.59 to −0.26)
Sub-Saharan Africa												
Central sub-Saharan Africa	15,740 (11,707–20,616)	8.23 (6.20–10.84)	0.06 (−0.01 to 0.15)	1979 (1408–2707)	0.93 (0.66–1.27)	0.06 (−0.02 to 0.17)	200 (61–577)	0.14 (0.04–0.44)	−0.27 (−0.56 to 0.25)	15,539 (5471–42,411)	8.89 (3.01–25.90)	−0.37 (−0.61 to 0.14)
Eastern sub-Saharan Africa	57,502 (45,197–74,287)	9.75 (7.73–12.58)	0.07 (0.05–0.10)	6733 (4847–8998)	1.03 (0.74–1.37)	0.04 (0.00–0.07)	855 (531–1300)	0.16 (0.10–0.24)	−0.40 (−0.62 to 0.07)	70,117 (44,006–106,205)	12.14 (7.68–18.18)	−0.43 (−0.64 to 0.05)
Southern sub-Saharan Africa	8588 (6705–11,139)	10.24 (8.00–13.27)	0.07 (0.03–0.11)	734 (530–970)	0.94 (0.68–1.24)	0.04 (0.00–0.08)	174 (124–239)	0.21 (0.15–0.29)	0.14 (−0.14 to 0.52)	12,905 (9285–17,368)	15.56 (11.23–20.95)	0.11 (−0.16 to 0.48)
Western sub-Saharan Africa	65,082 (51,314–84,002)	9.25 (7.31–12.0)	0.06 (0.04–0.08)	9662 (7092–12,809)	1.13 (0.83–1.50)	0.06 (0.03–0.09)	1872 (1155–2839)	0.27 (0.17–0.39)	−0.28 (−0.47 to 0.00)	160,548 (98,216–246,118)	21.2 (13.09–31.89)	−0.31 (−0.50 to −0.05)

Data in parentheses represent the 95% uncertainty intervals. 'SDI' stands for Socio-demographic Index.

Table 1: Prevalent cases, incident cases, death cases and DALYs for thalassmia in 2021 for both sexes and rate change of age-standardised rates by Global Burden of Disease (GBD).

has decreased by 0.25 per 100,000 cases (95% UI: –0.30 to –0.19) between 1990 and 2021 (Table 1). The number of deaths remained at 11,087 (95% UI: 7882–14,110), with an age-standardized mortality rates (ASMR) of 0.15 per 100,000 persons (95% UI: 0.11–0.20) (Table 1), showing a decrease of 0.48 per 100,000 persons (95% UI: –0.60 to –0.28) from 1990 to 2021 (Table 1).The global disability-adjusted life years (DALYs) for thalassemia in 2021 was 817,875 (95% UI: 578,580–1,043,254) (Table 1), with an age-standardized DALYs rates of 11.65 per 100,000 persons (95% UI: 8.24–14.94), which decreased by 0.49 (95% UI: –0.62 to –0.29) between 1990 and 2021 (Table 1).

Regional level
In 2021, studies conducted at various regional levels worldwide found that the ASPR of thalassemia was highest in regions with a Middle SDI, at 29.27 per 100,000 persons (95% UI: 24.14–35.43) (Table 1). Geographically, the ASPR was highest in East Asia, at 54.26 per 100,000 persons (95% UI: 42.77–69.17), followed by Southeast Asia, at 43.38 per 100,000 persons (95% UI: 35.4–51.9) (Table 1 and Fig. 1A). By contrast, high-income regions demonstrated significantly lower ASPRs, including Australasia at 7.09 per 100,000

persons (95% UI: 5.45–9.00), Western Europe at 5.09 per 100,000 persons (95% UI: 4.27–6.01), high-income Asia Pacific at 3.93 per 100,000 persons (95% UI: 3.13–4.86), and high-income North America at 1.53 per 100,000 persons (95% UI: 1.31–1.81) (Table 1 and Fig. 1A). During the period from 1990 to 2021, changes in the ASPR varied across different world regions. A slight increasing trend was observed in regions with a Low SDI, at 0.09 per 100,000 persons (95% UI: 0.07–0.11), and High-middle SDI, at 0.04 per 100,000 persons (95% UI: 0.01–0.07) (Table 1). In contrast, regions with a High SDI showed a non-significant change of less than 0.01 per 100,000 persons (95% UI: –0.03 to 0.03), and those with a Middle SDI experienced a downward trend of –0.24 per 100,000 persons (95% UI: –0.27 to –0.21) (Table 1). Geographically, the Caribbean showed an increasing trend at 0.16 per 100,000 persons (95% UI: 0.11–0.21), as did Tropical Latin America at 0.15 per 100,000 persons (95% UI: 0.13–0.18) and Andean Latin America at 0.13 per 100,000 persons (95% UI: 0.07–0.19) (Table 1). Southeast Asia exhibited the most significant downward trend, at –0.08 per 100,000 persons (95% UI: –0.17 to 0.02), followed by South Asia at –0.04 per 100,000 persons (95% UI: –0.13 to 0.06) and East Asia at –0.04 per
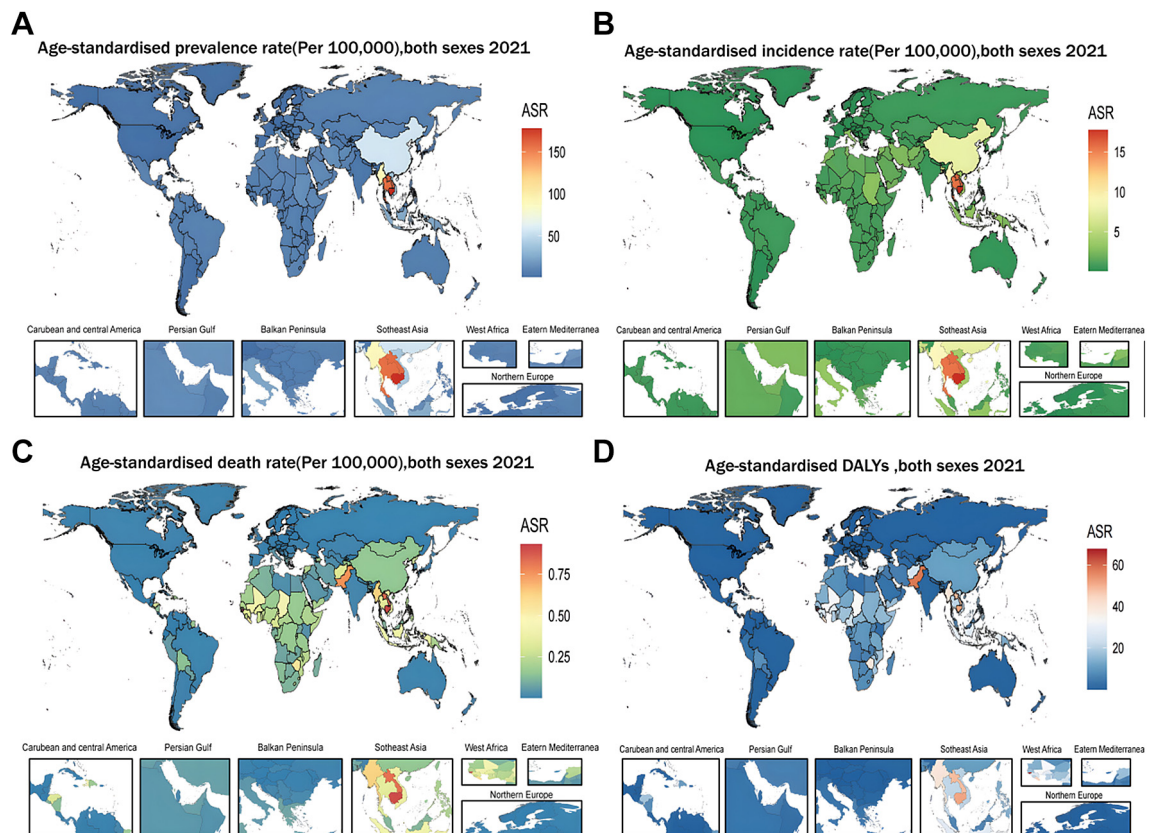
Fig. 1: Global distribution of thalassemia disease burden in 2021. (A) Age-standardized prevalence rates; (B) Age-standardized incidence rates; (C) Age-standardized mortality rates; (D) Age-standardized DALYs rates.

100,000 persons (95% UI: –0.07 to –0.01) (Table 1). The ASIR of thalassemia was highest in East Asia, at 7.35 per 100,000 persons (95% UI: 5.37–10.04), followed by Southeast Asia, at 4.48 per 100,000 persons (95% UI: 3.56–5.69) (Table 1 and Fig. 1B).

The ASMR of thalassemia was found to be highest in regions with a Low SDI, recorded at 0.22 per 100,000 persons (95% UI: 0.14–0.32), and lowest in High SDI regions at 0.01 per 100,000 (95% UI: 0.01–0.02) (Table 1). The most significant decline in the ASMR was observed in High-middle SDI regions, with a reduction of 0.74 per 100,000 persons (95% UI: –0.80 to –0.65) (Table 1). Geographically, the regions with the highest ASMR were Southeast Asia at 0.37 per 100,000 persons (95% UI: 0.29–0.45), Western sub-Saharan Africa at 0.27 per 100,000 persons, and Oceania at 0.21 per 100,000 persons (95% UI: 0.15–0.31) (Table 1 and Fig. 1C). It is noteworthy that from 1990 to 2021, the Caribbean experienced the most significant upward trend in ASMR, increasing to 0.21 per 100,000 persons (95% UI: –0.15 to 0.71). In contrast, other regions exhibited downward trends, with East Asia (–0.76 per 100,000 persons; 95% UI: –0.82 to –0.67), the High-income Asia Pacific (–0.76 per 100,000 persons; 95% UI: –0.83 to –0.65), and Western Europe (–0.73 per 100,000 persons; 95% UI: –0.76 to –0.72) showing the most pronounced declines (Table 1).

Globally, the age-standardized DALYs rate for thalassemia has also shown an overall downward trend. The most notable reductions were observed in East Asia (–0.77 per 100,000 persons; 95% UI: –0.83 to –0.67), the High-income Asia Pacific (–0.77 per 100,000 persons; 95% UI: –0.83 to –0.67), and Western Europe (–0.75 per 100,000 persons; 95% UI: –0.77 to –0.72) (Table 1 and Fig. 1D). Conversely, the regions with the highest age-standardized DALYs rates were Southeast Asia at 24.01 per 100,000 persons (95% UI: 18.70–29.26), Western sub-Saharan Africa at 21.20 per 100,000 persons (95% UI: 13.09–31.89), and Southern sub-Saharan Africa at 15.56 per 100,000 persons (95% UI: 11.23–20.95) (Table 1 and Fig. 1D).

National level

The ASPR of thalassemia ranges from approximately 15 to 22 per 100,000 individuals. Notably, Cambodia (177.47 per 100,000 persons; 95% UI: 136.14–227.35), Lao People's Democratic Republic (158.37 per 100,000 persons; 95% UI: 121.01–204.80), Thailand (157.11 per 100,000 persons; 95% UI: 126.78–195.60), Maldives (122.35 per 100,000 persons; 95% UI: 93.97–159.75), Myanmar (89.74 per 100,000 persons; 95% UI: 71.11–115.70), and China (55.43 per 100,000 persons; 95% UI: 43.61–77.78) have the highest ASPR (Fig. 1A and Supplementary Table S1). Conversely, the United States of America (1.35 per 100,000 persons; 95% UI: 1.15–1.59), Germany (1.49 per 100,000 persons; 95% UI: 1.22–1.77), Greenland (1.85 per 100,000 persons;

95% UI: 1.44–3.36), Chile (2.03 per 100,000 persons; 95% UI: 1.55–2.58), Uruguay (2.16 per 100,000 persons; 95% UI: 1.70–2.77), and Argentina (2.37 per 100,000 persons; 95% UI: 1.88–2.93) exhibited the lowest ASPR (Fig. 1A, Supplementary Table S1). From 1990 to 2021, variations in the change of the ASPR were observed across countries. Notably, Honduras (0.17 per 100,000 persons; 95% UI: 0.07–0.29), Brazil (0.15 per 100,000 persons; 95% UI: 0.13–0.18), and the United States Virgin Islands (0.15 per 100,000 persons; 95% UI: 0.03–0.27) experienced the most substantial relative increases in ASPR (Supplementary Table S2). The country-specific distribution of ASIR is detailed in Fig. 1B and Supplementary Table S3. Significant changes from 1990 to 2021 were particularly evident in Guatemala (0.34 per 100,000 persons; 95% UI: 0.16–0.50), Italy (0.30 per 100,000 persons; 95% UI: 0.22–0.38), and Germany (0.27 per 100,000 persons; 95% UI: 0.15–0.40) (Supplementary Table S4). In contrast, the most pronounced downward trends were observed in the United States of America (–0.55 per 100,000 persons; 95% UI: –0.67 to –0.36), Cyprus (–0.26 per 100,000 persons; 95% UI: –0.35 to –0.15), and Tajikistan (–0.22 per 100,000 persons; 95% UI: –0.31 to –0.12) (Supplementary Table S4).

The ASMR for the condition ranged from 0.11 to 0.20 per 100,000 population. In 2021, Guinea-Bissau (0.93 per 100,000 persons; 95% UI: 0.20–4.73), Cambodia (0.90 per 100,000 persons; 95% UI: 0.63–1.28), Lao People's Democratic Republic (0.82 per 100,000 persons; 95% UI: 0.58–1.13), Pakistan (0.75 per 100,000 persons; 95% UI: 0.34–1.15), and Kiribati (0.70 per 100,000 persons; 95% UI: 0.47–1.03) had the highest ASMR (Fig. 1C and Supplementary Table S5). From 1990 to 2021, the regions with the largest increases in ASMR were Taiwan (a province of China) (1.12 per 100,000 persons; 95% UI: 0.69–1.60), Turkmenistan (0.74 per 100,000 persons; 95% UI: 0.35–3.71), and Kazakhstan (0.69 per 100,000 persons; 95% UI: 0.35–3.74) (Supplementary Table S6). It is important to note that the confidence intervals for Turkmenistan and Kazakhstan suggest uncertainty in these estimates, possibly due to data limitations. Conversely, the countries with the most significant decreases in ASMR were Grenada (–0.99 per 100,000 persons; 95% UI: –1.00 to –0.98), Antigua and Barbuda (–0.84 per 100,000 persons; 95% UI: –0.90 to –0.75), and Singapore (–0.83 per 100,000 persons; 95% UI: –0.87 to –0.79) (Supplementary Table S6). For more information about DALYs, see Fig. 1D and Supplementary Tables S7 and S8.

Age and sex patterns

In 2021, the highest global prevalence rates of thalassemia was observed in children under the age of five, decreasing with age. The prevalence rates among males was higher than females up to the age of 35, after which

it was lower until the age of 69, with no significant gender differences observed beyond this age (Fig. 2A; Supplementary Tables S9 and S10). The hereditary nature of thalassemia manifested in a higher incidence rate within the under-5 age group. In 2021, the incidence rates of new thalassemia cases was higher in males (69,033) compared to females (50,645) (Fig. 2B; Supplementary Tables S11 and S12). The mortality rates was highest in the under-5 age group, followed by the 5–9 and 15–19 age groups, with no significant gender differences across age groups. Notably, in the 15–19 age group, the female mortality rates contribution per 100,000 was greater than that of males (0.17 vs. 0.10) (Fig. 2C; Supplementary Tables S13 and S14). The DALYs rates analysis revealed a trend similar to that of

the prevalence, with DALYs decreasing with age. However, there was an increased DALYs rates in the 15–19 age group compared to the 10–14 age group (Fig. 2D; Supplementary Tables S15 and S16). The largest disparities in DALYs rates between sexes were observed in children under 5 years old (females 62.67 vs. males 56.86), the 15–19 age group (females 13.05 vs. males 8.19), and the 5–9 age group (females 12.21 vs. males 14.15) (Fig. 2D; Supplementary Tables S15 and S16).

Overall temporal trends in gender and age structures

From 1990 to 2021, the prevalence rates and mortality rates of thalassemia in all age groups exhibited a general decline. Specifically, the prevalence rates were
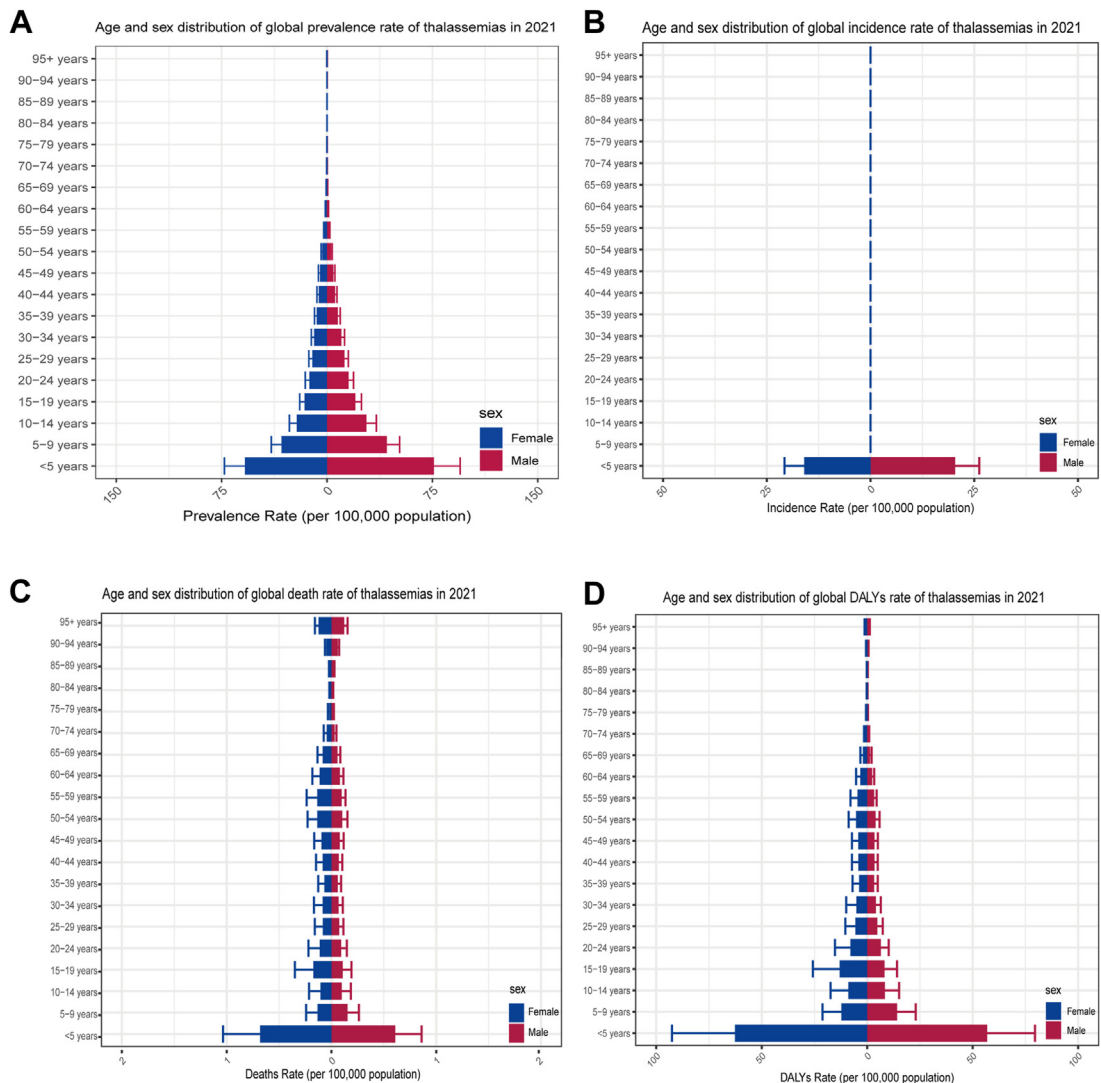
Fig. 2: Sex- and age-structured analysis of thalassemia disease burden in 2021. (A) Prevalence rates; (B) Incidence rates; (C) Mortality rates; (D) DALYs rates.

consistently higher in males compared to females throughout this period (Fig. 3A–B; Supplementary Tables S17 and S18). In children under 5 years of age, the prevalence rates generally decreased, albeit with notable fluctuations observed from 2015 to 2021 (Fig. 3C; Supplementary Table S17). The prevalence rates for the age groups of 5–14 and 15–39 years initially experienced minor fluctuations but ultimately followed a decreasing trend (Fig. 3D–E; Supplementary Table S17). Conversely, the prevalence rates for individuals aged 40–44 and 45–49 years demonstrated significant variability and an increase post-2010 (Fig. 3F–G; Supplementary Table S17). In the 50–69 year age bracket, an overall increase in prevalence rates was observed (Fig. 3H; Supplementary Table S17). The overall mortality rates trend across all six age groups showed a decrease (Supplementary Figure S1A–F; Supplementary Table S18). Notably, the mortality rate was higher in females than in males (Supplementary Figure S1C–F; Supplementary Table S18).

Temporal joinpoint analysis

Joinpoint regression analysis revealed that the overall trend in the ASPR of thalassemia was minor from 1990 to 2021 (AAPC = 0.20%; 95% CI: −0.30%–0.70%; P = 0.444), with an upward trend observed from 2018 to 2021 (APC = 9.20%; 95% CI: 4.80%–13.80%; P < 0.001) (Fig. 4A and Supplementary Table S19). The ASIR exhibited a global downward trend (AAPC = −1.47%; 95% CI: −1.85% to −1.09%; P < 0.001), with the most notable decline during the 2018–2021 period (APC = −7.68%; 95% CI: −10.89% to −4.36%; P < 0.001) (Fig. 4B and Supplementary Table S20). Similarly, the ASMR followed the same downward trend from 1990 to 2021 (AAPC = −1.80%; 95% CI: −2.10% to −1.50%; P < 0.001), but showed a significant increase from 2019 to 2021 (APC = 4.80%; 95% CI: 0.10%–9.60%; P < 0.05), with women contributing largely to this change (Fig. 4C and Supplementary Table S21). The trend in DALYs mirrored that of the mortality rate, with an overall decrease from 1990 to 2021 (AAPC = −1.95%; 95% CI: −2.28% to −1.62%; P < 0.001). However, a slight increase from 2019 to 2021 was observed, although it was not statistically significant (APC = 3.32%; 95% CI: −1.46%–8.33%; P = 0.166) (Fig. 4D and Supplementary Table S22).

An analysis of the top four regions with the highest global ASPR showed that Central Europe, eastern Europe, and central Asia showed a periodic downward trend from 2016 to 2021 (APC = −0.09%; 95% CI: −0.20% to 0.00%) and increased in other time periods (Fig. 4E, Supplementary Figure S2A, Supplementary Table S23). In contrast, Latin America and the Caribbean exhibited a consistent upward trend during the 1990 to 2021 (Fig. 4E, Supplementary Figure S2B, Supplementary Table S23). South Asia showed a turning point with an increase in ASPR from 2019 to 2021 (APC = 0.80%; 95% CI: 0.20%–1.40%; P < 0.05) (Fig. 4E, Supplementary Figure S2C, Supplementary Table S23). The ASPR steadily decreased from 1994 to 2019 in Southeast Asia, East Asia, and Oceania, with an even more pronounced decline from 2019 to 2021 (APC = −2.50%; 95% CI: −3.50% to −1.40%; P < 0.001) (Fig. 4E, Supplementary Figure S2D, Supplementary Table S23). The ASMR in Central Europe, Eastern Europe, and Central Asia increased from 1990 to 1995 (APC = 2.29%; 95% CI: 1.39%–3.20%; P < 0.001), followed by a continuous decline since 1995, with the most significant decrease from 2019 to 2021 (APC = −5.99%; 95% CI: −9.37% to −2.5%; P = 0.005) (Fig. 4F, Supplementary Figure S3A, Supplementary Table S24). The ASPR in Latin America and the Caribbean showed the most significant downward trend from 2007 to 2010 (APC = −2.09%; 95% CI: −4.23%–0.09%; P = 0.059), and maintained a decline from 2018 to 2021 (APC = −1.70%; 95% CI: −3.02% to −0.35%) (Fig. 4F, Supplementary Figure S3B, Supplementary Table S24). Due to improvements in thalassemia management, the ASMR in South Asia reached a turning point in 2017, with the ASMR beginning to decrease from 2017 to 2021 (APC = −3.79%; 95% CI: −5.20% to −2.36%; P < 0.001) (Fig. 4F, Supplementary Figure S3C, Supplementary Table S24). The ASMR in Southeast Asia, East Asia, and Oceania showed a periodic decline, with the most noticeable from 2000 to 2013 (APC = −3.90%; 95% CI: −3.99% to −3.81%; P < 0.001) (Fig. 4F, Supplementary Figure S3D, Supplementary Table S24).

Discussion

Thalassemia represents a significant public health challenge worldwide, with its impact on incidence and mortality drawing substantial research attention. Our analysis spans three decades, covering a wide geographic scope that includes six continents, 204 countries, and 20 age groups, thereby providing a detailed portrayal of the disease's burden across different populations and over time. Notably, this study introduces an innovative assessment of temporal trends in the burden of thalassemia, identifying for the first time critical junctures or pivotal years where significant shifts in disease metrics have occurred.

In 2021, the global incidence of thalassemia was reported as 119,679 cases, with the total number of cases reaching 13,104,071 (Table 1). However, these numbers should be interpreted with caution due to the wide UI (from 93,218 to 153,985 for incidence, and 1,099,973 to 1,572,219 for total cases), which suggest substantial uncertainty in these estimates. The observed increase in data from Middle SDI countries may also reflect demographic changes, such as population migration and birth rate trends, although these factors require further investigation to understand their impact on the
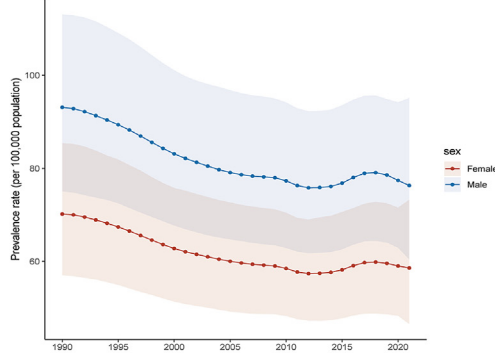
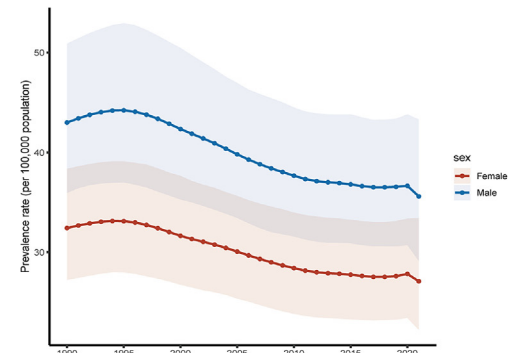**A** Temporal trend of global prevalence rate of thalassemia from 1990 to 2021
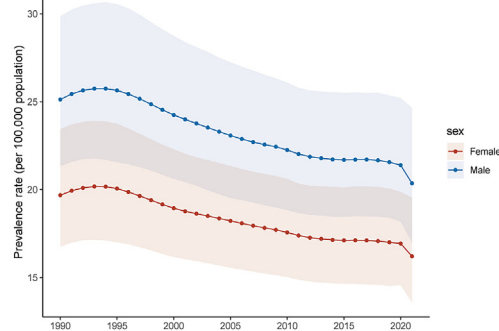
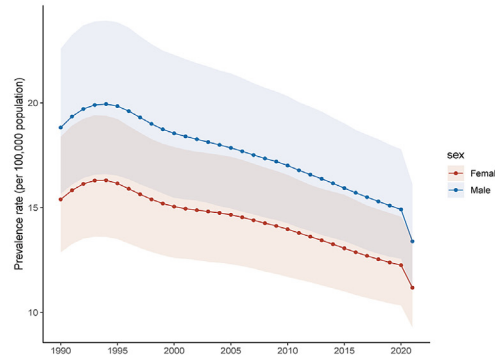**B** Temporal trend of global death rate of thalassemia from 1990 to 2021
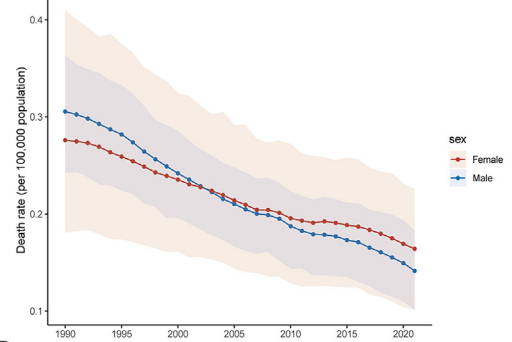
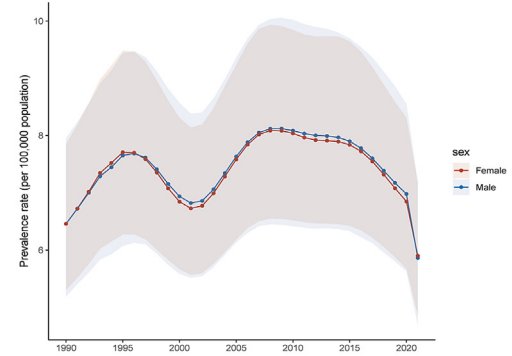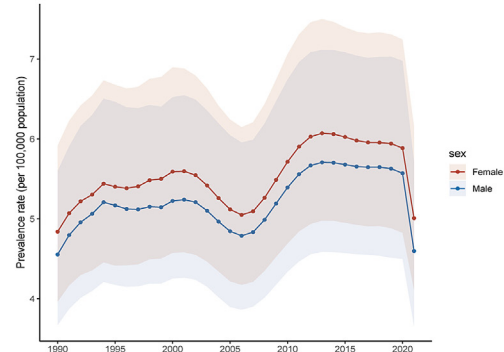**C** Temporal trend of global prevalence rate of thalassemia in <5 years from 1990 to 2021

D Temporal trend of global prevalence rate of thalassemia in 5–14 years from 1990 to 2021

E Temporal trend of global prevalence rate of thalassemia in 15–39 years from 1990 to 2021

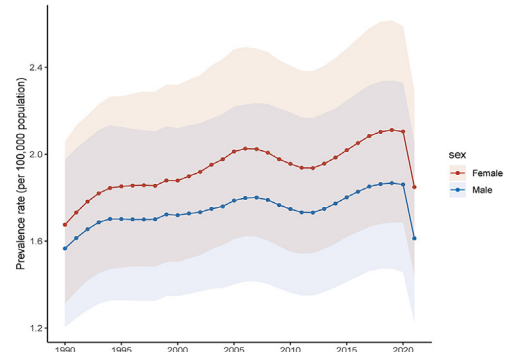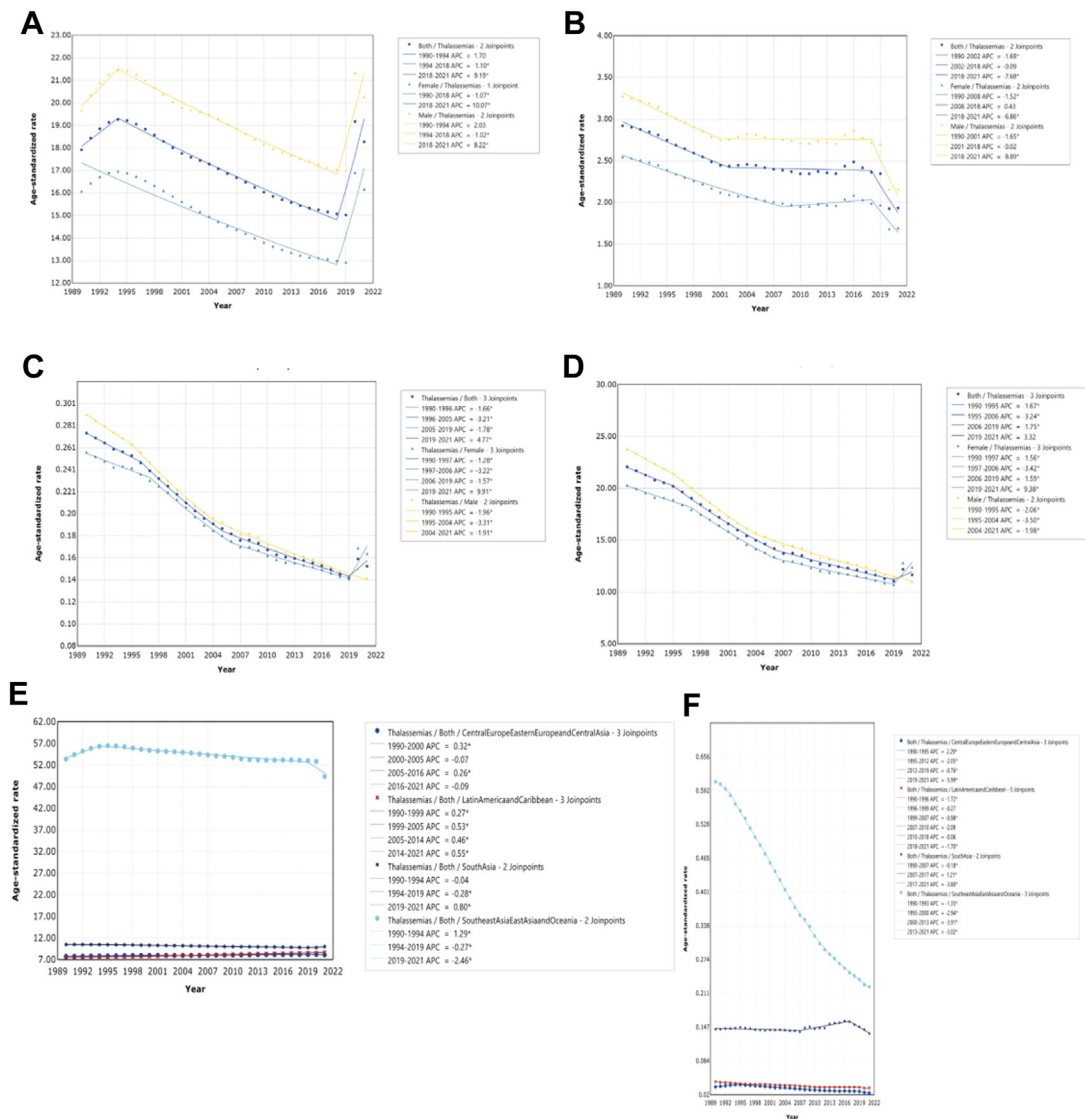**F** Temporal trend of global prevalence rate of thalassemia in 40–44 years from 1990 to 2021

G Temporal trend of global prevalence rate of thalassemia in 45–49 years from 1990 to 2021

H Temporal trend of global prevalence rate of thalassemia in 50–69 years from 1990 to 2021

Fig. 4: Joinpoint regression analysis of the thalassemia disease burden temporal trends, 1990–2021. (A) Age-standardized prevalence rates; (B) Age-standardized incidence rates; (C) Age-standardized mortality rates; (D) Age-standardized DALYs rates; (E) Age-standardized prevalence rates and (F) Age-standardized mortality rates of thalassemia in four regions (Central Europe, eastern Europe, and central Asia, Latin America and Caribbean, South Asia, Southeast Asia, east Asia, and Oceania), 1990–2021.

epidemiology of thalassemia.[22] Compared to 1990, the decrease in prevalence and incidence rates indicates a global improvement in managing the disease's spread. Many countries have effectively begun to implement preventive and prenatal screening.[23–25] Reproductive options, including in vitro fertilization coupled with preimplantation genetic diagnosis, have emerged as alternatives to selective termination, contributing to decreased births of thalassemia-affected babies in regions like the Mediterranean, the Middle East, the Indian subcontinent, and Southeast Asia. Concurrently, noninvasive prenatal diagnostic techniques are evolving to reduce the need for invasive sampling methods, offering safer options for early detection.[26,27] Despite these

Fig. 3: Global temporal trends in Thalassemia disease burden, 1990–2021. (A) Prevalence rates in all age groups; (B) Mortality rates in all age groups; (C–H) Trends in age-group-specific prevalence rates for Thalassemia. (C) < 5 years; (D) 5–14 years; (E) 15–39 years; (F) 40–44 years; (G) 45–49 years; (H) 50–59 years.

advancements, challenges remain in optimizing prenatal interventions. The coverage or acceptance of screening and prevention in some countries remains suboptimal.[28–33] These observations underscore the need for continued evaluation and improvement of thalassemia prevention and control strategies to ensure they are aligned with current population dynamics and healthcare practices.

In countries and regions distributed across various geographical locations, there has been a predominant decline in mortality rates (Table 1 and Supplementary Table S6). The reduction in DALYs rates indicate a significant decrease in the burden of workforce loss attributed to the disease. These improvements can be attributed to the positive effects of social development, technological advancements, industrialization, and enhancements in healthcare resources. Internationally recognized guidelines for thalassemia treatment have been published by various entities, including the International Federation of Thalassemia (TIF) and national health organizations in Australia, Canada, Italy, the United Kingdom, and the United States of America. These guidelines generally agree on management practices, though they exhibit some variability in monitoring for iron overload and the timing of chelation therapy.[34,35] Innovative therapeutic approaches have garnered attention.[36,37] Particularly methods regulating BCL11A gene expression, which show promise in potentially enabling patients to achieve long-term transfusion independence.[38,39] Additionally, the use of Luspatercept has been proven to effectively improve ineffective erythropoiesis associated with thalassemia.[40] However, these novel treatments are still in development and pose new challenges in terms of safety, cost-effectiveness, and economic burden. The data provided by our research are crucial for the advancement of these new therapies, including aiding in the identification of optimal candidate populations, as well as in the assessment of treatment efficacy and the effectiveness of information dissemination. The data observed an increase in the global life expectancy of thalassemia patients, particularly in the age group of 50–69 years (Fig. 3G and H), aligning with trends reported in earlier research.[7] This rise in age comes with a proportional increase in disease-related complications, which significantly contribute to DALYs rates in adult patients.[41–43] Among these complications, cardiac complications have the highest mortality rate[44] and with the extension of patient lifespans, there is a need to heighten vigilance against cardiac complications.[45] Despite Italy's high care standards for thalassemia, a questionnaire revealed that less than a quarter of thalassemia major patients in the country perceive themselves to be at high risk for cardiovascular disease (CVD).[46] These studies indicate the necessity of bolstering education and awareness regarding disease prognosis among thalassemia patients, which would be beneficial in further reducing mortality caused by thalassemia.

The Joinpoint regression analysis indicated an inflection point in the trend of thalassemia disease burden data in 2018 and 2019. Following these points, there has been a trend of declining ASIR, whereas ASPR, ASMR, and age-standardised DALYs rates have shown an increase. This shift may be associated with the intensification of thalassemia management policies by global health organizations and governments around the time of 2018. The publication of updated management guidelines by the TIF in 2017 enhanced standardized guidance.[47,48] Concurrently, the World Bank increased its financial contributions to the management of anemic diseases,[49] promoting the management efficiency of thalassemia from an economic perspective. Strategic advances, such as the widespread implementation of early screening and diagnosis, may be the direct cause of the reduced incidence rates following the inflection points. However, the optimization of treatment has led to improved patient management, resulting in an increase in the number of individuals living with the disease. Patients who might have otherwise had a shorter life expectancy are experiencing extended survival times, which, against the backdrop of an aging population with the disease, may have contributed to the observed post-inflection point rise in ASMR and age-standardised DALYs rates. It is noteworthy that the novel coronavirus (COVID-19) pandemic, which emerged at the end of 2019 and early 2020, has had an impact on the implementation of prevention and treatment measures for thalassemia, potentially maintaining the epidemiological trend of thalassemia burden in the short term.[50–53] However, as the reallocation of medical resources returns to pre-pandemic levels, we may observe significant changes in the epidemiological trends of thalassemia in the coming years.

The research conducted in this study also analyzed gender differences in the disease burden of thalassemia. Although its inheritance pattern is not directly dependent on gender, gender may indirectly impact the epidemiology and health outcomes of thalassemia through societal, cultural, biological, and accessibility-to-care factors. In fact, gender inequality persists globally, with a higher male birth rate compared to females as of 2021. This difference is particularly pronounced in high-prevalence regions of thalassemia, such as South Asia.[54] Moreover, due to social, cultural, and economic constraints, women in regions with significant gender disparities often receive less medical care than men, potentially resulting in more male thalassemia patients being diagnosed and receiving early treatment at birth. This disparity may lead to an uneven gender distribution in thalassemia prevalence (Fig. 2A) and an increased mortality rate among female patients in higher age groups (Fig. 2C) due to delayed diagnosis or lack of systematic treatment. From a biological perspective, studies indicate that females have a higher tolerance to iron toxicity compared to males, resulting in

a lower incidence of cardiac complications and a longer life expectancy.[6,55,56] Additionally, female thalassemia patients of childbearing age may experience exacerbated anemia due to periodic blood loss from menstruation. The increased demand for iron during pregnancy and childbirth poses a greater health burden for patients already affected by disruptions in iron metabolism.[55] In the absence of appropriate medical management, these factors could contribute to the rising mortality rate among female thalassemia patients aged 14 and above (Supplementary Figure S1C–F).

This study, like other GBD estimation efforts, has notable limitations. Firstly, the GBD database predominantly compiles data from national and regional reports and publications rather than direct country reports, potentially leading to issues with data completeness, currency, and quality—particularly in low-income regions. While GBD modeling techniques aim to standardize data, these limitations can still affect data accuracy and comparability. Secondly, variations in disease management, including diagnosis, recording, and reporting across different countries and regions, may compromise comparability. Such disparities can result in underreporting, with the true burden often becoming clear only through detailed micromapping in countries with higher disease incidence[57,58]; Thirdly, although this study broadens the analysis to include all thalassemia types, it does not differentiate the specific burden of each subtype: β-thalassemia, hemoglobin E/β-thalassemia, and α-thalassemia, as well as to differentiate between TDT and non-transfusion-dependent thalassemia (NTDT). Potentially concealing certain epidemiological features.

In summary, this study utilized data from GBD 2021 to delineate the burden of thalassemia globally, regionally, and nationally, analyzing trends over a period from 1990 to 2021. The findings indicate a general decline in the disease burden, yet an increase in the number of elderly patients affected by thalassemia was observed. These findings offer valuable epidemiological information for the development of innovative treatments, while underscoring the necessity for ongoing improvements in the diagnosis, treatment, and management policies of thalassemia.

Contributors
Z.H.and J.J.: Conceptualization, Supervision, Funding acquisition, Writing-review & editing; Y.T. and Y.L.: Data Curation, Writing-original draft preparation, Writing-review & editing, Visualization, Software; Y.L., J.M.and X.Y.:Writing-review & editing; S.W.: Writing-review & editing, Funding acquisition.

Data sharing statement
The data from this study can be accessed openly through the GBD 2021 online database, as outlined in the Methods section.

Declaration of interests
All authors hereby attest that they do not have any conflicts of interest related to this article.

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