Clinical Kidney Journal, 2025, vol. 18, no. 5, sfaf138

https://doi.org/10.1093/ckj/sfaf138
Advance Access Publication Date: 19 May 2025
Original Article

ORIGINAL ARTICLE

Global, regional and national epidemiology of anemia attributable to chronic kidney disease, 1990–2021

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ABSTRACT

Background. Chronic kidney disease (CKD) presents a significant global health challenge, with anemia frequently manifesting in the more advanced stages. This study aimed to evaluate the global burden and cross-country inequality of CKD-related anemia from 1990 to 2021.

Methods. Data on CKD-related anemia were extracted from the Global Burden of Disease 2021 study. Trends in prevalence, years lived with disability (YLDs) and corresponding estimated annual percentage changes (EAPCs) from 1990 to 2021 were analyzed at global, regional and national levels. Health inequity analysis methodologies were employed to evaluate cross-country inequality based on sociodemographic index.

Results. In 2021, global CKD-related anemia cases reached 63 751 624 [95% uncertainty interval (UI), 59 045 051–68 372 650], representing a 96.24% increase from 1990 (32 486 224; 95% UI 30 356 876–35 047 084). Notwithstanding this increase, global prevalence [EAPC –0.27; 95% confidence interval (CI) –0.34 to –0.21] and YLDs rates (EAPC –0.66; 95% CI –0.70 to –0.62) generally declined. Females were disproportionately affected, comprising 55.75% of prevalence cases and 65.87% of YLDs numbers in 2021. From 1990 to 2021, the burden increased in individuals with CKD-related anemia associated with type 1 diabetes. Significant cross-country inequalities in prevalence were observed and persisted [slope index of inequality: 255.04 (389.56–120.51) in 1990 to 423.30 (572.78–273.81) in 2021; health concentration index: –0.09 (–0.12 to –0.07) in 1990 to –0.14 (–0.17 to –0.11) in 2021].

Conclusions. Despite the global decline in prevalence and YLDs rates of CKD-related anemia, the number of cases continued to increase, and the burden disproportionately concentrated in less developed countries and territories. This investigation also revealed a gender disparity and the influence of specific causes.

Keywords: anemia, chronic kidney disease, disease burden, estimated annual % changes, health inequalities

INTRODUCTION

In 2017, an estimated 700 million individuals were affected by chronic kidney disease (CKD) globally, resulting in 1.2 million deaths, making it the 12th leading cause of death worldwide [1, 2]. To achieve the United Nations Sustainable Development Goal of reducing premature deaths from non-communicable diseases by one-third by 2030, proactive efforts to address

Received: 26.11.2024; Editorial decision: 28.4.2025

KEY LEARNING POINTS

What was known:

- Chronic kidney disease (CKD) presents a significant global health challenge, with anemia frequently manifesting in the advanced stages.
- However, disparities in CKD-related anemia at global, regional and national levels remain insufficiently characterized.
- Accurate assessment of the anemia burden attributable to CKD is crucial for developing effective, context-specific interventions to improve anemia management and prevention.

This study adds:

- Our research indicated that the overall global prevalence and years lived with disability rates of CKD-related anemia from 1990 to 2021 had generally declined, reflecting global advancements in prevention and treatment strategies. However, the number of cases continued to increase, primarily due to demographic shifts such as population growth and aging.
- This research also highlighted a gender disparity, with females bearing a disproportionately higher burden of CKD-related anemia compared with males.
- CKD-related anemia linked to type 1 diabetes showed a persistent upward trend, and substantial differences between countries were observed, underscoring the influence of cause-specific and socioeconomic factors on the burden of CKD-related anemia.

Potential impact:

- We believe that this study contributes significantly to the literature by addressing the existing knowledge gap regarding the estimation of the burden and temporal trends of CKD-related anemia at global, regional and national levels.
- This analysis facilitates evaluation of the efficacy of past policy interventions on disease prevention and therapy, as well as identification of prospective areas of focus.
- These population-based research outcomes offer crucial insights to inform resource allocation and guide the development of effective interventions aimed at mitigating the global burden of CKD-related anemia.

CKD and its comorbidities are essential. CKD leads to multiple complications, with anemia being one of the most prevalent. The prevalence of anemia in patients with CKD significantly increases with disease progression, although it is unclear if this is a causal relationship [3, 4]. It was also reported that CKD-related anemia was likely associated with increased risks of cognitive and sleep disorders and cardiovascular comorbidities [5], but despite this current treatments aimed at managing anemia do not fully mitigate these systemic risks. The primary symptoms associated with CKD-related anemia, such as fatigue and dyspnea, can further adversely affect patients' occupational productivity and quality of life. Furthermore, moderate CKD patients with severe anemia have higher hospital admission rates and greater direct medical costs than those without severe anemia [5]. CKD-related anemia poses a global health challenge, contributing to adverse health outcomes and imposing substantial medical and economic burdens [6].

The prevalence of anemia varies by region, age and gender, underscoring the need for targeted interventions aligned with global health objectives for disease reduction [7, 8]. Despite this, disparities in CKD-related anemia at global, regional and national levels remain insufficiently characterized. Accurate assessment of the anemia burden attributable to CKD is crucial for developing effective, context-specific interventions to improve anemia management and prevention. This study analyzed the prevalence and years lived with disability (YLDs) due to CKD-related anemia within the Global Burden of Disease (GBD) framework from 1990 to 2021. By examining global, regional and national trends, as well as cross-country inequalities, we aimed to provide a comprehensive assessment of the CKD-related anemia burden, and offer evidence-based recommendations for effective global strategies to prevent and manage CKD-related anemia.

MATERIALS AND METHODS

Study design

This study utilized data from the GBD 2021, accessible via the Global Health Data Exchange [9]. The GBD 2021 evaluated the global burden of 371 diseases and injuries across 204 countries and territories from 1990 to 2021 [10, 11]. To model the burden of different causes of disease, the GBD 2021 used various statistical strategies tailored to the specific characteristics of each cause, including Bayesian hierarchical models and meta-regression models. These models integrated diverse data sources, including vital statistics, health surveys and disease registries, while addressing data gaps, inconsistencies and uncertainties. The results were then synthesized into a consistent set of cause-specific estimates for each location, age group, sex and year, providing comprehensive estimates of the global disease burden [10, 11]. Pursuant to US Executive Order No. 7724 (16 May 2012) and Resolution No. 510 (7 April 2016), all GBD studies utilize publicly available secondary databases without identifiable information. Consequently, related research does not require ethics committee review.

Case definition and data collection

Anemia is characterized by a reduction in red blood cell count, often accompanied by decreased hemoglobin levels or changes in red blood cell morphology [7]. In the GBD 2021, anemia prevalence was estimated by generating counterfactual distributions based on age- and sex-specific prevalence of anemia-causing conditions and assessing their impact on blood hemoglobin concentration [10, 11]. In the GBD 2021, the age- and sex-specific anemia prevalence for CKD was analyzed as

part of overall anemia causal attribution. CKD is marked by a persistent loss of kidney function, assessed through the estimated glomerular filtration rate (eGFR) and the urinary albumin-to-creatinine ratio (ACR). The International Classification of Diseases, 10th Revision codes for CKD range from N18.1 to N18.9 and for anemia in CKD with D63.1. The GBD study attributes CKD-related anemia etiology to type 1 diabetes (T1D), type 2 diabetes (T2D), glomerulonephritis and hypertension, as well as other and unspecified causes through modeling [10, 11].

In this study, we assessed the global burden of CKD-related anemia by analyzing its prevalence, YLDs and associated rates, which were obtained directly from the GBD 2021 dataset. The GBD algorithm reported these rates per 100 000 populations, along with 95% uncertainty intervals (UIs) for each rate. Indicators for CKD-related anemia were collected across various dimensions: sex, 20 distinct age groups (each representing a 5-year interval), 5 CKD causes, 5 sociodemographic index (SDI) groups, 21 regions based on epidemiological and geographical similarities, and 204 countries and territories. Countries and territories were classified into five groups based on their SDI quintiles: high SDI, high-middle SDI, middle SDI, low-middle SDI and low SDI regions. The SDI is a composite measure reflecting social and economic factors that influence health outcomes. It is calculated as the geometric mean of three indicators, each ranging from 0 to 1: the total fertility rate for individuals under 25 years old, the average years of education for those aged 15 years and older, and the lag-distributed per capita income. A score of 0 indicates the highest fertility rate, lowest educational attainment and lowest per capita income [12].

Statistical analysis

Trend analysis

To analyze temporal trends in the burden of CKD-related anemia, we calculated estimated annual percentage changes (EAPCs) and evaluated these trends at global, regional and national levels. The analysis was further stratified by age, sex, cause and the SDI at the global level. The mean EAPCs were calculated using linear regression, with 95% confidence intervals (CIs) established through linear modeling. A declining trend in the rate is indicated when the upper limit of the 95% CI for the EAPC is negative. Conversely, an increasing trend is suggested when the lower limit of the 95% CI is positive [13].

Cross-country inequality analysis

The burden of CKD-related anemia across countries and territories was assessed using two key metrics: the slope index of inequality for absolute inequality and the health inequality concentration index for relative inequality. Both metrics, recommended by the World Health Organization, offer a comprehensive view of health disparities [14].

A regression analysis was performed to calculate the slope index of inequality, using the country-level age-standardized prevalence rate (ASPR) of CKD-related anemia as the dependent variable. The independent variable was the relative social status scale, determined by the midpoint of cumulative population intervals ranked according to the SDI. Due to the presence of heteroscedasticity in the age-standardized YLDs rates, a robust regression model was implemented. This model utilized iteratively reweighted least squares in conjunction with a Huber weighting function to improve precision.

The health inequality concentration index was calculated utilizing the Lorenz concentration curve, which delineates the cumulative distribution relationship between the population ranked by the SDI and the burden of CKD-related anemia. The index is subsequently derived through numerical integration of the area under the curve [15]. All analyses were conducted employing R (version 4.2.2; Posit PBC, Boston, MA, USA).

RESULTS

Global CKD-related anemia burden and trends

Figures 1 and 2, and Tables 1 and 2, along with Supplementary data, Tables S1 and S2, illustrate the trends in the burden of prevalence and YLDs of CKD-related anemia from 1990 to 2021. In 2021, the global number of CKD-related anemia cases reached 63 751 624 (95% UI 59 045 051–68 372 650), representing an approximate 96.24% increase from 1990 (32 486 224; 95% UI 30 356 876–35 047 084). Despite this rise, the prevalence per 100 000 population declined from 841.18 (95% UI 783.12–906.48) in 1990 to 762.12 (95% UI 707.32–817.37) in 2021, with an EAPC of –0.27 (95% CI –0.34 to –0.21). Similarly, the number of YLDs cases in 2021 was 1 699 516 (95% UI 1 131 250–2 433 689), marking an approximate 74.78% increase from 1990 (972 375; 95% UI 650 009–1 385 335). Nevertheless, the YLDs rate per 100 000 population decreased from 25.09 (95% UI 16.78–35.65) in 1990 to 20.34 (95% UI 13.54–29.09) in 2021, with an EAPC of –0.66 (95% CI –0.70 to –0.62).

Regarding sex, CKD-related anemia imposed a heavier burden on females in 2021, accounting for 55.75% of prevalence cases and 65.87% of YLDs cases. From 1990 to 2021, the reduction in YLDs rates was more pronounced in males (EAPC –1.14; 95% CI –1.16 to –1.12) than in females (EAPC –0.39; 95% CI –0.44 to –0.34). Similarly, the improvement in prevalence appeared to be greater in males (EAPC –0.33; 95% CI –0.39 to –0.27) compared with females (EAPC –0.23; 95% CI –0.30 to –0.16).

Regarding age, the prevalence of CKD-related anemia was observed to increase with age in 2021. Despite the prevalence decreased across most age groups from 1990 to 2021, there had been no significant decline and a trend toward increase among individuals aged 75–79 (EAPC 0; 95% CI –0.06 to 0.06) and 80–84 (EAPC 0.12; 95% CI 0.05 to 0.18). From 1990 to 2021, YLDs rates declined across all age groups, consistent with the overall trend.

Regarding causes, from 1990 to 2021, the burden of CKD-related anemia decreased in both prevalence and YLDs rates for CKD caused by glomerulonephritis, hypertension, T2D and other unspecified causes. However, CKD-related anemia caused by T1D exhibited an increasing burden, with an EAPC of 0.51 (95% CI 0.39 to 0.63) in prevalence and an EAPC of 0.04 (95% CI –0.07 to 0.15) in YLDs rates.

Among the various SDI regions, in 2021, the low-middle SDI region had the highest prevalence (1050.06; 95% UI 971.42–1140.28) and YLDs rates (38.05; 95% UI 25.87–53.82) for CKD-related anemia, followed by the low SDI region. From 1990 to 2021, reductions in prevalence were less pronounced in the low and low-middle SDI regions, with prevalence EAPCs of –0.08 (95% CI –0.11 to –0.06) and –0.08 (95% CI –0.13 to –0.02), respectively. In contrast, the high-middle SDI region experienced the greatest improvements, with a prevalence EAPC of –0.97 (95% CI –1.01 to –0.93) and a YLDs rate EAPC of –1.52 (95% CI –1.57 to –1.47).

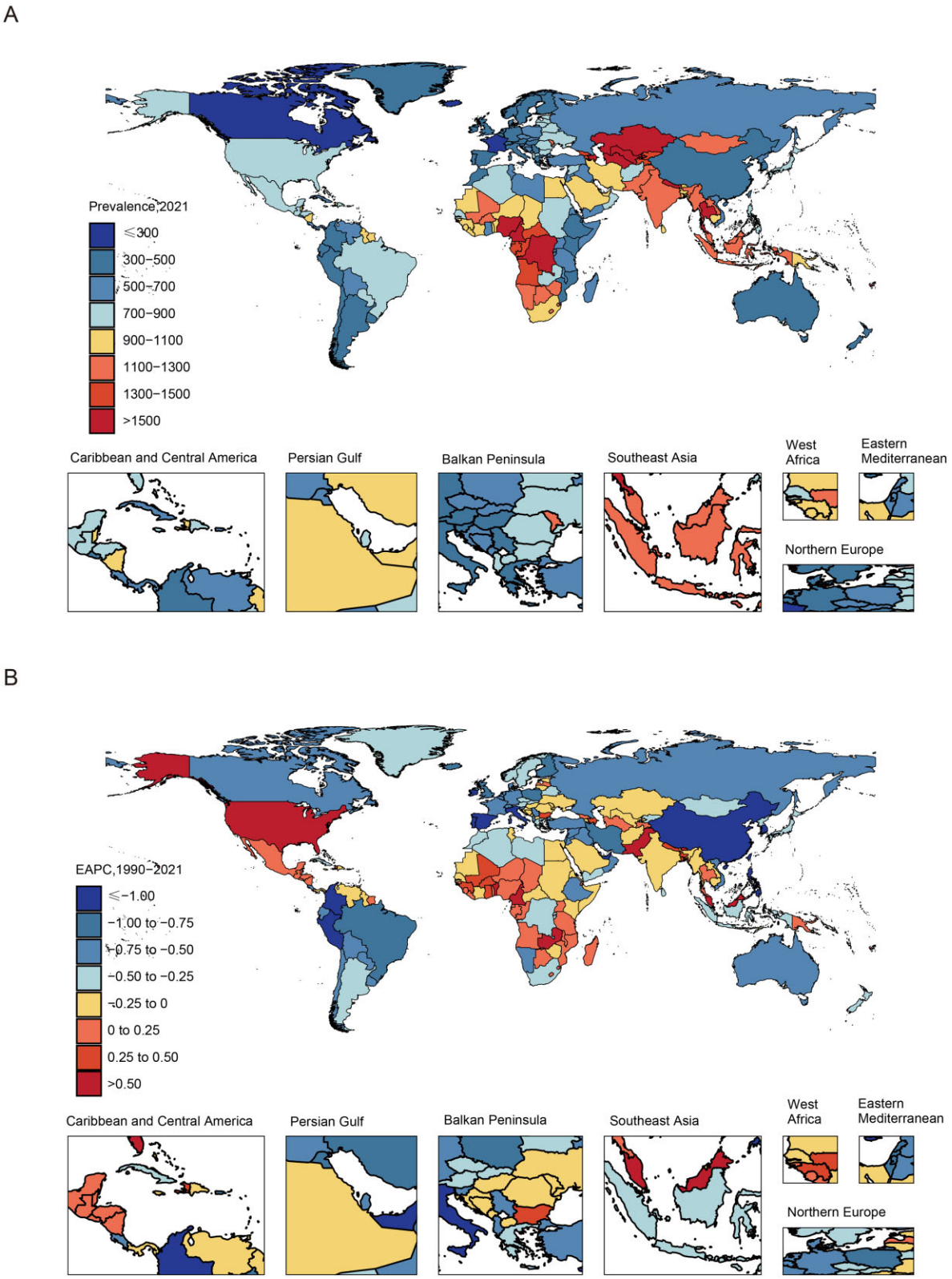

Figure 1: **(A)** Global prevalence of anemia attributable to CKDs in 2021. **(B)** Changes in the overall trend of prevalence of anemia attributable to CKDs. Trend changes were assessed by the EAPC in age-standardized prevalence rates.

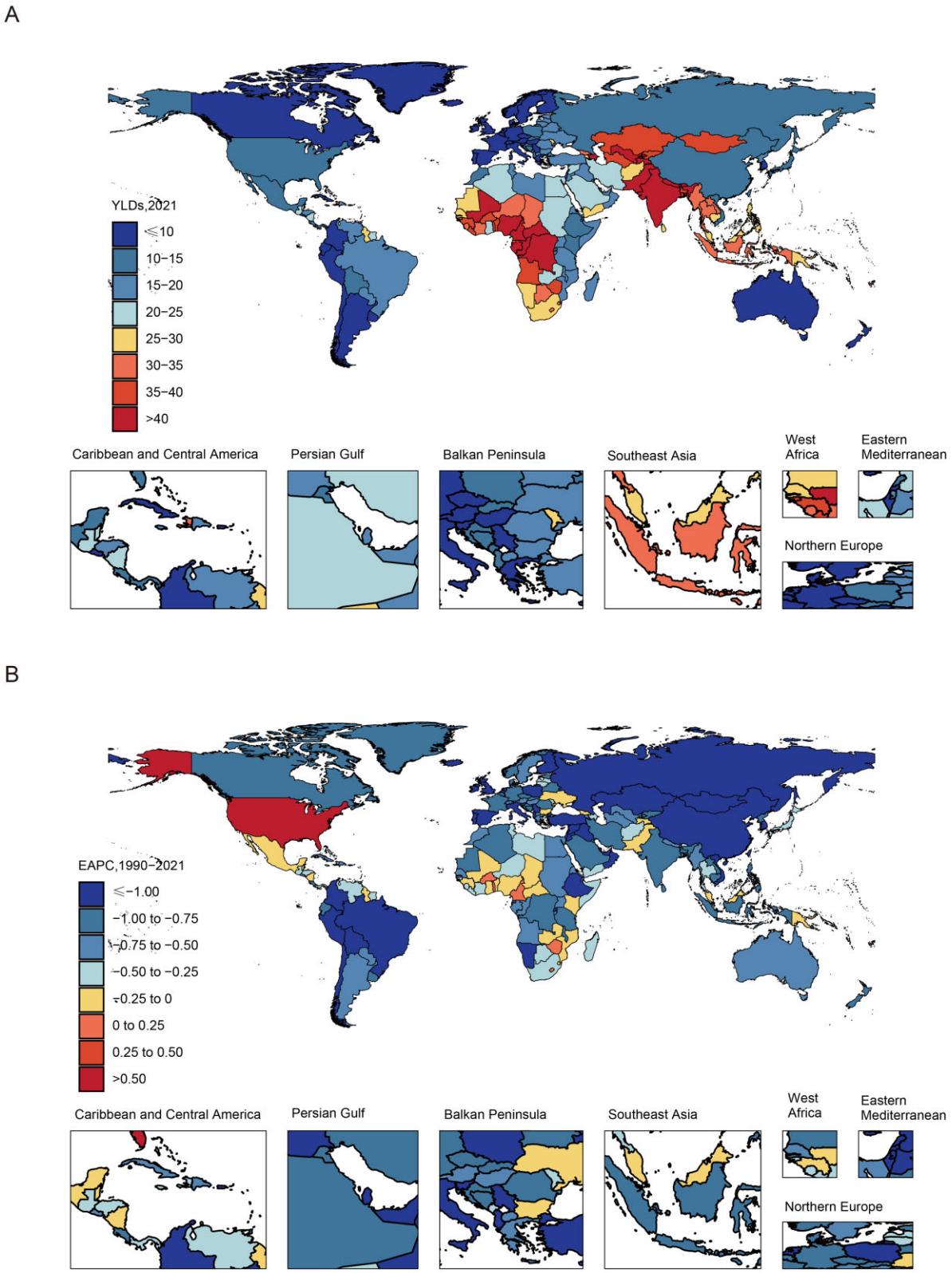

Figure 2: (**A**) Global YLDs rates of anemia attributable to CKDs in 2021. (**B**) Changes in the overall trend of the burden of anemia attributable to CKDs. Trend changes were assessed by the EAPC in age-standardized YLDs rates.

Table 1: Prevalence of anemia attributable to CKD and corresponding EAPCs from 1990 to 2021 at the global level, further stratified by sex, cause and the SDI.

	Cases, 1990	Prevalence, 1990	Cases, 2021	Prevalence, 2021	EAPC
Global	32 486 224.06 (30 356 875.99 –35 047 084.48)	841.18 (783.12–906.48)	63 751 624.42 (59 045 050.9 –68 372 649.66)	762.12 (707.32–817.37)	–0.27 (–0.34 to –0.21)
By sex					
Male	14 346 016.01 (13 323 900.53 –15 630 185.11)	839.1 (780.83–910.92)	28 208 709.26 (26 097 778.68 –30 409 323.89)	748.1 (691.69–807.21)	–0.33 (–0.39 to –0.27)
Female	18 140 208.05 (16 913 628.38 –19 524 600.88)	854.93 (798.01–921.56)	35 542 915.15 (32 942 945.69 –38 267 108)	784.53 (728.64–842.42)	–0.23 (–0.3 to –0.16)
By cause					
CKD due to glomerulonephritis	1 270 006.04 (1 130 446 –1 415 130.79)	26.88 (23.68–30.27)	2 128 965.43 (1 873 888.04 –2 405 454.77)	25.72 (22.66–28.94)	–0.11 (–0.16 to –0.05)
CKD due to hypertension	2 664 233.56 (2 431 183.72 –2 923 330.3)	72.63 (66.55–79.48)	5 658 673.54 (5 224 477.13 –6 156 843.13)	68.17 (63–74.31)	–0.13 (–0.18 to –0.08)
CKD due to T1D	233 394.92 (205 641.26 –262 901.91)	4.82 (4.22–5.45)	418 153.09 (361 552.51 –477 293.73)	4.99 (4.32–5.69)	0.51 (0.39 to 0.63)
CKD due to T2D	3 884 470.05 (3 520 738.17 –4 297 081)	101.2 (91.59–111.59)	7 979 798.39 (7 271 504.1 –8 787 112.64)	93.18 (85.12–102.47)	–0.2 (–0.25 to –0.14)
CKD due to other and unspecified causes	24 434 119.5 (22 749 124.94 –26 515 757.07)	635.65 (591.72–689.42)	47 566 033.97 (43 987 030.04 –51 165 099.39)	570.07 (527.3–613.09)	–0.32 (–0.39 to –0.24)
By SDI					
High SDI	6 831 433.52 (6 294 907.52 –7 497 740.92)	631.2 (583.76–687.86)	12 937 734.1 (11 594 439.81 –14 338 944)	575.32 (517.79–636.52)	–0.15 (–0.29 to –0.01)
High-middle SDI	6 546 839.43 (6 049 890.89 –7 127 758.98)	714.28 (658.63–777.3)	9 876 782.34 (9 030 632.15 –10 648 516.03)	526.27 (483.55–565.57)	–0.97 (–1.01 to –0.93)
Middle SDI	9 868 168.14 (9 081 277.05 –10 734 605.59)	958.14 (883.95–1046.64)	20 291 028.31 (18 699 076.19 –21 983 141.44)	798.65 (737.73–861.88)	–0.54 (–0.59 to –0.49)
Low-middle SDI	6 735 512.77 (6 240 338.43 –7 312 830.88)	1077.42 (996.26–1174.43)	15 019 550.51 (13 936 959.76 –16 277 998.63)	1050.06 (971.42–1140.28)	–0.08 (–0.13 to –0.02)
Low SDI	2 472 885.03 (2 274 376.25 –2 695 336.47)	1016.33 (931.79–1110.53)	5 573 562.11 (5 150 094.85 –6 019 434.95)	995.84 (916.54–1080.2)	–0.08 (–0.11 to –0.06)

CKD-related anemia burden and trends by region

The burden of CKD-related anemia differed significantly among 21 geographic regions. In 2021, Central Asia had the highest prevalence at 1615.07 (95% UI 1455.29–1800.63), while South Asia reported the highest YLDs rate at 46.47 (95% UI 31.7–65.28). Conversely, Western Europe exhibited the lowest rates, with a prevalence of 383.47 (95% UI 346.65–423.88) and a YLDs rate of 5.98 (95% UI 3.73–9.09). From 1990 to 2021, the greatest increases in prevalence and YLDs rates were observed in high-income North America, with EAPCs of 0.77 (95% CI 0.55 to 0.99) and 0.65 (95% CI 0.28 to 0.82), respectively. In contrast, East Asia experienced the largest declines, with EAPCs of –1.51 (95% CI –1.61 to –1.4) for prevalence and –2.56 (95% CI –2.66 to –2.46) for YLDs rate (Supplementary data, Tables S3–S4).

CKD-related anemia burden and trends by country/territory

In 2021, Nepal exhibited the highest prevalence and YLDs rates in the burden of CKD-related anemia among 204 countries and territories, with a prevalence of 2298.92 (95% UI 1904.13–2765.01) and a YLDs rate of 84.28 (95% UI 54.64–123.86). Conversely, Iceland reported the lowest prevalence at 255.29 (95% UI 210.36–314.62), while Canada demonstrated the lowest YLDs rate at 3.77 (95% UI 2.21–6.12). From 1990 to 2021, Fiji experienced the most substantial increase in prevalence (EAPC 0.97; 95% CI 0.79–1.16), and the United States of America exhibited the largest increase in YLDs rate (EAPC 0.77; 95% CI 0.6–0.94). In contrast, the Republic of Korea demonstrated the most significant decreases in both prevalence and YLDs rate, with EAPCs of –2.59

Table 2: YLDs of anemia attributable to CKD and corresponding EAPCs from 1990 to 2021 at the global level, further stratified by sex, cause and the SDI.

	Cases, 1990	YLDs, 1990	Cases, 2021	YLDs, 2021	EAPC
Global	972 374.68 (650 008.9 –1 385 335.44)	25.09 (16.78–35.65)	1 699 515.97 (1 131 250.02 –2 433 688.72)	20.34 (13.54–29.09)	–0.66 (–0.7 to –0.62)
By sex					
Male	363 831.25 (242 839.82 –518 598.02)	22.38 (14.95–31.57)	580 116.87 (379 680.57 –841 698.01)	15.81 (10.36–22.71)	–1.14 (–1.16 to –1.12)
Female	608 543.44 (407 383.94 –867 081.81)	28.29 (18.89–40.31)	1 119 399.11 (746 449.5 –1 608 622.6)	24.83 (16.56–35.73)	–0.39 (–0.44 to –0.34)
By cause					
CKD due to glomerulonephritis	36 812.08 (24 371.29 –54 102.83)	0.78 (0.52–1.16)	54 508.22 (35 646.94 –82 633.94)	0.66 (0.43–1)	–0.49 (–0.54 to –0.43)
CKD due to hypertension	74 819.82 (49 512.36 –106 554.96)	2.05 (1.37–2.91)	138 672.48 (92 028.27 –198 889.5)	1.67 (1.11–2.41)	–0.61 (–0.64 to –0.57)
CKD due to T1D	6408.8 (4133.64–9528.69)	0.13 (0.08 –0.19)	9811.63 (6172.21–14 983.45)	0.12 (0.07–0.18)	0.04 (–0.07 to 0.15)
CKD due to T2D	136 060.51 (91 365.08 –194 284.81)	3.55 (2.38–5.07)	265 807.78 (173 681.26 –384 697.67)	3.11 (2.03–4.51)	–0.36 (–0.41 to –0.3)
CKD due to other and unspecified causes	718 273.47 (480 502.75 –1 025 750.55)	18.59 (12.41–26.51)	1 230 715.86 (817 388.91 –1 768 439.12)	14.77 (9.83–21.18)	–0.74 (–0.78 to –0.7)
By SDI					
High SDI	116 697 (73 288.73 –172 849.36)	10.86 (6.86–16.08)	219 455.75 (138 759.31 –328 837.04)	9.48 (5.96–14.33)	–0.3 (–0.44 to –0.17)
High-middle SDI	161 891.67 (105 818.72 –233 309.26)	17.96 (11.79–25.63)	212 507.32 (136 907.89 –309 322.77)	11.37 (7.33–16.54)	–1.52 (–1.57 to –1.47)
Middle SDI	301 289.32 (201 302.91 –429 323.26)	30.69 (20.54–43.39)	535 886.59 (353 697.25 –770 787.65)	21.55 (14.24–30.81)	–1.11 (–1.14 to –1.07)
Low-middle SDI	284 512.04 (192 875.41 –401 690.12)	46.64 (31.74–65.62)	528 031.84 (357455.68 –744045.73)	38.05 (25.87–53.82)	–0.66 (–0.69 to –0.62)
Low SDI	107 236.75 (72 771.22 –149 542.37)	45.82 (31.06–63.05)	202 492.12 (136 829.01 –287 496.88)	38.72 (26.28–54.37)	–0.56 (–0.59 to –0.54)

(95% CI –2.89 to –2.28) and –2.92 (95% CI –3.17 to –2.67), respectively (Supplementary data, Tables S5–S6).

Cross-country inequalities

Among the 204 countries and territories analyzed, we observed significant absolute and relative SDI-related inequality in the burden of CKD-related anemia, in both prevalence and YLDs. This burden was disproportionately concentrated in countries and territories with lower SDIs. Furthermore, these inequalities in prevalence had persisted and increased over time. In 1990, the slope index of absolute inequality showed that ASPR among the countries and territories with the lowest and highest SDIs was 255.04 (389.56–120.51), rising to 423.30 (572.78–273.81) by 2021. The concentration index revealed a relative gradient of inequality of –0.09 (–0.12 to –0.07) ($P < .05$) in 1990, which had deteriorated to –0.14 (–0.17 to –0.11) ($P < .05$) by 2021. In contrast, inequalities in YLDs rates remained relatively stable from 1990 to 2021 (Fig. 3, Table 3).

DISCUSSION

This study analyzed the global burden and trends of CKD-related anemia from 1990 to 2021. The key findings are as follows: (i) while the overall global prevalence and YLDs rates had generally declined, the number of cases of CKD-related anemia continued to rise; (ii) females experienced a disproportionately higher burden; (iii) the prevalence of CKD-related anemia increased with age, and there had been no significant decline and a trend toward increase among individuals aged 75–79 and 80–84 years; (iv) CKD-related anemia caused by T1D demonstrated an increasing disease burden; and (v) the CKD-related anemia burden remained disproportionately concentrated in less developed countries.

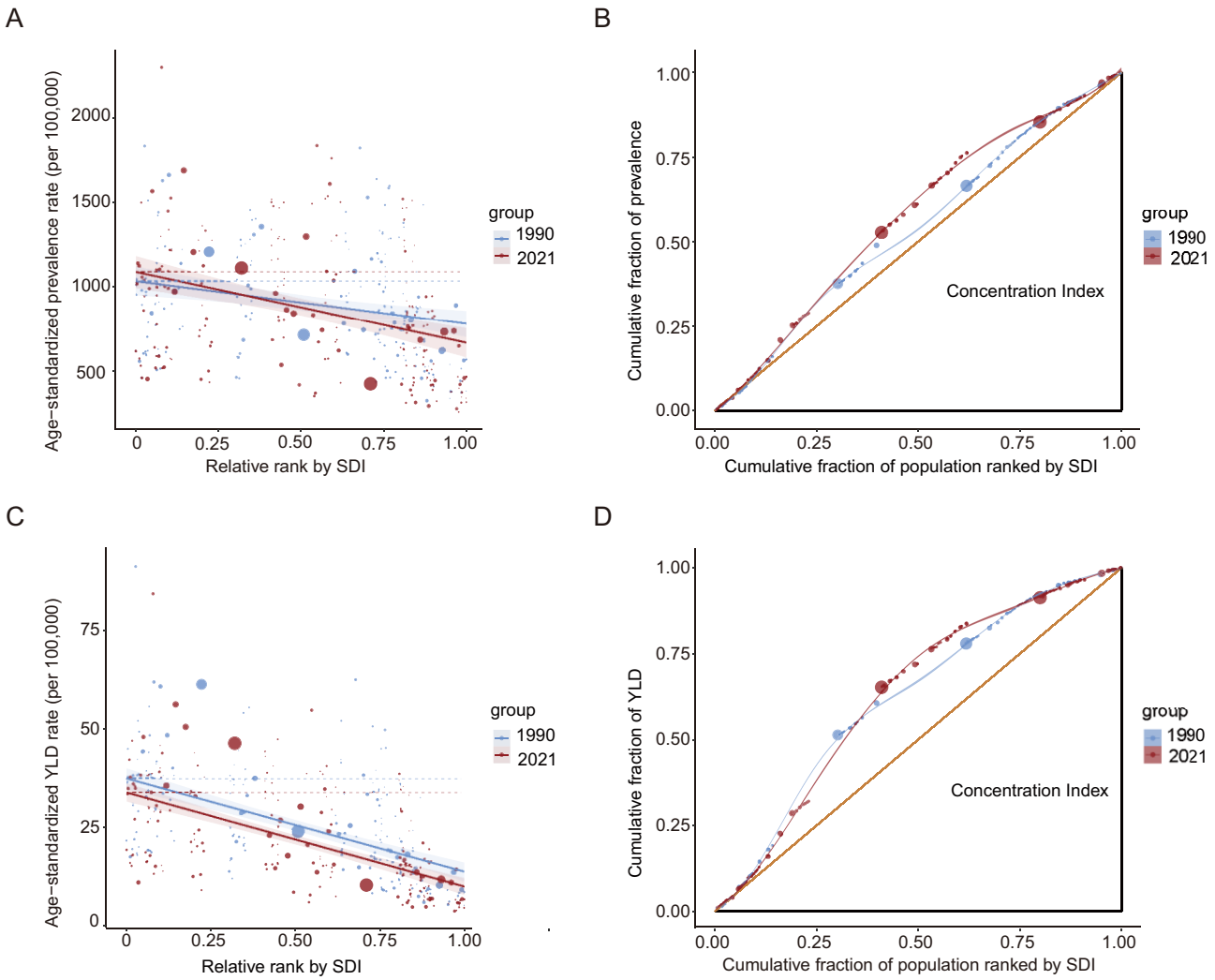

Figure 3: Inequalities in the burden of anemia attributable to CKDs based on development status. The SDI was utilized as a measure of the level of sociodemographic development. (**A**) Health inequality regression curves of prevalence; (**B**) health inequality concentration curves of prevalence; (**C**) health inequality regression curves of YLDs; (**D**) health inequality concentration curves of YLDs.

Table 3: SDI-related inequalities in age-standardized prevalence and YLDs rates of anemia attributable to CKD.

	Slope index of inequality (absolute gradient)		Health concentration index (relative gradient)	
Health inequality metrics	Value	95% CI	Value	95% CI
Prevalence				
1900	−255.04	(−389.56 to −120.51)	−0.09	(−0.12 to −0.07)
2021	−423.3	(−572.78 to −273.81)	−0.14	(−0.17 to −0.11)
YLDs				
1900	−23.65	(−28.34 to −18.96)	−0.25	(−0.28 to −0.21)
2021	−23.89	(−28.25 to −19.53)	−0.26	(−0.29 to −0.22)

From 1990 to 2021, the number of prevalence cases of CKD-related anemia nearly doubled globally. This increase can be attributed to multiple factors. Primarily, studies indicated a significant global trend of population growth and aging, which elevated the absolute number of CKD-related anemia cases [16]. Importantly, it was reported that CKD prevalence showed no significant improvement from 1990 to 2021, with an EAPC of 0.01 (−0.02 to 0.04) [17]. However, our study revealed a slight decline in the ASPR of CKD-related anemia over the study period, with an EAPC of −0.27 (−0.34 to −0.21). This suggests that

advancements in treatment and public health measures have helped to mitigate the burden of anemia in CKD patients, even as CKD prevalence seemed to continue to rise.

Our research indicated a global reduction in the burden of CKD-related anemia attributed to glomerulonephritis, hypertension and T2D. Over the past three decades, improvements in the management and treatment techniques of diabetes, hypertension and CKD, have effectively slowed CKD progression, which could eventually decrease the number of patients with CKD-related anemia [18, 19]. Additionally, patients with T2D may benefit from novel antidiabetic therapies, such as sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), has further contributed to these advancements [20]. In particular, SGLT2i have demonstrated an ability to improve anemia in patients with CKD, likely through mechanisms such as enhanced erythropoietin production, reduced hepcidin levels, and anti-inflammatory effects [21, 22]. These effects appear to be independent of their impact on kidney function, although the precise mechanisms remain under investigation. Despite its global prevalence and significant contribution to the CKD burden, these therapeutic advancements may help explain the more favorable anemia trends observed in T2D.

In contrast, the prevalence of CKD-related anemia associated with T1D has increased, indicating a divergent trend. This divergence may be partially attributed to differences in underlying disease mechanisms. T1D patients showed higher susceptibility to autoimmune-related anemias, such as autoimmune gastritis and pernicious anemia [23]. The prevalence of autoimmune gastritis and pernicious anemia in T1D patients was notably higher—5%–10% and 2.6%–4%, respectively—compared with 2% and 0.15%–1% in the general population [24, 25]. T1D is associated with an increased risk of CKD progression, and chronic inflammation may contribute to renal damage alongside metabolic and hemodynamic factors [26]. This inflammation leads to dysregulation of iron metabolism and elevated hepcidin levels, which impair iron utilization and erythropoiesis, further aggravating anemia [27]. These factors, combined with the autoimmune nature of the disease, may make anemia in T1D-associated CKD more difficult to manage compared with other CKD causes. Early screening and tailored interventions are crucial for optimizing outcomes and reducing anemia burden in T1D-associated CKD patients.

Advancements in medical practice have likely contributed to improvements in the prevalence and YLD rates of CKD-related anemia worldwide [28]. The commercialization of erythropoiesis-stimulating agents (ESAs) has revolutionized the treatment of CKD-related anemia. In 1989, the US Food and Drug Administration approved the first ESAs for clinical use. It was reported that ESAs therapy reduced the need for blood transfusions in dialysis patients and alleviated anemia-related symptoms [29]. However, ESA treatment remains underutilized in non-dialysis CKD patients in many countries, which may limit its overall impact on global trends. Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) represent a notable advancement in the treatment of CKD-related anemia. These agents function by stabilizing HIFs through the inhibition of prolyl hydroxylase enzymes, thereby enhancing endogenous erythropoietin production to targeted physiological levels while suppressing hepcidin [30]. Clinical trials have demonstrated that HIF-PHIs exhibit efficacy comparable to that of ESAs in correcting anemia [31]. Although their use remains limited in most countries, these oral agents are emerging as a valuable therapeutic option for CKD-associated anemia.

Our study revealed that from 1990 to 2021, females exhibited a higher prevalence of CKD-related anemia. Research has demonstrated that CKD was more prevalent in females than males [32]. Besides, females tend to have lower hemoglobin levels than males across all stages of CKD, potentially making them more vulnerable to anemia [33, 34]. This could be attributed to several factors, including physiological differences such as lower iron stores, greater blood loss due to menstruation and differences in red blood cell turnover [35]. Additionally, females may experience more severe adverse health outcomes from CKD-related anemia compared with males, as evidenced by the higher YLD rates observed in females with CKD-related anemia. Given these findings, a gender-specific approach may help optimize the management of CKD-related anemia in females. The difference in iron status can impact the effectiveness of iron supplementation and ESA/HIF-PHD inhibitor therapies. These treatments rely on adequate iron availability for optimal efficacy, which may necessitate different treatment thresholds or ESA dose adjustments to achieve target hematocrit levels in females [36, 37]. However, it is unknown whether females need a different Hb target than males under ESA/HIF-PHD inhibitors therapy. Further clinical research is required to fully understand these gender-based variations. Additionally, clinicians should consider the potential influence of menstruation and iron deficiency, which are more prevalent in women, when assessing and managing anemia in female CKD patients.

Developmental disparities are evident, with lower SDI regions experiencing a higher burden of CKD-related anemia. These regions frequently lack advanced medical infrastructure, diagnostic equipment and qualified healthcare personnel, resulting in delays in early screening, diagnosis and treatment of CKD [38]. The global median prevalence of nephrologists is 11.8 per million population, with disparities as high as 80-fold between low-income and high-income countries [39]. Additionally, health education and disease awareness significantly influence personal health, guide clinical practice and affect healthcare-seeking behavior [40]. Individuals with higher socioeconomic status and education levels are more likely to be aware of their CKD status due to better access to resources that enhance the availability and quality of medical services [41]. Socioeconomic status and the unequal distribution of wealth or income are well-established social determinants of health, significantly influencing the outcomes and complications of CKD. The marked decline in the prevalence and YLD rate in East Asia is closely associated with substantial investments in healthcare infrastructure driven by economic growth in the region [5]. However, lower SDI regions often suffer from economic underdevelopment and poverty, making it challenging for patients to afford long-term CKD and anemia treatment costs [41].

To address the global challenges posed by CKD-related anemia, efforts should focus on enhancing access to affordable and effective interventions. Improving access to anemia screening, iron supplementation, ESAs and HIF-PHD inhibitors could help reduce the burden of CKD-related anemia. Addressing healthcare disparities specific to CKD and anemia may offer a more immediate approach. While ESAs have revolutionized anemia management, their cost and need for injections and cold chain for storage limit access in lower SDI countries. HIF-PHD inhibitors, though innovative, are also not always affordable. However, as oral medications not requiring a cold chain for storage, HIF-PHD inhibitors are more suitable for remote and underdeveloped regions lacking refrigeration infrastructure, potentially

improving treatment access. In resource-limited settings, international collaboration is essential to facilitate the transfer of treatment modalities and expertise from high-income countries to those in need. Health authorities should proactively develop and disseminate clinical guidelines for managing CKD-related anemia, with treatment strategies adapted to local contexts, considering economic development, healthcare infrastructure and patient demographics to ensure effective and sustainable care.

This study has some limitations. Firstly, our analysis relied on the GBD database, which, despite its methodological advancements, robustness and reliability, is inherently constrained by the quality of the available data. Secondly, it is noteworthy that the anemia information of GBD 2021 primarily focused on hemoglobin levels and did not directly collect data on anemia treatment and iron stores. Additionally, in certain regions, particularly in low SDI and low-middle SDI countries, GBD statistics are often inadequate and sparse, with such data obtained through statistical modeling. This limitation may impact the analysis and potentially lead to biased estimates of the burden [42]. Nevertheless, the GBD study currently represents the sole effort that allows global analysis and cross-national comparison. More high-quality data sets are still needed in the future.

In conclusion, this study demonstrated that the overall global prevalence and YLDs rates of CKD-related anemia from 1990 to 2021 have generally declined, reflecting global advancements in prevention and treatment strategies. However, the number of cases continued to increase, primarily due to population growth and aging. This investigation also revealed a gender disparity and the influence of cause-specific and socioeconomic factors on the burden of CKD-related anemia. These population-based findings provide crucial insights to inform resource allocation and guide the development of effective interventions aimed at mitigating the global burden of CKD-related anemia.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

FUNDING

This project was supported by the National Natural Science Foundation of China (No. 82174308), Natural Science Research Project of Guangdong Province (No. 2024Al515011955), the Project of Guangzhou Basic and Applied Basic Research Foundation (No. 2023A03J0743), the Specific Fund of State Key Laboratory of Dampness Syndrome of Chinese Medicine (No. SZ2023ZZ03 and No. SZ2021ZZ16), the Guangzhou City-school-enterprise joint funding project (No. SL2023A03J00958) and the Guangzhou Science and Technology Project (No. 202206010076).

AUTHORS' CONTRIBUTIONS

Data curation, formal analysis, and initial manuscript preparation were conducted by W.L. and W.G. J.C., R.W., and Y.S. contributed significantly to data interpretation and substantial manuscript revision. The study's conceptualization and design were supervised by Z.L. and L.Z., who also reviewed the manuscript. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data of this investigation are publicly accessible through the GBD 2021 database, which is available at https://vizhub.healthdata.org/gbd-results/.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest or personal relationships that could have appeared to influence the work reported in this paper.

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Received: 26.11.2024; Editorial decision: 28.4.2025