

Global, SexSpecific, and Socioeconomic Disparities in Chronic Kidney Disease Burden: An AgePeriodCohort Analysis

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Introduction. Chronic kidney disease (CKD) is a major global public health challenge, driven by aging, diabetes, hypertension, and socioeconomic disparities. This study analyzed the global CKD burden from 1990 to 2021 by sex and Socio-demographic Index (SDI) to inform targeted interventions.

Methods. Using Global Burden of Disease (GBD) 2021 data for 204 countries and territories, we assessed incidence, prevalence, mortality, and disability-adjusted life years (DALYs). Age-standardized rates (ASRs) per 100,000 were based on the GBD World Standard Population. Temporal trends were measured as percentage changes in ASRs (1990–2021) and visualized by SDI quintile and sex. Age–Period–Cohort (APC) modeling with median constraints estimated rate ratios (RRs) and 95% confidence intervals (CIs) using the NCI Webtool.

Results. From 1990 to 2021, global age-standardized CKD burden increased substantially. The largest increases attributable to risk factors were for high body mass index (76.59% globally; 107.81% in low-middle SDI), high fasting plasma glucose (46.59% globally; 88.76% in high SDI), and high systolic blood pressure (44.31% in low-middle SDI). Males had higher mortality and DALY rates across all SDI levels; females had higher incidence and prevalence. A positive cohort gradient was more evident among males. The 1982 birth cohort RR was 1.14 (95% CI 1.01–1.29) in males and 1.00 (95% CI 0.87–1.14) in females, suggesting rising modeled generational burden among younger adult male cohorts.

Conclusion. The global CKD burden has risen markedly, with persistent sex and socioeconomic disparities. Accelerating burden among younger generations requires age- and sex-sensitive prevention, improved healthcare access, and targeted interventions tailored to regional SDI levels.

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INTRODUCTION

Chronic kidney disease (CKD) has emerged as one of the most pressing global health challenges of the 21st century.^{1,2} Characterized by progressive loss of kidney function, CKD often leads to

severe complications such as kidney failure, cardiovascular disease, and increased mortality. The disease is driven by a complex interplay of clinical, environmental, and socioeconomic factors, including diabetes mellitus, hypertension, obesity,

population aging, and lifestyle changes.³ Over the past three decades, the global burden of CKD has risen dramatically, positioning it as a leading cause of morbidity and mortality worldwide.^{2,3}

The prevalence and burden of CKD are deeply influenced by socioeconomic development, as measured by the Sociodemographic Index (SDI). Countries with lower SDI scores — often characterized by limited healthcare access, education, and economic resources — bear a disproportionately higher burden of CKD. For instance, while highSDI countries report an average CKD prevalence of 5–7%, lowSDI countries experience rates as high as 15–20%. This disparity underscores the critical role of social determinants of health in shaping the epidemiology of CKD.^{4,5} The global burden of CKD has increased constantly over the past three decades. In 2021, an estimated 673.7 million people were living with CKD, accounting for 8.54% of the global population — a 92.0% increase from 1990. This rising trend underscores the urgent need for targeted public health interventions.^{6–8}

The economic and societal impact of CKD is profound. The disease places a significant financial burden on healthcare systems, particularly due to the high costs associated with longterm management, including dialysis and kidney transplantation. Additionally, CKD severely impairs patients' quality of life, limiting their ability to work and participate in daily activities. These challenges are exacerbated in low and middleincome countries, where healthcare infrastructure is often inadequate, and access to early diagnosis and treatment is limited. Addressing the global burden of CKD requires a comprehensive approach that integrates clinical, public health, and policy interventions.^{7–9}

This study aims to analyze the global burden of CKD from 1990 to 2021, focusing on socioeconomic determinants and disparities in prevalence and mortality across regions. Using the SDI, it identifies trends, risk factors, and inequalities, particularly between high and lowincome countries. The research provides actionable insights for policymakers, emphasizing strategies such as improving healthcare access, early detection, and addressing socioeconomic drivers of CKD. Ultimately, it seeks to inform interventions that reduce CKD prevalence, enhance health equity, and alleviate the disease's societal and economic impact.

Although previous studies have examined the

global burden of CKD using GBD 2021 data, the present study provides a complementary analysis by applying an Age-Period-Cohort (APC) framework to characterize age-, period-, and cohort-related patterns in CKD burden. In addition, we examine sex-specific differences and stratify risk-attributable CKD burden across SDI groups. These analyses provide a more detailed description of temporal, sex-specific, and socioeconomic patterns in the global CKD burden and may help identify populations and periods warranting further investigation.

MATERIALS AND METHODS

Study population and data

This study was designed as a secondary ecological analysis of CKD estimates from the Global Burden of Disease (GBD) 2021 study. We analyzed populationlevel estimates of CKD incidence, prevalence, mortality, and disabilityadjusted life years (DALYs) across 204 countries and territories from 1990 to 2021, with stratification by sex, age, and SDI. All estimates were obtained from the GBD 2021 Results Tool, and no individuallevel patient data were used in the present analysis.¹⁰

Country Classification

Countries were stratified based on the SDI, a composite measure that evaluates social and economic development by integrating indicators such as income per capita, educational attainment, and fertility rates.¹¹ For this study, countries were categorized into five SDI groups: high, highmiddle, middle, lowmiddle, and low SDI. This classification facilitates a nuanced understanding of disparities in CKD burden across different development contexts. Additionally, agestandardized rates (ASRs) were applied to enable equitable comparisons across populations with varying age structures. By standardizing rates, this approach minimizes confounding effects of demographic differences, allowing for more accurate crosscountry and crossregional analyses. The use of SDI and ASRs ensures that the study's findings are both robust and actionable, providing a foundation for targeted interventions to reduce CKD burden and improve health equity globally.

Chronic kidney disease definition and case ascertainment

In the GBD 2021 framework, CKD was defined

based on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR). CKD stages 1–2 were defined by $\text{ACR} \geq 30 \text{ mg/g}$ and $\text{eGFR} > 60 \text{ mL/min/1.73 m}^2$, and stages 3, 4, and 5 by eGFR of 30–59, 15–29, and $< 15 \text{ mL/min/1.73 m}^2$, respectively. Unlike the KDIGO clinical definition, the GBD framework does not formally require persistence of these abnormalities for at least three months. In GBD, etiologyspecific CKD estimates for type 1 diabetes, type 2 diabetes, hypertension, glomerulonephritis, and other/unspecified causes are derived through the GBD modeling framework using available registry and clinical data. In the present study, overall and causespecific CKD estimates were obtained directly from the GBD 2021 Results Tool rather than from individuallevel patient records.^{5,12,13}

The primary outcome measures were incidence, prevalence, mortality, and DALYs. DALYs, a critical measure of disease burden, combine years of life lost (YLL) due to premature mortality and years lived with disability (YLD), calculated as $\text{DALY} = \text{YLL} + \text{YLD}$. YLL is calculated as $\text{YLL} = N \times L$, where N represents the number of deaths in a specific age group and L denotes the standard life expectancy at the age of death (in years). YLD is calculated as $\text{YLD} = \text{DW} \times P$, where DW is the disability weight (a value between 0 and 1 reflecting the severity of disability) and P is the number of individuals living with the disease.⁷ Age-standardized rates (ASRs) were used to enable comparisons across populations with different age structures, and all estimates were reported with their corresponding 95% uncertainty intervals (UIs).

Statistical analysis

This study employed a descriptive epidemiological approach to analyze the global burden of CKD from 1990 to 2021. All primary estimates (incidence, prevalence, mortality, DALYs, YLLs, and YLDs) and their corresponding 95% UIs were directly extracted from the GBD 2021 database using the GBD Results Tool (<https://vizhub.healthdata.org/gbd-results/>). The GBD uses a Bayesian metaregression framework (DisModMR) and the Cause of Death Ensemble model (CODEm) to generate estimates with 95% UIs, which reflect both sampling and nonsampling uncertainty.¹⁰

Temporal trends were assessed by calculating the percentage change in each metric between 1990

and 2021, and visualized using heat maps stratified by SDI quintiles and sex to illustrate the temporal evolution of CKD burden across the four key indicators (incidence, prevalence, mortality, and DALYs) over the 32-year study period. Differences were described using point estimates and 95% UIs; no formal pairwise hypothesis tests were performed.

To disentangle age, period, and cohort effects, an APC analysis was performed using the National Cancer Institute (NCI) Webtool, which estimates rate ratios (RRs) and 95% confidence intervals (CIs) for independent generational and temporal trends, using a reference cohort (1947) and reference period (2002–2006).^{14,15} All age-standardized rates (ASRs) reported in this study were calculated by the GBD collaboration using the GBD World Standard Population as the reference. Heat maps were generated using R software (version 4.5.0) with the ggplot2 package, and additional data visualization and percentage change calculations were performed using Microsoft Excel 2016. No formal statistical significance threshold (e.g., P -value) was applied, as this is a descriptive trend analysis based on populationlevel estimates with 95% UIs.

Ethical consideration

This study used data sourced from the GBD website. Since the data were obtained from publicly accessible sources, no formal ethical approval was necessary for this research.

RESULTS

Study design and population

The global age-standardized burden of CKD increased substantially between 1990 and 2021. In 1990, the global age-standardized mortality rate was 18.13 (95% UI: 16.26–21.03) per 100,000 for males and 12.64 (95% UI: 11.44–13.99) per 100,000 for females. By 2021, these rates rose to 21.91 (95% UI: 19.66–23.60) per 100,000 for males and 15.90 (95% UI: 14.22–17.27) per 100,000 for females. Similarly, the global age-standardized incidence rate increased from 180.89 (95% UI: 167.97–195.41) per 100,000 for males and 201.88 (95% UI: 187.73–218.45) per 100,000 for females in 1990, to 220.11 (95% UI: 207.07–233.07) per 100,000 for males and 246.03 (95% UI: 231.84–260.67) per 100,000 for females in 2021. The global age-standardized DALY rate also rose from 546.41 (95% UI: 476.93–612.62) per

Table 1. Age-standardized rates of CKD burden by Sociodemographic Index: deaths, incidence, DALYs, YLLs, and YLDs per 100,000 population (1990 vs. 2021)

Location	Year	Sex	Death per 100,000 (95% UI)	Incidence per 100,000 (95% UI)	Prevalence per 100,000 (95% UI)	DALYs per 100,000 (95% UI)	YLDs per 100,000 (95% UI)	YLLs per 100,000 (95% UI)
Global	1990	Male	18.13 (16.26-21.03)	180.89 (167.97-195.41)	7812.80 (7301.88-8356.28)	546.41 (476.93-612.62)	107.26 (77.29-138.14)	439.16 (382.89-497.98)
		Female	12.64 (11.44-13.99)	201.88 (187.73-218.45)	8293.08 (7778.75-8870.27)	426.90 (389.12-467.43)	101.19 (72.54-129.73)	325.71 (298.82-358.94)
	2021	Male	21.91 (19.66-23.60)	220.11 (207.07-233.07)	7808.96 (7288.71-8366.60)	603.40 (546.08-663.35)	108.48 (77.91-139.24)	494.92 (447.83-537.25)
		Female	15.90 (14.22-17.27)	246.03 (231.84-260.67)	8182.65 (7653.14-8764.76)	465.69 (424.02-511.12)	102.09 (73.91-131.15)	363.59 (330.00-398.67)
High SDI	1990	Male	11.65 (10.94-12.14)	242.21 (224.62-261.48)	6529.04 (6109.92-6950.11)	329.09 (299.01-359.37)	97.45 (70.26-124.28)	231.64 (221.69-242.26)
		Female	7.85 (7.04-8.27)	260.14 (241.53-281.08)	7203.54 (6756.22-7675.51)	241.27 (215.42-264.75)	82.17 (59.26-103.93)	159.10 (149.11-165.64)
	2021	Male	16.94 (15.28-17.96)	269.60 (253.04-286.49)	6490.59 (6081.65-6909.00)	415.46 (377.93-450.22)	103.60 (74.38-132.72)	311.85 (289.76-329.06)
		Female	12.05 (10.08-13.22)	285.08 (267.73-303.76)	6977.03 (6557.86-7421.00)	311.34 (279.21-341.31)	88.27 (63.65-111.32)	223.07 (199.62-239.69)
High middle SDI	1990	Male	14.81 (13.43-17.34)	158.53 (146.43-172.24)	7157.53 (6680.08-7667.57)	419.91 (375.18-480.17)	93.44 (66.34-119.99)	326.47 (295.59-375.50)
		Female	9.50 (8.55-10.56)	164.46 (151.60-178.15)	8035.44 (7524.07-8619.04)	321.82 (289.34-358.96)	90.24 (64.39-116.74)	231.58 (211.25-259.17)
	2021	Male	14.56 (12.64-16.68)	193.41 (181.38-205.50)	6853.17 (6384.86-7374.11)	369.27 (328.08-415.88)	85.71 (61.01-109.93)	283.56 (247.72-325.85)
		Female	10.40 (9.03-11.78)	218.41 (205.94-232.42)	7645.37 (7141.34-8223.58)	290.31 (259.40-324.21)	83.39 (60.38-107.04)	206.92 (184.77-236.06)
Middle SDI	1990	Male	21.35 (18.83-25.00)	159.33 (146.57-172.63)	8158.97 (7612.17-8756.74)	623.81 (545.23-713.87)	117.10 (83.64-150.87)	506.71 (441.02-578.94)
		Female	17.37 (15.56-19.55)	182.84 (167.90-199.01)	8726.26 (8157.04-9352.59)	553.65 (497.30-610.64)	119.98 (85.52-155.14)	433.67 (393.18-484.89)
	2021	Male	24.45 (20.58-27.14)	214.26 (201.79-226.96)	8098.56 (7550.63-8700.62)	669.83 (578.13-737.31)	115.21 (82.31-149.29)	554.62 (472.55-613.14)
		Female	18.14 (16.13-19.93)	250.36 (236.00-264.82)	8446.79 (7892.03-9061.61)	532.21 (476.04-587.63)	113.01 (80.92-144.57)	419.20 (376.10-462.38)
Low middle SDI	1990	Male	21.48 (17.64-27.68)	147.53 (136.31-160.05)	9229.61 (8593.69-9882.36)	685.12 (567.69-801.78)	124.44 (88.47-161.81)	560.68 (455.46-674.27)
		Female	15.73 (13.69-18.98)	158.73 (146.52-172.68)	9347.73 (8720.24-10016.60)	531.94 (468.32-614.24)	120.20 (86.04-155.43)	411.73 (361.12-490.81)
	2021	Male	27.17 (23.84-31.41)	194.79 (180.20-208.64)	9042.62 (8406.49-9720.19)	781.69 (687.51-882.96)	128.38 (91.81-165.30)	653.32 (574.52-737.40)
		Female	19.59 (17.47-22.01)	214.51 (199.30-230.24)	9270.82 (8645.18-9936.56)	599.95 (540.99-680.54)	121.42 (88.30-156.25)	478.52 (422.77-542.09)
Low SDI	1990	Male	35.40 (29.28-44.47)	116.45 (107.52-125.58)	8147.21 (7607.07-8702.30)	975.53 (823.74-1171.99)	104.63 (74.25-135.55)	870.90 (714.28-1060.23)
		Female	24.18 (21.23-29.46)	126.92 (117.35-138.88)	8027.80 (7483.49-8586.84)	731.59 (653.54-841.00)	113.15 (79.77-147.29)	618.44 (550.27-732.07)
	2021	Male	34.24 (29.43-40.36)	145.69 (134.52-157.44)	7972.93 (7430.23-8545.46)	902.15 (775.78-1081.09)	106.33 (76.05-139.52)	795.82 (678.31-972.30)
		Female	25.05 (21.73-29.09)	163.86 (151.11-176.81)	7988.49 (7455.25-8562.74)	687.31 (601.43-795.40)	111.48 (79.75-145.10)	575.83 (500.31-670.77)

100,000 for males and 426.90 (95% UI: 389.12–467.43) per 100,000 for females in 1990, to 603.40 (95% UI: 546.08–663.35) per 100,000 for males and 465.69 (95% UI: 424.02–511.12) per 100,000 for females in 2021 (Table 1).

Sex-Specific Burden

Males consistently exhibited higher age-standardized mortality and DALY rates across all SDI levels throughout the study period. In 2021, the global age-standardized mortality rate for males (21.91 per 100,000) was 38% higher than for females (15.90 per 100,000), and the DALY rate for males (603.40 per 100,000) was 30% higher than for females (465.69 per 100,000). In contrast, females showed higher age-standardized incidence and prevalence rates. In 2021, the global age-standardized incidence rate for females (246.03 per 100,000) was 12% higher than for males (220.11 per 100,000). These sex-specific patterns were consistent across all SDI groups (Table 1).

SDI-Specific Burden

The heat maps demonstrate a broadly inverse

association between SDI levels and mortality/DALY rates, and a broadly direct relationship between SDI levels and incidence rates. although this gradient was not strictly monotonic across all SDI categories.

The low and low-middle SDI regions consistently exhibited the highest mortality and DALY rates, while high SDI regions displayed the lowest rates. In 2021, the low SDI region had the highest age-standardized mortality rate at 34.24 (95% UI: 29.43–40.36) per 100,000 for males and 25.05 (95% UI: 21.73–29.09) per 100,000 for females, compared to 16.94 (95% UI: 15.28–17.96) per 100,000 for males and 12.05 (95% UI: 10.08–13.22) per 100,000 for females in the high SDI region. Conversely, incidence rates were highest in high SDI regions (269.60 per 100,000 for males and 285.08 per 100,000 for females in 2021) and lowest in low SDI regions (145.69 per 100,000 for males and 163.86 per 100,000 for females in 2021) (Table 1, Appendix 1).

Cause-Specific CKD Patterns

Figure 1 highlights marked sex disparities in the percentage contribution of underlying causes to

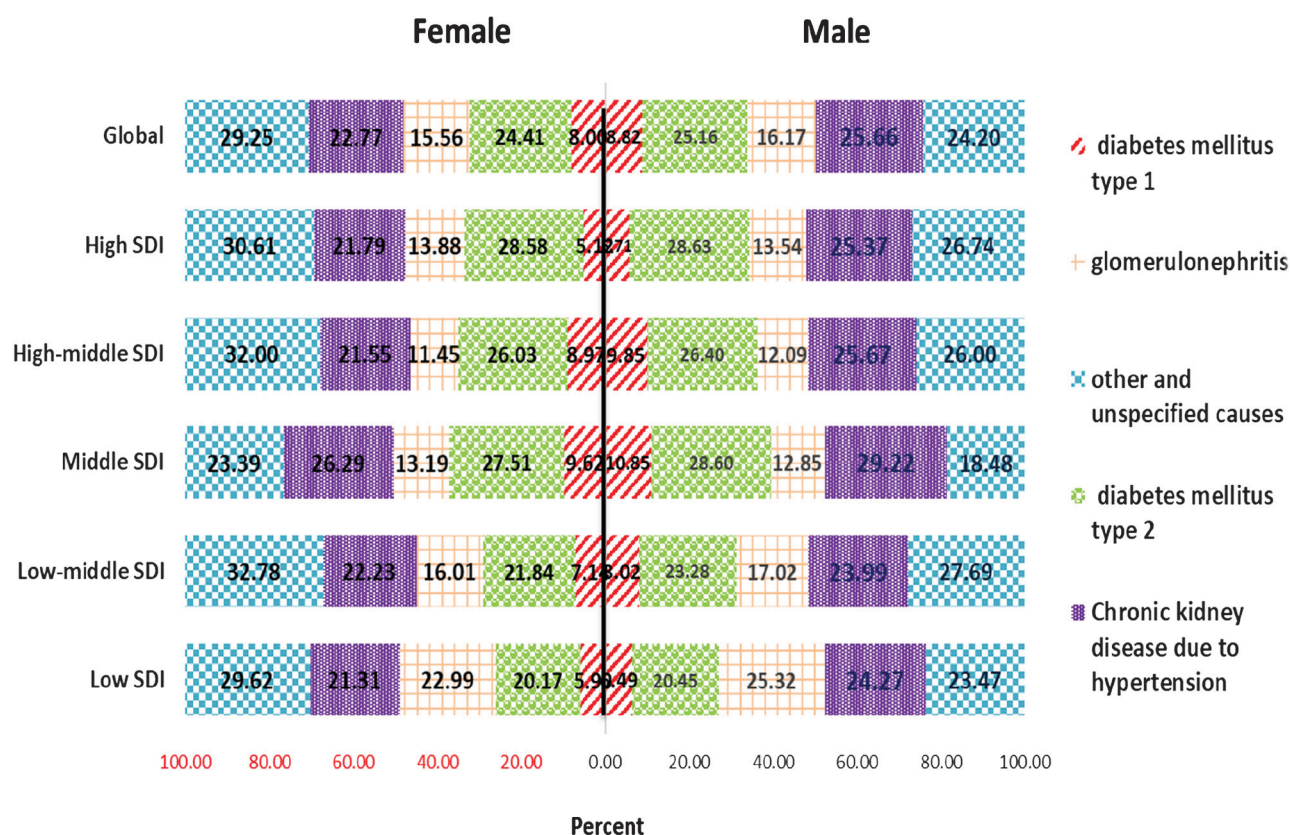


Figure 1. Percentage contribution of main causes to CKD-related DALYs in 2021, stratified by SDI and sex.

CKD-related DALYs. Women exhibited higher rates of “other and unspecified causes,” particularly in the low-middle SDI region (32.78% vs. 27.69% in men). Conversely, men demonstrated a greater burden of CKD attributable to hypertension, with the highest percentage in the middle SDI region (29.22% vs. 26.29% in women). Glomerulonephritis was more prevalent among men globally, reaching the highest rate in the low SDI region (25.32% vs. 22.99% in women). A similar trend was observed for both type 1 and type 2 diabetes, with men exhibiting higher rates, most notably in the high SDI region for type 2 diabetes (28.63% vs. 28.58% in women) and the middle SDI region for type 1 diabetes (10.58% vs. 9.62% in women) (Figure 1).

Risk-Attributable CKD Burden

The percentage changes in global CKD burden attributable to key risk factors from 1990 to 2021 showed the most substantial increases for high body mass index (BMI), with a 76.59% increase globally (77.47% in men and 74.49% in women). CKD burden attributable to high fasting plasma glucose (high FPG) increased by 46.59% globally (44.26% in men and 46.93% in women), and CKD burden attributable to high systolic blood pressure (SBP) increased by 27.11% globally (25.23% in men and 27.27% in women). Regionally, the low-middle SDI region saw a 107.81% increase in CKD burden attributable to high BMI, while the high SDI region showed a marked 88.76% increase in CKD burden attributable to high FPG (Table 2, Figure 2).

Age-Specific Patterns

Males exhibit systematically higher DALYs across all age groups and Cohort trends reveal males face accelerating CKD burdens in younger generations (Figure 3).

The APC analysis (Appendix 2) identified a higher cohort-related rate ratio for more recent birth cohorts among males, with weaker evidence of a similar pattern among females. The 1982 birth cohort had a rate ratio of 1.14 (95% CI: 1.01–1.29) relative to the specified reference cohort, compared with 1.00 (95% CI: 0.87–1.14) in females — a confidence interval spanning 1.0 and consistent with no meaningful cohort effect in this sex. This finding indicates a higher modeled DALY rate within the APC framework and should not be interpreted as evidence of a causal or independent generational

Table 2. Changes in age-standardized rates of GBD-defined risk-attributable contributors to CKD burden (per 100,000 population, 1990 and 2021)

Region	Year	Dietary risks (95% UI)	High body-mass index (95% UI)	High fasting plasma glucose (95% UI)	High systolic blood pressure (95% UI)	Impaired kidney function (95% UI)	Low physical activity (95% UI)	Other environmental risks (95% UI)	Suboptimal temperature (95% UI)
Global	1990	84.12 (49.75–120.66)	69.13 (35.06–106.00)	127.88 (78.92–182.86)	101.83 (53.28–146.98)	479.67 (438.38–523.74)	9.63 (3.73–17.02)	14.72 (–1.89–35.69)	23.17 (17.26–30.13)
	2021	93.52 (54.29–134.38)	122.08 (66.25–180.18)	187.46 (123.18–257.57)	129.44 (67.23–190.06)	529.43 (484.78–577.04)	10.81 (4.14–19.18)	17.52 (–2.26–42.15)	25.70 (17.97–35.12)
	%Change	11.17	76.59	46.59	27.11	10.37	12.25	19.02	10.91
High SDI	1990	57.95 (33.65–83.18)	64.68 (33.97–94.57)	79.96 (50.40–114.39)	80.23 (42.18–113.92)	277.60 (249.89–303.19)	7.40 (2.86–13.15)	5.75 (–0.75–13.88)	15.96 (12.86–18.04)
	2021	76.04 (45.79–106.63)	119.83 (68.69–167.37)	150.94 (104.05–201.07)	89.82 (45.31–129.30)	358.46 (324.68–390.13)	9.75 (3.75–17.16)	6.58 (–0.86–15.84)	23.11 (17.61–29.02)
	%Change	31.21	85.26	88.76	11.95	29.12	31.75	14.43	44.79
High-middle SDI	1990	59.10 (34.04–85.56)	65.11 (33.26–99.79)	104.29 (64.73–150.91)	78.90 (40.18–113.99)	360.77 (325.30–401.56)	8.02 (3.14–14.17)	8.15 (–1.03–19.96)	20.81 (16.70–25.00)
	2021	51.19 (29.01–75.46)	89.04 (47.48–132.50)	125.60 (82.12–173.36)	80.32 (39.92–119.49)	324.55 (293.60–361.15)	8.26 (3.23–14.47)	8.27 (–1.05–19.97)	17.42 (13.75–21.64)
	%Change	–13.38	36.75	20.43	1.79	–10.03	2.99	1.47	–16.29
Middle SDI	1990	104.68 (60.14–151.54)	74.99 (37.30–120.40)	178.35 (112.50–252.60)	113.65 (58.10–168.03)	585.38 (530.79–653.23)	12.43 (4.75–21.92)	18.06 (–2.27–43.31)	27.04 (20.61–34.60)
	2021	105.15 (60.22–151.78)	135.25 (72.54–202.01)	221.63 (145.09–306.94)	147.53 (78.08–215.64)	596.22 (535.49–650.29)	12.83 (4.81–22.67)	20.12 (–2.66–48.42)	26.04 (18.98–33.64)
	%Change	0.44	80.35	24.26	29.81	1.85	3.21	11.40	–3.69
Low-middle SDI	1990	107.74 (61.11–156.87)	65.55 (33.75–104.30)	146.88 (89.95–210.64)	127.76 (64.74–188.26)	609.15 (544.48–685.62)	10.77 (4.04–19.46)	28.14 (–3.65–68.31)	25.07 (12.28–42.58)
	2021	123.91 (69.82–182.13)	136.22 (71.43–204.33)	234.50 (150.60–332.48)	184.38 (95.94–267.88)	686.72 (622.74–765.77)	11.41 (4.09–20.81)	34.60 (–4.43–81.53)	31.30 (14.42–51.80)
	%Change	15	107.81	59.65	44.31	12.73	5.94	22.95	24.85
Low SDI	1990	155.10 (88.07–227.53)	71.68 (35.64–119.85)	189.06 (111.12–275.99)	171.67 (83.42–256.75)	853.26 (759.30–969.65)	12.11 (4.62–22.16)	39.37 (–5.03–96.79)	33.68 (22.47–49.98)
	2021	153.10 (87.25–226.01)	107.94 (52.88–174.77)	226.37 (140.67–324.67)	195.23 (99.89–290.87)	791.46 (702.41–906.49)	10.64 (3.74–19.84)	40.53 (–5.34–98.95)	31.21 (18.59–46.52)
	%Change	–1.28	50.58	19.73	13.72	–7.24	–12.13	2.94	–7.05

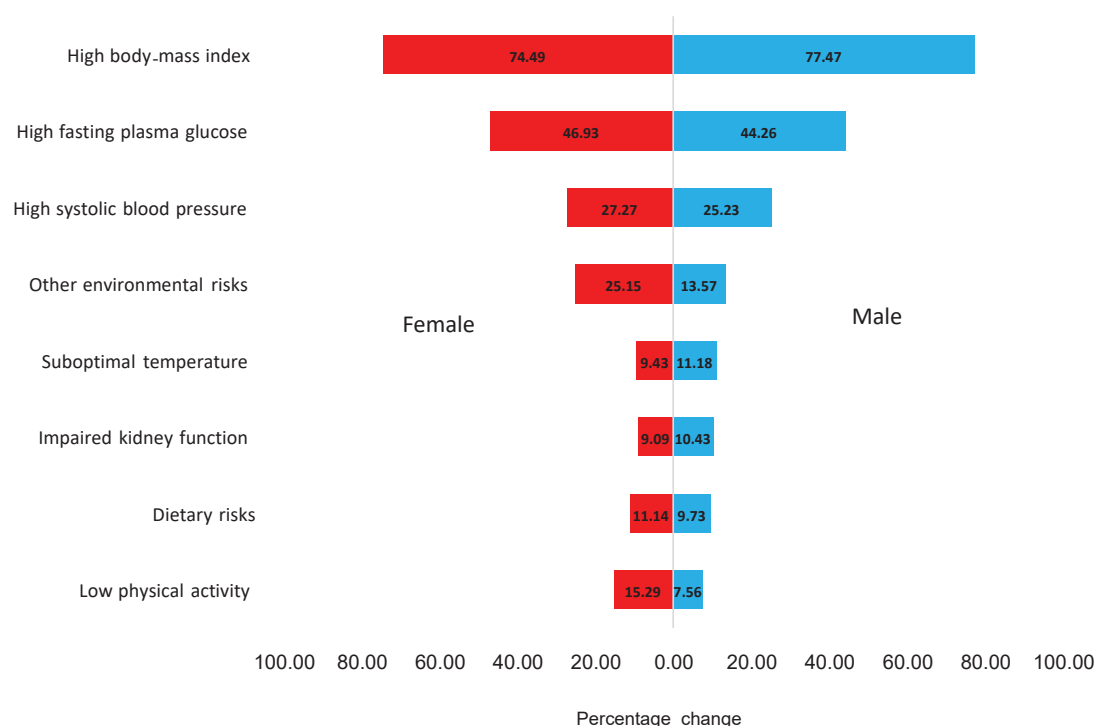


Figure 2. Percentage change in age-standardized CKD burden attributable to selected GBD-defined risk factors from 1990 to 2021, by sex.

SDI levels, females exhibited higher incidence and prevalence rates. Second, the APC analysis identified a statistically significant upward cohort effect for recent birth cohorts (e.g., rate ratio for the 1982 male cohort: 1.14; 95% CI: 1.01–1.29), indicating a higher modeled DALY rate ratio among more recent birth cohorts; however, this ecological cohort pattern cannot by itself establish a causal generational risk of CKD among younger adult birth cohorts. Third, the burden attributable to high BMI increased substantially between 1990 and 2021, with the largest relative increase observed in the low-middle SDI region (107.81%).

CKD remains a major public health problem worldwide. It not only affects the quality of life of individuals but also imposes a heavy economic and social burden on healthcare systems. The findings from this study reveal a substantial and evolving global burden of CKD from 1990 to 2021, with marked disparities between sexes and across different socioeconomic regions.^{1,2}

Our analysis directly demonstrates that while CKD mortality rates are higher among men compared to women, the incidence rate was higher among women. These sex disparities are consistently

increase in CKD risk.

The age distribution of CKD burden also varied substantially across SDI levels (Figure 4). In high-SDI countries, the age-specific DALY burden shifted toward older ages. Among individuals aged ≥ 75 years, the DALY rate approximately doubled from 1,950 to 3,800 per 100,000, while the absolute number of DALYs nearly tripled between 1990 and 2021. In middle-SDI regions, the most pronounced relative increases were observed among individuals aged 50–54 and 65–69 years, with increases of approximately 38% and 42%, respectively. In contrast, in low-SDI countries, the burden remained more concentrated in younger age groups, with individuals aged 40–44 years consistently accounting for more than 18% of total DALYs.

DISCUSSION

This study provides a comprehensive assessment of the global CKD burden using GBD 2021 data, incorporating an APC analysis together with sex-specific and SDI-stratified evaluations. Three principal findings emerged. First, while age-standardized mortality and DALY rates were consistently higher in males across all

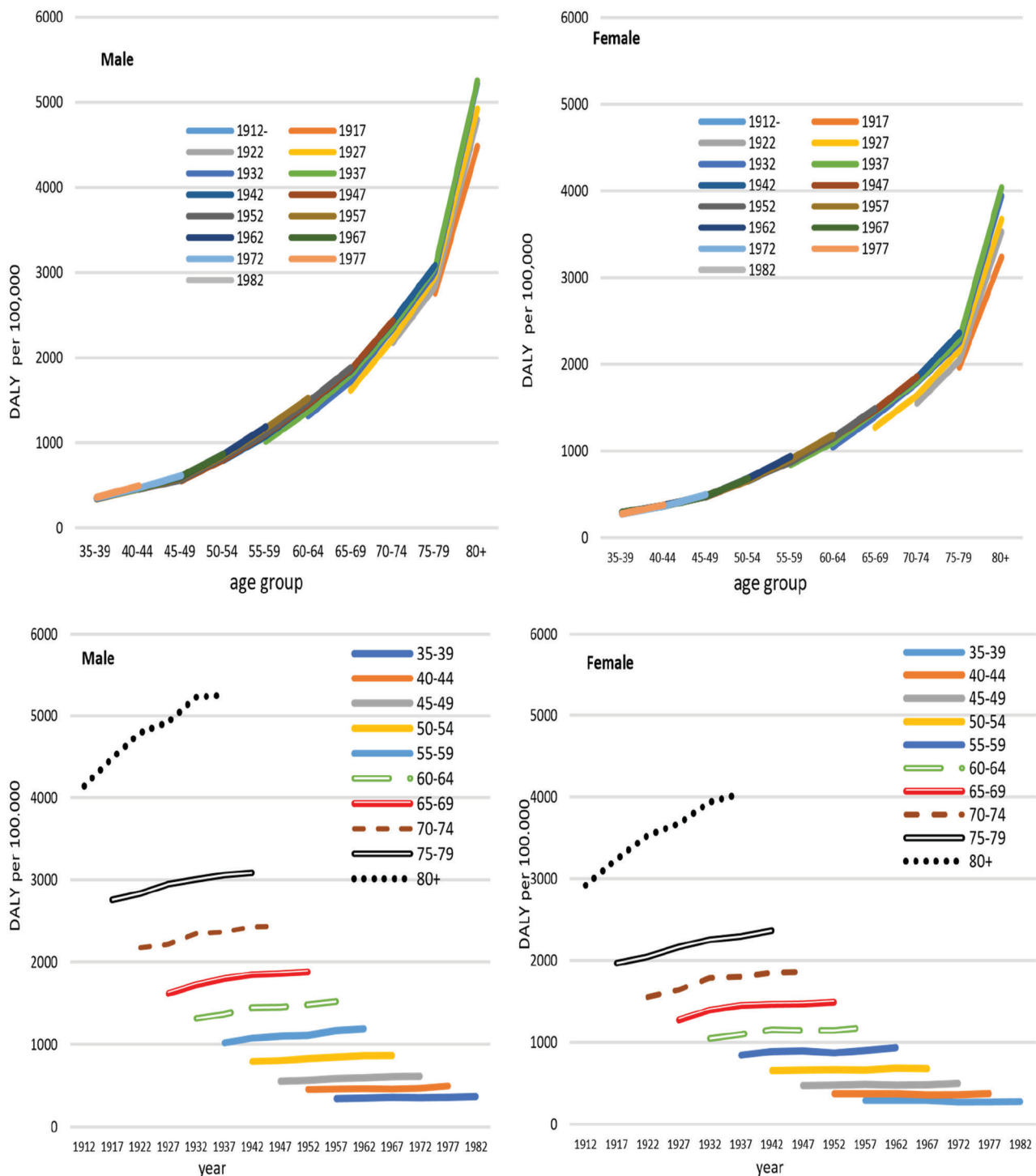


Figure 3. Agespecific DALY rates per 100,000 population for CKD globally, stratified by sex, age group, and birth cohort.

reflected across key health indicators, including DALYs and YLDs. While the underlying drivers of these disparities were not directly analyzed in this study, previous literature has suggested that differences in healthcare access, lifestyle

habits, and biological factors may contribute to these inequities.^{12,16,17} Further research is needed to disentangle the relative contributions of these factors. Nevertheless, our findings underscore the importance of considering sexspecific needs when

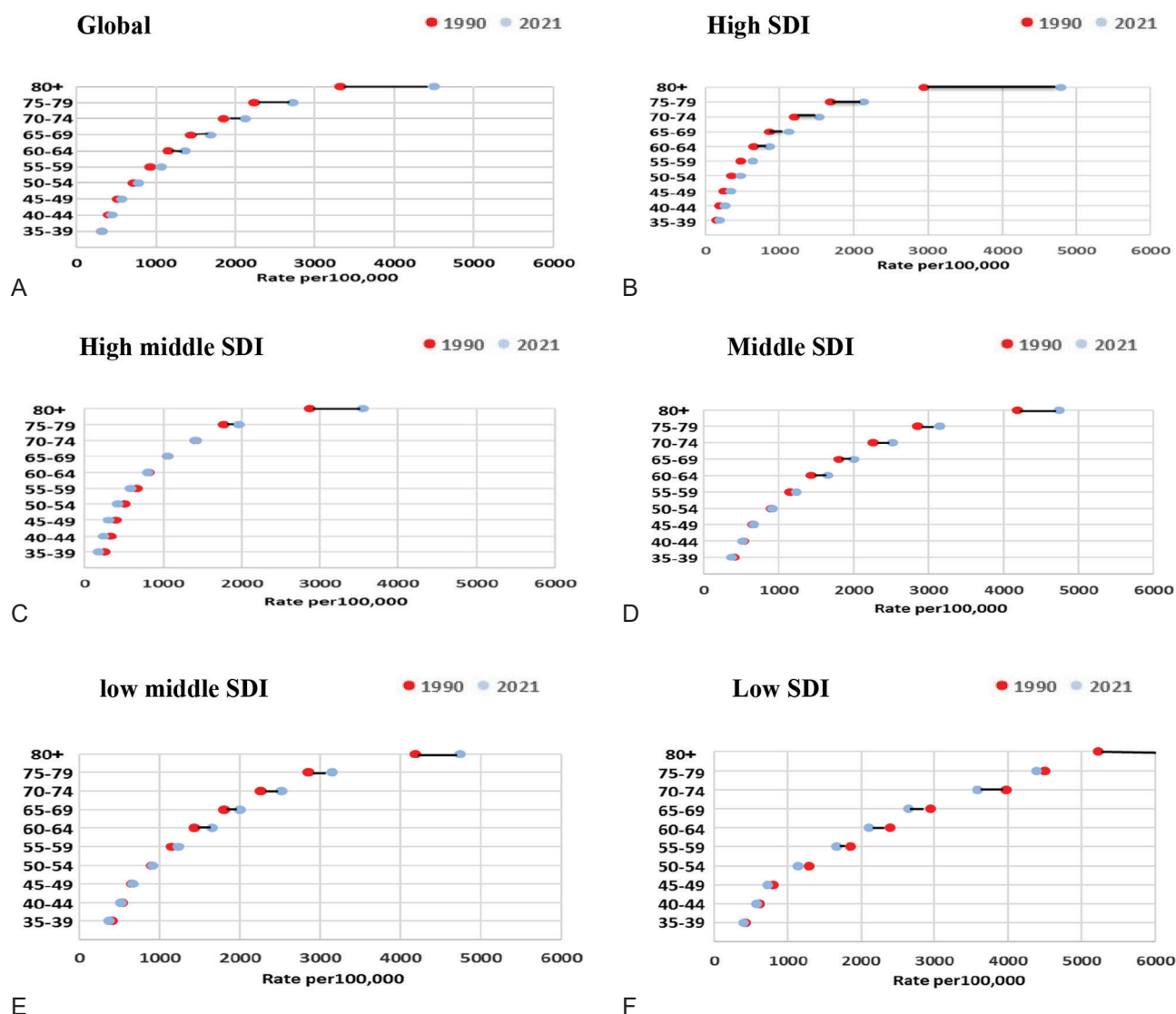


Figure 4. Agespecific DALY rates of CKD by age group and SDI from 1990 to 2021.

designing health interventions.

The main risk factors for CKD vary significantly across different SDI levels. From 1990 to 2021, notable changes in CKD burden attributable to risk factors show that men have experienced greater increases in burden attributable to high BMI (77.47% vs. 74.49% in women) and impaired kidney function (10.43% vs. 9.09%), whereas women have faced higher increases in burden attributable to high FPG (46.93% vs. 44.26% in men) and high SBP (27.27% vs. 25.23%). These sexspecific patterns in riskattributable burden highlight the need for differentiated prevention approaches. While the mechanisms underlying these patterns were not directly investigated in this study,

previous literature has hypothesized potential roles for biological factors and sociocultural determinants.¹⁷⁻¹⁹ Further studies are needed to elucidate these mechanisms. Based on our findings, we recommend that prevention strategies be tailored to address the distinct risk profiles observed in men and women.

In lowSDI regions, our analysis showed that CKDrelated mortality remained markedly higher than in other SDI groups throughout the study period, despite lower reported incidence. This paradox probably reflects welldocumented health system constraints, including limited access to dialysis, delayed referral pathways, and underdiagnosis — as highlighted by previous

studies in their global assessment of kidney dysfunction burden.²⁰ While the present study did not directly examine health system factors, previous reports suggest that inadequate infrastructure, low public awareness, and limited primary care capacity may contribute to these persistent disparities. Therefore, our findings imply that reducing CKD mortality in lowSDI settings may require health system strengthening and earlier detection strategies, rather than relying solely on screening expansion.^{8,20,21} These hypotheses require further investigation. Nevertheless, our findings support the recommendation that strengthening healthcare systems and increasing public awareness in lowSDI regions should be prioritized.

Conversely, in highSDI regions, the incidence of CKD is higher compared to other SDI groups. While the factors driving this higher incidence were not directly analyzed in this study, previous literature has hypothesized potential roles for lifestyle changes, dietary patterns, urbanization, and obesity.⁸ Based on our findings, we recommend that educational and preventive programs be reinforced in highSDI regions to address the rising incidence of CKD.

Our analysis directly demonstrates that CKD exhibits pronounced sexspecific disparities in DALYs globally, with males consistently showing higher burdens across all SDI levels. The causespecific patterns also differ between sexes, with hypertension dominating as the leading cause among males, while females face varying primary causes depending on regional development levels. While the underlying mechanisms driving these sexspecific patterns were not directly analyzed in this study, previous literature has hypothesized potential roles for genetic, lifestyle, and sociocultural factors.²² Based on our findings, we recommend that policymakers focus on addressing these disparities by implementing targeted interventions that consider the distinct risk profiles observed in men and women.

Limitations and strengths

The study relies on secondary data from the GBD database, which may vary in quality and completeness across different countries and time periods, potentially affecting the reliability of the findings. Differences in diagnostic protocols and identification of CKD in various countries and over time can impact result comparability.

Additionally, the study lacks data on the impact of other metabolic factors such as triglycerides, cholesterol, or uric acid on CKD burden. Also, the inability to analyze precise socioeconomic factors and data from various ethnic groups may result in overlooking regional and ethnic differences in CKD burden. Furthermore, the inherent collinearity between age, period, and birth cohort in APC models may influence the precision of cohort effect estimates, despite using standard median constraints to mitigate this issue.

While the study has several limitations, it also possesses numerous strengths. It provides a comprehensive analysis of CKD burden and disparities between sexes and socioeconomic regions over a substantial period from 1990 to 2021. It highlights significant trends and underscores the importance of tailored health interventions to address CKD disparities.

CONCLUSION

In conclusion, the global burden of CKD has increased substantially over the past three decades. The APC analysis identified higher modeled DALY rate ratios for some more recent birth cohorts, particularly among males, relative to the specified reference cohort; however, this pattern should not be interpreted as evidence of a causal generational risk. This generational shift, coupled with persistent sex and socioeconomic disparities, demands a dual approach: strengthening primary prevention of obesity, diabetes, and hypertension in midlife populations, and ensuring equitable access to early diagnosis and treatment, especially in low and middleSDI regions. However, several important questions remain unanswered. Future research should focus on: (1) elucidating the specific earlylife environmental and lifestyle exposures driving the cohort effect through longitudinal birth cohort studies; (2) evaluating the costeffectiveness of lowering CKD screening age thresholds in different SDI settings; and (3) investigating the role of genetic and epigenetic factors that may modify sexspecific susceptibility to CKD. Addressing these questions will be essential for developing truly personalized and effective prevention strategies.

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DATA AVAILABILITY

We used publicly available data from the GBD website for this study. Please cite data included in this download as: Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021 (GBD 2021) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2022. Available from <https://vizhub.healthdata.org/gbd-results/>.

Declaration of Generative AI and AI-assisted Technologies

During the preparation of this manuscript, the authors used AI solely for language editing and improving the clarity and readability of the English text. The authors reviewed and edited the content and take full responsibility for the accuracy, originality, and integrity of the manuscript.

AUTHOR CONTRIBUTIONS

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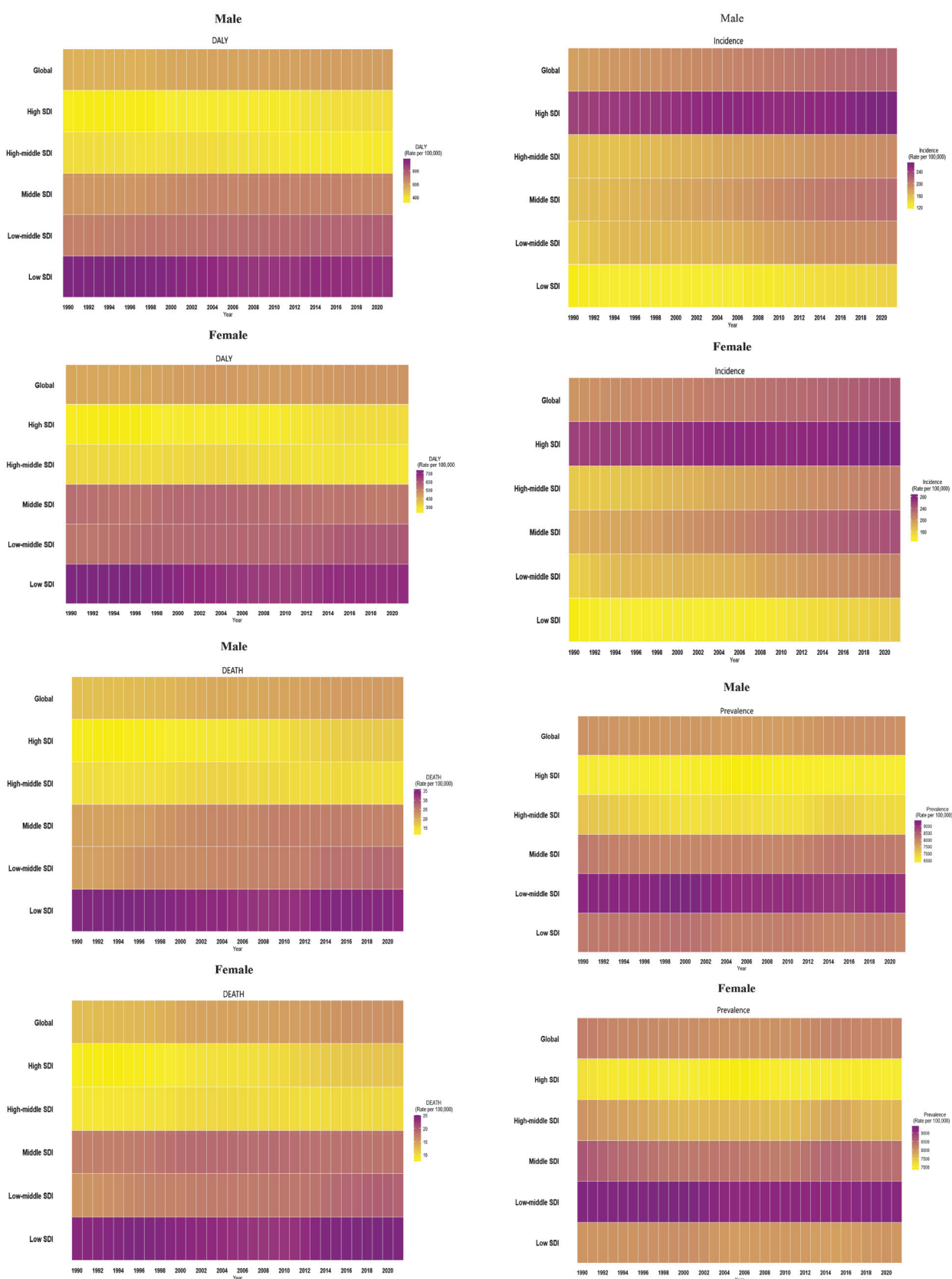
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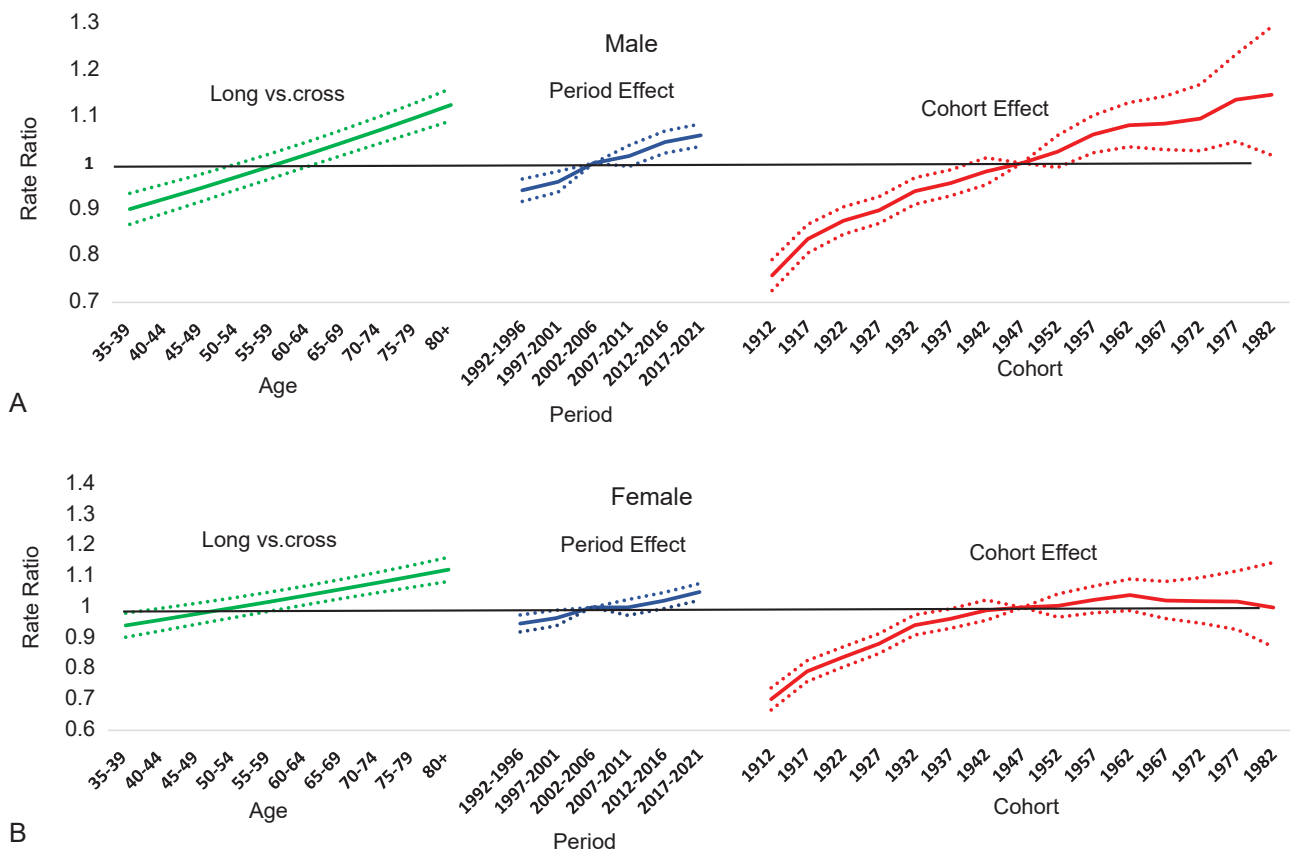
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Appendix Figure 1. Three-decade (1990–2021) heatmap of age-standardized CKD burden, including DALYs, incidence, deaths, and prevalence, stratified by sex and SDI.



Appendix Figure 2. AgePeriodCohort analysis of CKD DALY globally, 1992-2021: longitudinal to cross-sectional rate ratios, period and cohort effects (with 95% CIs), by sex.