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ORIGINAL ARTICLE

Early-onset gastric cancer global burden profile, trends, and contributors

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ABSTRACT

Objective: This study aimed to assess the global, regional, and national burden of early-onset gastric cancer (EOGC) and the attributable risk factors from 1990–2021 with projections extending to 2040.

Methods: The EOGC burden was quantified using incidence, prevalence, mortality, and disability-adjusted life years (DALYs) with calculation of age-standardized rates. The risk factor contributions were analyzed and disparities were evaluated using the slope index of inequality. Future trends for 2021–2040 were estimated using a Bayesian age-period-cohort model.

Results: There were approximately 125,000 new cases of EOGC globally in 2021 with an estimated 336,000 individuals living with EOGC and 78,000 associated deaths, contributing to 3.86 million DALYs. The highest EOGC incidence rates existed among individuals 45–49 years of age. The global age-standardized incidence, prevalence, mortality, and DALY rates demonstrated an overall decline between 1990 and 2021. Smoking and high-salt dietary intake were the leading risk factors for DALYs with regional and gender-based variations. Smoking accounted for > 10% of DALYs in Central Europe and East Asia, while high-salt dietary intake accounted for approximately 8% of DALYs. Despite the overall decline in the EOGC burden, disparities across geographic regions widened. Projections indicated a continued gradual reduction in EOGC burden through 2040.

Conclusion: Although the global burden of EOGC has decreased, significant disparities persist across geographic regions, age groups, and genders. Public health interventions should combine smoking prevention strategies (e.g., youth education and tobacco taxation) with cessation programs with dietary salt reduction initiatives.

KEYWORDS Risk factors; early-onset gastric cancer; incidence; mortality; disability-adjusted life years

Introduction

Gastric cancer (GC) remains a significant global health burden, ranking fifth in incidence and mortality worldwide[1]. Studies have demonstrated that approximately 50% of GC patients present with metastasis to a single site at the time of initial diagnosis, while approximately 12% exhibit multi-site metastatic involvement[2]. Despite significant advances in surgical techniques, radiotherapy, chemotherapy, targeted therapies, and immunotherapy, the prognosis for advanced GC remains poor with a 5-year survival rate of merely 5% and a median overall survival of approximately 12 months[3,4]. Public health efforts, socioeconomic development, and advances in treatment have decreased the GC incidence and mortality over the past 5 decades by reducing *Helicobacter pylori* transmission and improving clinical outcomes. However, substantial disparities in incidence and mortality remain across different age groups, regions, and populations, emphasizing the need for further research to develop prevention and screening strategies.

Early-onset gastric cancer (EOGC) occurs in individuals < 50 years of age and exhibits distinct clinical and pathologic characteristics compared to late-onset gastric cancer (LOGC)[5]. EOGC is often marked by highly invasive pathologic forms, diffuse histologic features, increased rates of peritoneal metastasis, and a higher proportion of signet ring cells, all of which contribute to poorer clinical outcomes. Genetic factors have an important role in EOGC, the underlying mechanisms of which primarily involve abnormal DNA methylation and chromosome instability[6].

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EOGC pathogenesis is predominantly attributed to environmental exposures. A meta-analysis[7] confirmed that smoking increases the EOGC risk by 72% for each increment of 10 cigarettes/d [odds ratio (OR): 1.72, 95% confidence interval (CI): 1.51–1.96], while high-salt diets elevate the risk by 23% for each 5-g increment/d [relative risk (RR): 1.23, 95% CI: 1.12–1.35][8].

The Global Burden of Disease (GBD) 2021 data (1990–2021) were analyzed to quantify these risks by assessing the EOGC incidence [age-standardized incidence rate (ASIR)], mortality [age-standardized mortality rate (ASMR)], and disability-adjusted life years (DALYs) with projections to 2040 using Bayesian age-period-cohort (BAPC) modeling. Our study aimed to evaluate the global and regional EOGC burden attributable to smoking and high-salt diets, identify disparities *via* the slope index of inequality (SII), and guide targeted prevention strategies.

This corollary study extends previous GBD-based GC research findings (e.g., GBD 2017 Gastric Cancer Collaborators)[9] in several key ways. First, in addition to providing updated data from the latest GBD 2021 dataset, the current analysis specifically focused on EOGC, addressing an underexplored subgroup with unique epidemiologic characteristics. Second, the study assessed the contributions of two major modifiable risk factors (smoking and high-salt diets) to the burden of EOGC, thereby offering a more nuanced understanding of their differential impacts across genders and geographic regions. Finally, based on these targeted analyses, more precise recommendations are offered for tailored preventive strategies, thus enhancing the public health relevance and practical applicability of the study findings.

Materials and methods

Overview

The analysis utilized estimates from the GBD 2021 study, which assessed the health impact of 371 diseases and injuries with 88 risk factors. The GBD 2021 is a publicly available database that does not include participant privacy information. The current study focused on patients with EOGC from 1990–2021 by extracting data on the incidence, prevalence, mortality, DALYs, and the 95% uncertainty intervals (UIs). The data used in the current study can be accessed using the GBD Results Tool (http://ghdx.healthdata.org/gbd-results-tool).

Measurement of disease burden

Eight metrics were used to assess the EOGC burden, as follows: incidence; prevalence; mortality; DALYs; ASIR; age-standardized prevalence rate (ASPR); age-standardized death rate (ASDR); and ASMR. The definitions and calculation methods for these metrics have been outlined in previous studies. Multiple imputation was widely applied to the GBD 2021 database. Bayesian meta-regression (DisMod-MR) was utilized for estimating incidence and missing data was addressed through cascade analyses. Data points and biases were adjusted *via* meta-regression, Bayesian regularization, and trimming techniques prior to modeling.

Joinpoint regression analysis

Joinpoint Regression Program software (version 4.9.10) was used to evaluate the ASPR, ASIR, ASMR, and ASDR[10]. Joinpoint regression is a statistical method used to analyze trend changes in time series data by identifying "joinpoints," splitting the time series into multiple phases and calculating the annual percent change (APC) for each segment. The Monte Carlo permutation test, the default model optimisation method of the Joinpoint software, was used to select the optimal number of joinpoints. The number of connection points recommended by the software was used for analysis. The corresponding APC and 95% CI were also calculated with this model and the average annual percent change (AAPC) was further calculated. The lower limit of the AAPC estimate and the 95% CI exceeded zero, indicated an upward trajectory within the specified interval. In contrast, AAPC estimates plus the upper limit of the 95% CI below zero indicated a downward trend. The trend was stable when the 95% CI of AAPC included zero. The optimal number of joinpoints in the current study was three, as determined by minimum AIC values and permutation tests ($P < 0.05$). Residuals were normally distributed, with no significant heteroscedasticity (Breusch-Pagan test). The model exhibited good fit ($R^2 = 0.89$) and no significant autocorrelation (Durbin-Watson statistic = 1.95), confirming model reliability.

Estimation framework

DisMod-MR 2.1, a Bayesian meta-regression tool, was primarily used to model the prevalence and incidence of most

diseases and injuries in GBD 2021[11]. Cancer registries were matched by gender, age, year, and geographic region to estimate mortality-to-incidence ratios (MIRs), then modeled using cause-specific logistic regressions. These MIRs were subsequently pooled with cancer-specific mortality data to generate estimates of incidence and prevalence with 95% UIs[12]. DisMod-MR 2.1 and MIRs models are commonly used to estimate epidemiologic parameters in GBD research. Prior distributions for incidence, prevalence, and mortality were normal with 20,000 MCMC iterations (PSRF < 1.05). Including covariates, such as geographic region and diagnosis year in MIRs modeling, improved accuracy and generalizability. Bayesian approaches using prior distributions were utilized to manage zero-death samples.

Attributable risk factors

Risk factor exposure data from GBD 2021 were modeled using spatiotemporal Gaussian process regression or DisMod-MR 2.1.9. Quantitative relative risk estimates for each risk-outcome pair were combined with exposure estimates to calculate population attributable fractions (PAFs). These PAFs were then multiplied by the corresponding outcome rates to estimate the burden associated with each risk factor. The current study specifically focused on two risk factors for EOGC (smoking and high-salt diets), which were automatically incorporated within the GBD 2021 framework.

Decomposition analysis and trend projections

A decomposition method was used to analyze the drivers of EOGC burden, dividing the changes into three components (population aging, overall population growth, and epidemiologic changes). A BAPC model, implemented using the R package, BAPC, was used to predict future trends in EOGC burden from 2021–2040.

Health inequality analysis

Health inequality analysis utilized the SII to quantify the unequal distribution of the EOGC burden. This metric regressed national, age-standardized EOGC disease metrics against a social status scale based on GDP per capita using weighted regression models with log-transformed data.

Secondary data analysis

GBD-derived data

The following pre-calculated age-standardized metrics were directly extracted based on the GBD 2021 database: ASPR; ASIR; ASMR; and ASDR.

Author-conducted analyses

Joinpoint regression, decomposition analysis, BAPC projections, and SII analysis were all independently performed by the authors using raw GBD data.

Results

EOGC burden in 2021

EOGC accounted for approximately 125,000 incident cases (95% UI: 107,000–144,000), 336,000 prevalent cases (95% UI: 286,000–391,000), 78,000 mortality (95% UI: 68,000–90,000), and 3.86 million DALYs (95% UI: 3.4–4.4 million) globally in 2021. The geographic regions with the highest ASIR, ASPR, ASDR, and ASMR included Afghanistan, Mongolia, North Korea, South Korea, and China. The countries with the lowest metrics included Morocco, Kuwait, Nigeria, Sweden, and Norway (**Figure 1**, **Table S1**). Females < 30 y of age had higher incidence, mortality, and DALY rates than males. The burden in males > 30 y of age increased significantly, peaking between 45 and 49 years of age. Males consistently exhibited higher prevalence rates than females with the highest rates occurring between 45 and 49 years of age (**Figure 2**).

Trends in the EOGC burden, 1990–2021

The global burden of EOGC exhibited a significant decline from 1990–2021. The global ASIR demonstrated an AAPC of −2.4 (95% CI: −2.5 to −2.3) with females exhibiting a steeper decline than males. The global ASPR also decreased with an AAPC of −1.8 (95% CI: −1.9 to −1.7). A declining trend was noted in the global ASMR with an AAPC of −2.9 (95% CI: −3.0 to −2.8); males had a more pronounced decrease than females. Similarly, the global ASDR decreased with an AAPC of −2.9 (95% CI: −3.0 to −2.8; **Figure 3**).

Upward trends in the ASIR, ASPR, ASMR, and ASDR occurred in some sub-Saharan African countries, including Lesotho and Zimbabwe (**Tables S2 and S3**).

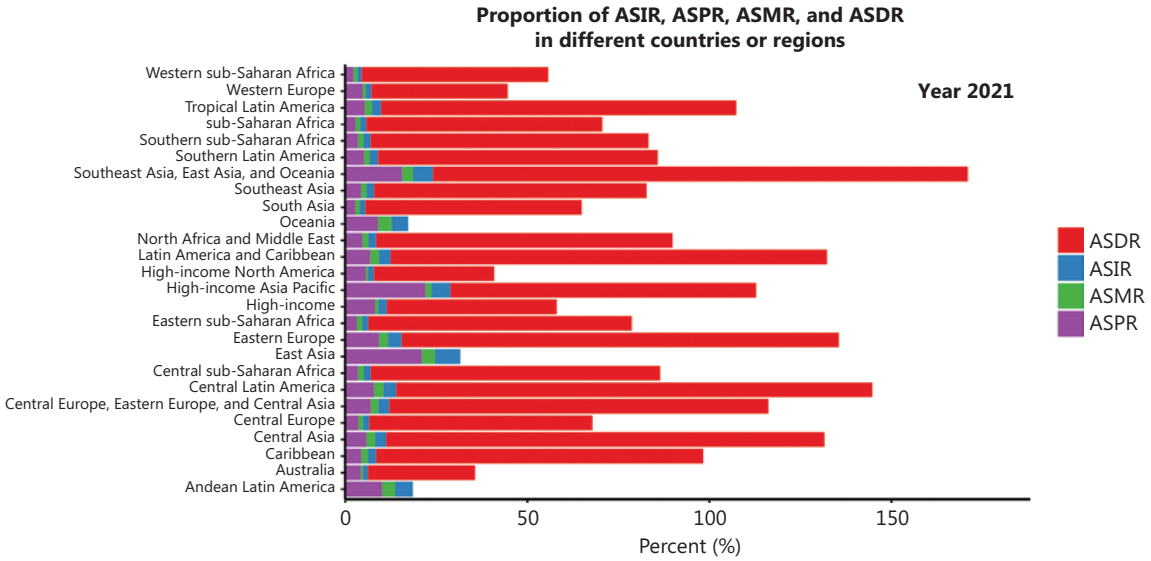


Figure 1 Proportion of EOGC ASIR, ASPR, ASMR, and ASDR in different regions globally in 2021. Red indicates ASDR, blue represents ASIR, green corresponds to ASMR, and purple illustrates ASPR. Longer bars reflect higher proportions of the respective disease metrics within each region. ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate.

These trends highlight the global progress in reducing the EOGC burden, while also emphasizing regional disparities that require targeted intervention.

Risk factor analysis for EOGC

Contribution to DALYs

Analysis of DALYs in 2021 showed that smoking contributed to 7.1% of global DALYs with 10.5% in males and 1.4% in females. High-salt diets accounted for 7.7% of DALYs with 7.9% in males and 7.3% in females.

Significant differences were observed across the 21 GBD regions and SDI levels for both risk factors. Smoking contributed to > 9% of DALYs in Central Europe, East Asia, Eastern Europe, and Western Europe, while in Eastern and Northern sub-Saharan Africa the contribution was < 2%. High-salt diets exhibited relatively stable contributions to DALYs across all regions, ranging from 6.4%–8.2%. In regions with a high-middle social development index (SDI), smoking accounted for 10% of DALYs with the contribution decreasing progressively at lower SDI levels. High-salt diets maintained consistent contributions across all SDI levels (**Table 1**).

Contribution to ASDR

Smoking was the primary risk factor globally for attributable ASDR in EOGC in 2021. The ASDR attributed to smoking was 12.6 (95% UI: 9.9–16.2) with values of 23.2 (95% UI: 17.9–30.2) for males and 1.9 (95% UI: 1.5–2.2) for females. The ASDR attributable to high-salt diets was 10.6 (95% UI: 0.0–52.9) with 13.6 (95% UI: 0.0–66.9) for males and 7.6 (95% UI: 0.0–39.4) for females (**Tables S4 and S5**).

Analysis of trends in risk factors for EOGC (1990–2021)

DALYs attributable to risk factors

The DALYs attributable to smoking declined from 496,000 (95% UI: 387,000–600,000) in 1990 to 273,000 (95% UI: 215,000–348,000) in 2021. DALYs reduced from 458,000 (95% UI: 348,000–555,000) to 253,000 (95% UI: 197,000–326,000) in males, while DALYs decreased from 38,000 (95% UI: 32,000–45,000) to 20,000 (95% UI: 16,000–24,000) in females. DALYs decreased from 417,000 (95% UI: 0–2,070,000) in 1990 to 296,000 (95% UI: 0–1,477,000) for high-salt diets in 2021. DALYs reduced from 265,000 (95% UI: 0–1,330,000) to 190,000 (95% UI: 0–941,000) in males, while DALYs decreased from 151,000 (95% UI: 0–765,000) to 105,000 (95% UI: 0–543,000) in females (**Figure 4**). These results showed a significant decline in DALYs attributable to smoking, especially among males, while the trend for females was less pronounced. In contrast, changes in DALYs attributable to high-salt diets remained relatively minor over the 20-year period.

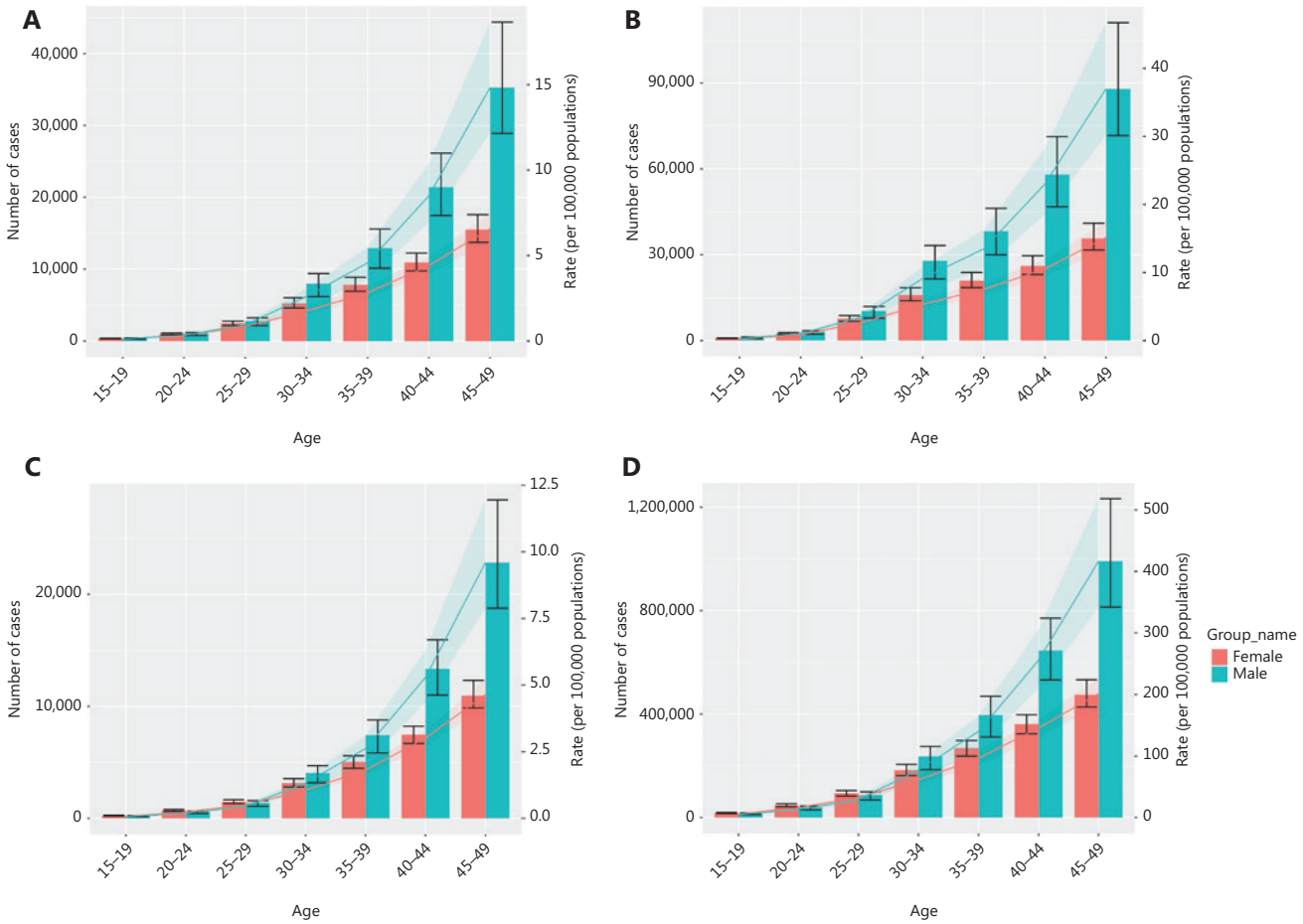


Figure 2 Age-specific burden of EOGC in 2021. (A) Incidence and ASIR; (B) Prevalence and ASPR; (C) Mortality and ASMR; (D) DALYs and ASDR. Females are represented by the red line, while males are depicted by the blue line. The x-axis represents various age groups (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45–49 y). The y-axis shows the corresponding rates and case numbers. These visualizations emphasize the differences in EOGC burden based on gender and age. ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate.

ASDR attributable to risk factors

The ASDR due to smoking decreased from 42 (95% UI: 32.6–50.9) in 1990 to 12.6 (95% UI: 9.9–16.2) in 2021. The ASDR declined from 76.1 (95% UI: 57.9–92.8) to 23.2 (95% UI: 17.9–30.2) in males, while the ASDR dropped from 6.6 (95% UI: 5.4–7.9) to 1.9 (95% UI: 1.5–2.2) in females. The ASDR decreased from 26.6 (95% UI: 0.1–131.9) in 1990 to 10.6 (95% UI: 0.0–52.9) for high-salt diets in 2021. The ASDR fell from 33.5 (95% UI: 0.0–167.7) to 13.6 (95% UI: 0.0–66.9) in males, while the ASDR dropped from 19.3 (95% UI: 0.0–97.9) to 7.6 (95% UI: 0.0–39.4) for females (**Figure 5**). These findings indicated a significant decrease in the ASDR attributable to smoking with a more pronounced reduction in males compared to females. In contrast, changes in the ASDR due to high-salt diets were comparatively minor during the same time period.

Age-specific trends in ASDR attributable to risk factors

Further analysis by age group revealed the most significant declines in the ASDR attributable to smoking and high-salt diets occurred in the 40–44 year age group, while the smallest declines in both risk factors were noted in the 30–34 year age group (**Figure 6**).

Decomposition analysis and projected trends

Decomposition analysis

The decomposition analysis indicated that global epidemiologic changes were the primary contributors to the decline in the EOGC incidence, mortality, and DALYs. The impact of these changes varied across SDI levels. Specifically, in high-SDI,

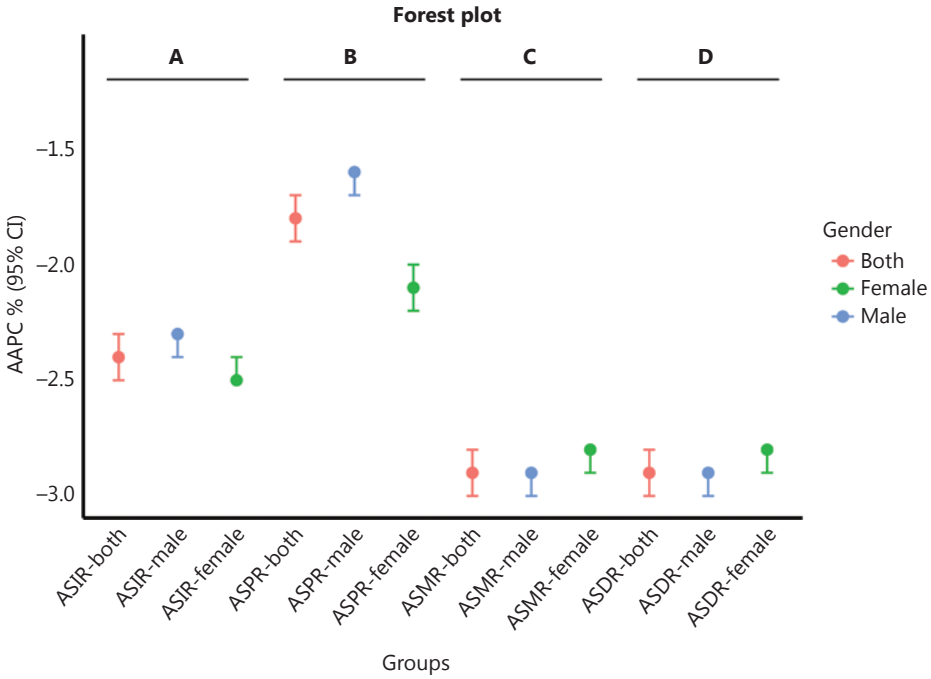


Figure 3 Forest plots illustrating the average annual percentage change in global ASIR, ASPR, ASMR, and ASDR from 1990 to 2021. The y-axis represents the average annual percentage change. A negative value indicates a decrease, with larger absolute values reflecting a greater decline. (A) ASIR for the overall population (red), males (blue), and females (green); (B) ASPR for the overall population (red), males (blue), and females (green); (C) ASMR for the overall population (red), males (blue), and females (green); (D) ASDR for the overall population (red), males (blue), and females (green). ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate.

high-middle SDI, and middle-SDI regions, the contribution of epidemiologic changes to the reduction in EOGC burden grew as the SDI decreased, while in low-middle SDI and low-SDI regions rapid population growth emerged as the predominant factor driving the increase in the EOGC burden. Population growth emerged as the dominant factor contributing to the global increase in the EOGC burden across all SDI levels, except in high-SDI regions, where epidemiologic changes had a primary role in reducing the EOGC burden (**Figure S1**).

Projected trends

Projection analysis suggested that the ASIR, ASPR, ASMR, and ASDR for EOGC will continue to decline from 2021–2040. However, the disease burden in males is expected to remain significantly higher than females, which indicates males are a higher-risk population for EOGC (**Figure 7**).

Health inequality analysis

Substantial disparities in the burden of EOGC exist across various SDI levels with these disparities increasing over time. Data from 2021 revealed that countries with higher SDI values experienced lower incidence, prevalence, mortality, and DALYs compared to 1990. This trend was especially prominent in low-SDI countries, where health inequalities were more pronounced (**Figure S2**). Analysis using the slope index of inequality demonstrated a decline in the overall burden of EOGC since 1990, signifying a reduction in the total EOGC burden. Nevertheless, health inequality remains a persistent challenge.

Discussion

The current study has provided the first comprehensive analysis of EOGC burden from 1990–2021. The findings revealed significant global reductions in the ASIR, ASMR, and ASDR over this period. Among the above-mentioned key findings, the inverse relationship in EOGC incidence between males and females < 30 years of age compared to those 45–49 years of age represents a novel observation. Previous studies, which have not specifically addressed the EOGC burden, likely contributed to the oversight of this phenomenon. Consequently,

Table 1 Percentage contribution of two risk factors for DALYs in 2021

Location	Risk factors	
	Smoking % (95% UI)	Diet high in sodium % (95% UI)
Global	7.1 (5.8–8.3)	7.7 (0.0–38.9)
Global male	10.5 (8.8–12.1)	7.9 (0.0–39.8)
Global female	1.4 (1.1–1.6)	7.3 (0.0–37.3)
5 SDI quintiles regions		
High SDI	7.9 (6.6–9.2)	7.8 (0.0–39.7)
High-middle SDI	10.0 (8.2–11.6)	8.0 (0.0–40.0)
Middle SDI	7.6 (6.1–9.1)	7.9 (0.0–40.0)
Middle-low SDI	4.2 (3.5–4.9)	7.6 (0.0–38.1)
Low SDI	2.4 (2.0–2.9)	6.4 (0.0–34.5)
21 GBD regions		
Andean Latin America	2.5 (2.1–3.0)	7.6 (0.0–38.7)
Australia	7.2 (6.0–8.3)	7.7 (0.0–39.6)
Caribbean	3.4 (2.8–4.1)	7.0 (0.0–36.6)
Central Asia	7.4 (6.2–8.5)	7.8 (0.0–39.5)
Central Europe	10.8 (9.1–12.5)	8.2 (0.0–40.9)
Central Latin America	2.8 (2.4–3.3)	7.8 (0.0–39.2)
Central sub-Saharan Africa	2.5 (2.0–3.1)	5.7 (0.0–32.7)
East Asia	10.1 (8.1–12.0)	8.2 (0.0–40.8)
Eastern Europe	10.9 (9.2–12.6)	7.8 (0.0–40.0)
Eastern sub-Saharan Africa	1.9 (1.5–2.3)	6.3 (0.0–34.1)
High-income Asia Pacific	7.1 (5.9–8.4)	8.1 (0.0–40.5)
High-income North America	7.1 (5.9–8.3)	7.9 (0.0–39.9)
North Africa and Middle East	5.6 (4.5–6.7)	5.5 (0.0–31.2)
Oceania	5.8 (4.5–7.2)	5.7 (0.0–32.4)
South Asia	3.2 (2.5–3.8)	7.8 (0.0–39.4)
Southeast Asia	6.6 (5.4–7.9)	7.9 (0.0–39.5)
Southern Latin America	8.5 (7.1–9.9)	7.9 (0.0–39.7)
Southern sub-Saharan Africa	4.7 (3.8–5.6)	7.1 (0.0–37.0)
Tropical Latin America	4.0 (3.3–4.8)	7.7 (0.0–39.4)
Western Europe	9.0 (7.6–10.5)	7.6 (0.0–39.2)
Western sub-Saharan Africa	1.6 (1.3–1.9)	6.4 (0.0–34.9)

most existing literature has concluded that the gastric cancer incidence is universally higher among men than women[13]. Furthermore, regional variations in the EOGC burden primarily arise from differing local responses to salt and tobacco control policies. High dietary salt intake impairs the gastric mucosal protective barrier, facilitating *H. pylori* colonization and the infiltration of additional carcinogenic substances[14]. Similarly, heightened awareness regarding the relationship between smoking and gastric carcinogenesis has stimulated research into the mechanisms underlying tobacco-induced GC. For example, recent studies have identified a significant association between tobacco smoke exposure and GC through exosomes derived from GC stem cells[15].

The EOGC burden was shown to differ significantly across geographic regions. High-burden regions, including East Asia and Oceania, reported the highest ASIR, ASMR, and ASDR in 2021. These findings align with previous studies that associated GC prevalence with dietary factors (e.g., high-sodium diets) and environmental exposures (e.g., *H. pylori* infection)[16]. The mean daily salt intake among Chinese young adults was 13.9 g. Furthermore, the prevalence of *H. pylori* infection is notably higher in East Asian regions compared to other global areas[17]. The current study demonstrated that the prevalence of *H. pylori* infection varies across different ethnic groups. Among Caucasians in the United States, the *H. pylori* infection rate ranges from 19%–77%, whereas in African Americans the *H. pylori* infection rate ranges from 62%–90%[18].

In contrast, regions like sub-Saharan Africa and Southeast Asia displayed rising ASIR trends despite the global declines. These trends are typically linked to factors, such as limited healthcare access, inadequate early detection, and the prevalence of risk factors (high dietary salt intake and smoking)[19]. The reductions observed in high-SDI regions are probably due to healthcare advances, the implementation of efficient screening programs, and public health efforts focused on minimizing exposure to known carcinogens[20,21]. Additionally, poorer hygiene conditions and inadequate food preservation methods are likely to contribute to the increasing incidence rates of EOGC in regions, such as sub-Saharan Africa and Southeast Asia[22].

The rising EOGC burden in low SDI regions highlights significant disparities in healthcare equity, underscoring the urgent need for targeted interventions to mitigate modifiable risk factors[23]. Several potential strategies can be used to reduce regional disparities in the EOGC incidence. First, enhancing health promotion strategies and cancer

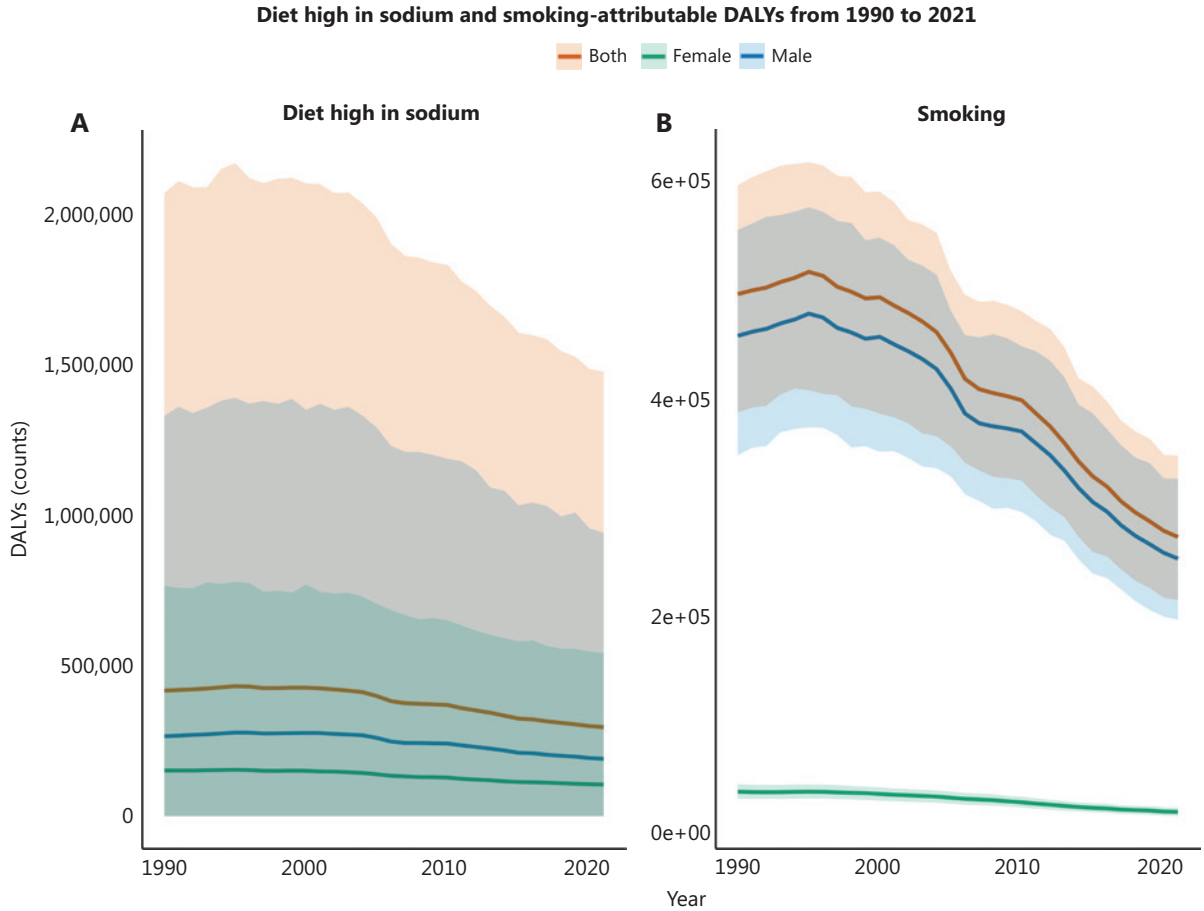


Figure 4 Trends in DALYs attributed to two risk factors from 1990 to 2021. (A) Changes in DALYs for the overall population (yellow), females (green), and males (blue); (B) Changes in DALYs due to smoking: overall population (yellow), females (green), and males (blue). DALYs, disability-adjusted life years.

awareness is crucial. Ongoing efforts in early diagnosis and treatment have shown promise, particularly in regions where such initiatives have successfully led to a reduction in the EOGC incidence. Second, improving environmental and lifestyle factors is essential and involves tackling modifiable risk factors, including smoking, dietary patterns (high-sodium diet) and environmental exposures (*H. pylori* infection). Third, strengthening healthcare services and early detection is vital. Implementing targeted interventions to enhance healthcare access and early detection in regions, such as sub-Saharan Africa and Southeast Asia, is necessary because limited healthcare services contribute to the increase in EOGC incidence and mortality. By addressing these areas, we can work towards reducing the disparities in EOGC incidence and improving health outcomes in vulnerable populations.

Japan established that endoscopic screening reduces GC mortality by 67% compared to radiographic screening prior to 2015, highlighting the pivotal role of gastroscopy in GC prevention[24]. In addition to limited healthcare access, inadequate food hygiene conditions may further contribute to the ASIR in sub-Saharan Africa and Southeast Asia. The lack of sufficient refrigeration infrastructure leads to a reliance on salt-preserved or smoked foods. Yan et al.[25] reported that the overall OR for the association between refrigerator use and GC risk was 0.70 (95% CI: 0.56–0.88). Poor food storage conditions elevate the risk of bacterial contamination, thereby exacerbating *H. pylori*-induced gastritis. In contrast, low-temperature food storage appears to be protective, showing a negative association with the risk of *H. pylori* infection (adjusted OR: 0.044, 95% CI: 0.009–0.206)[26]. A meta-analysis showed that consumption of salted fish is associated with an increased risk

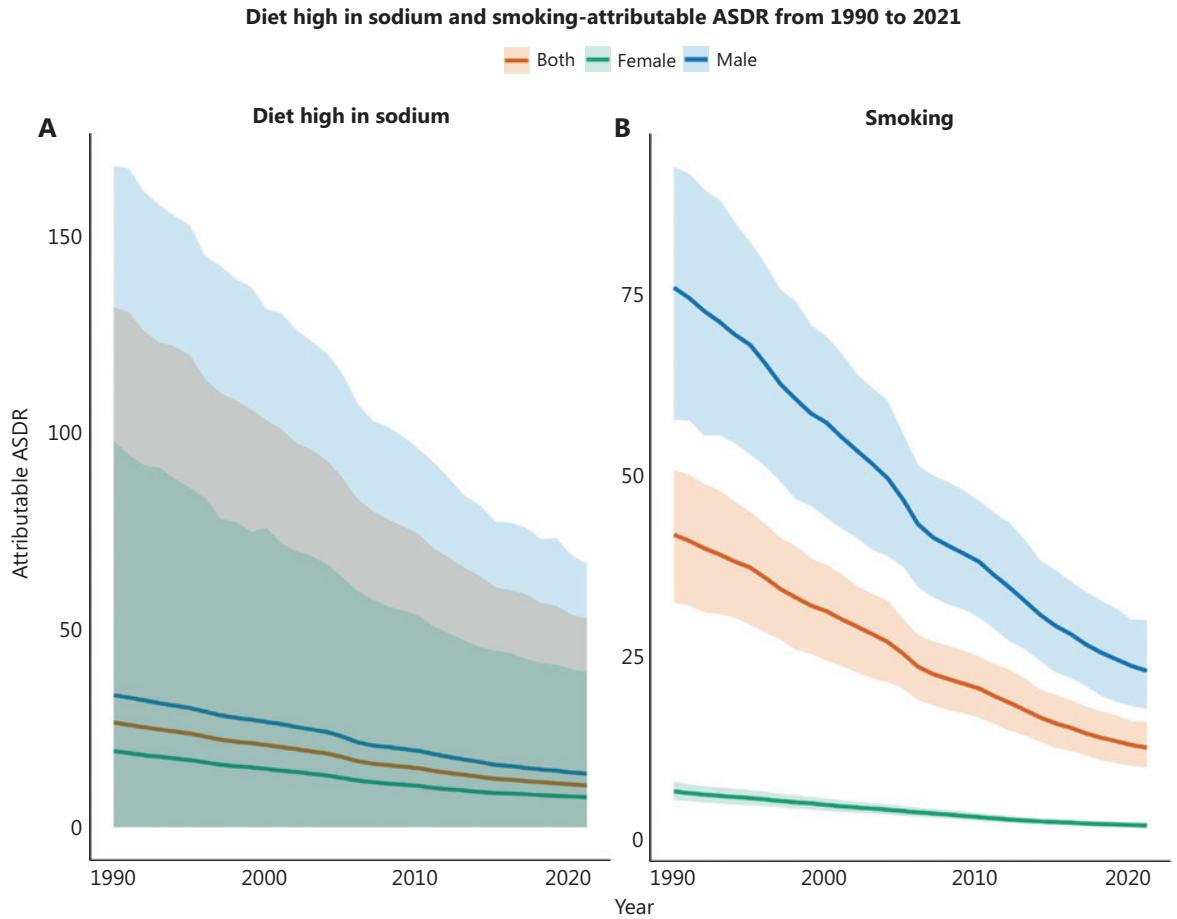


Figure 5 Trends in attributable ASDR for two risk factors from 1990 to 2021. (A) Changes in ASDR due to a high-salt diet: overall population (yellow); females (green); and males (blue); (B) Changes in ASDR due to smoking: overall population (yellow); females (green); and males (blue). ASDR, age-standardized death rate.

of GC (RR: 1.17, 95% CI: 0.99–1.38). Reducing the intake of salted foods represents an important public health intervention[27]. This finding emphasizes the critical need for integrated interventions that combine improvements in food storage infrastructure with existing screening programs.

The findings highlighted notable gender and age differences in the EOGC burden. Females experienced a higher EOGC burden before 30 years of age, potentially linked to hormonal variations and reproductive factors[28]. In contrast, males had a sharp rise in burden after 30 years of age, peaking between 45 and 49 years of age. Previous studies indicated that lifestyle factors, such as elevated smoking and alcohol consumption rates in males, may contribute to these disparities[29].

These gender and age differences highlight distinct patterns of EOGC incidence with important implications for treatment strategies. In patients < 40 years of age, females represented 50.1%–63.6% of EOGC cases compared to 23.5%–26.4% of LOGC cases. This disparity may be attributed to hormonal factors, such as the protective effects of estrogen on gastric mucosal barriers and the role in mitotic nuclear activity, both of which could influence carcinogenesis. Taupin and Podolsky[30] demonstrated that estrogen upregulates the expression of trefoil factor family genes, which encode proteins critical for protecting the gastric mucosa from damage induced by endogenous and exogenous factors. *In vitro* experiments further indicated that estrogen could induce apoptosis in estrogen receptor-positive AGS gastric cancer cells[31]. Additionally, Frise et al.[32] reported that women in whom the first childbirth occurred before 24 years of age exhibited a 45% reduction in gastric adenocarcinoma risk (OR: 0.55, 95% CI: 0.31–0.96).

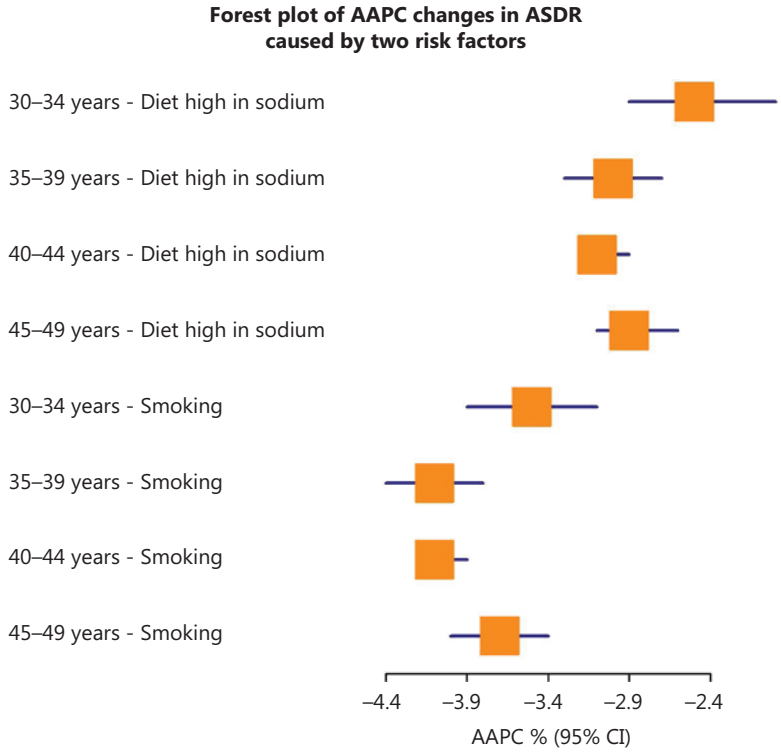


Figure 6 Forest plot depicting changes in ASDR attributed to two risk factors across various age groups from 1990 to 2021. The horizontal axis represents the AAPC, where a negative value indicates a decrease, and the larger the absolute value, the greater the decrease. The ordinate axis displays the age groups and the corresponding risk factors. AAPC, average annual percent change; ASDR, age-standardized death rate.

Treatment strategies for female patients with EOGC should consider gender-specific biological differences, including the impact of hormonal levels. Additionally, young patients with EOGC display distinct clinical and pathologic features compared to older adults with LOGC. EOGC is predominantly characterized by poorly or undifferentiated histology (68.3%–76.9%), while LOGC typically presents with moderately or well-differentiated histology (52.2%–66.9%). These findings implied that EOGC may require more aggressive chemotherapy and radiotherapy approaches. Moreover, the relatively better physiologic status and fewer co-morbidities in younger patients may enable more intense and prolonged treatment, affecting treatment planning.

Our findings highlighted smoking and high-salt diets as significant modifiable risk factors for EOGC, which are associated with a considerable burden of disease as reflected by DALYs. Existing evidence suggests that the similar DALY burden attributed to high-salt diets between genders is primarily due to consistent dietary habits, rather than differences in biological susceptibility.

Hawkes et al.[33] concluded that the globalized food system exposes all populations, regardless of gender, to similar levels of sodium through processed foods. Additionally, a meta-analysis of 60 studies by Shangguan et al.[34] shown that the impact of food labeling on consumer dietary behavior showed highly similar patterns across genders.

The gender disparity in smoking-attributable burden is largely sociologically driven. Studies have shown that smoking prevalence remains significantly higher among males worldwide and tobacco control efforts have been more impactful in male populations[35]. These factors contribute to the observed disparity in smoking-attributable disease burden between genders. Smoking contributes to 7% of global DALYs with a greater impact on males (10.5%) than females (1.3%). Likewise, high-salt diets account for 7.6% of global DALYs, reflecting regional dietary patterns, especially in East Asia[36]. These risk factors demonstrate regional variations. Smoking is a significant risk factor for EOGC in Eastern Europe, underscoring the necessity for enhanced tobacco control measures in these regions[37]. In East Asia high salt consumption emphasizes the

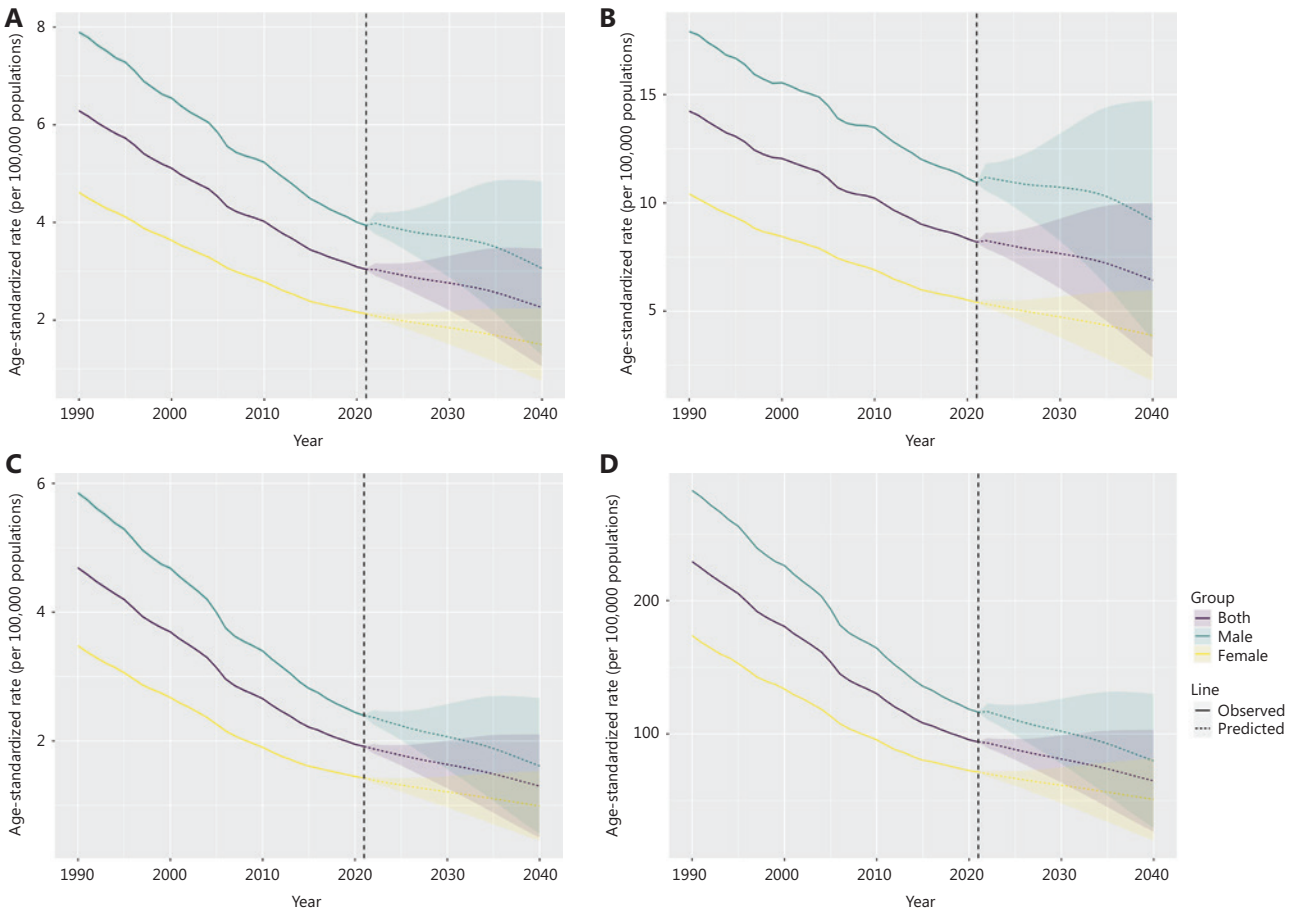


Figure 7 Predicted disease burden of EOGC from 2021 to 2040 for the entire population (red), females (yellow), and males (green). (A) ASIR; (B) ASPR; (C) ASMR; (D) ASDR. ASDR, age-standardized death rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; EOGC, early-onset gastric cancer.

need for dietary education and regulation to reduce the EOGC incidence[38]. Reductions in DALYs related to smoking and high-salt diets in high-SDI regions indicate that public health initiatives, such as smoking cessation programs and salt reduction campaigns, have been effective[39].

Studies have identified smoking as an independent risk factor for GC with smokers facing a 50% increased risk of developing the disease compared to non-smokers. This risk rises in a dose-dependent manner with prolonged smoking.

Research has demonstrated that smoking accounted globally for approximately 17.96% (1.72 million) of deaths and 17.15% (38.13 million) of DALYs attributable to GC in 2019[40]. While the ASMR and ASDR associated with smoking-related GC have declined across all regions and in the majority of countries, some nations experienced notable increases exceeding 10%. Projections suggest that by 2044, despite an anticipated global reduction in age-standardised rates for GC linked to smoking, the absolute burden of the disease will likely escalate with the estimated deaths and DALYs rising to 2.22 million and 42.14 million, respectively.

Additionally, the mortality risk for GC patients who smoke is 101% higher than for non-smokers and even higher (115%) in individuals infected with *H. pylori*. Given the strong link between smoking and GC, it is recommended that smoking be discontinued to mitigate this risk. Smokers, particularly those with *H. pylori* infection, should undergo aggressive screening and preventive measures. Yan et al. observed that *H. pylori* eradication therapy significantly reduced the risk of GC by 43% [hazard ratio (HR): 0.57, 95% CI: 0.33–0.98]. More pronounced reductions in GC risk were noted among patients without precursor lesions (HR: 0.37; 95% CI: 0.15–0.95) and those without dyspeptic symptoms (HR: 0.44; 95% CI: 0.21–0.94)[41].

Excessive salt intake increases the risk of GC. Compared to populations with low salt intake, moderate salt intake raises the

risk by 20%, while high salt intake increases the risk by 25% with this effect being more pronounced in Asian populations. Therefore, prevention strategies for EOGC should focus on reducing high-salt food consumption. In high-risk populations with elevated salt intake, preventive measures, including regular endoscopic examinations and early intervention, are essential for mitigating gastric cancer development. For individuals with GC and high salt intake, personalized dietary recommendations to reduce salt consumption may enhance treatment outcomes and prognosis. Vences-Mejía et al. conducted an experiment involving high-salt injection in rats, revealing that excessive salt intake induces irreversible damage to the gastric mucosa, including mitochondrial dysfunction and DNA fragmentation[42]. Furthermore, a high-salt diet was shown to enhance the risk of GC by modulating the expression of *H. pylori* outer membrane proteins[43]. Given the substantially high EOGC burden observed in China (**Figure 1**), targeted policy interventions are critically needed. First, initiating GC screening at an earlier age in high-risk regions could facilitate timely detection and effective management of precancerous lesions or early-stage cancers. Second, public health policies should strengthen existing tobacco control measures and intensify efforts to reduce dietary salt intake because both smoking and high-salt diets significantly contribute to gastric carcinogenesis. Lastly, scaling up population-wide *H. pylori* eradication programs could substantially mitigate infection-driven GC risk, thereby reducing EOGC incidence over the long term.

The results highlight the necessity of a multifaceted approach to address the disease EOGC burden. First, public health campaigns focused on reducing smoking rates and encouraging healthier eating habits, particularly in high-risk areas, should be prioritized. Second, early detection strategies, such as endoscopic screening in endemic regions, can substantially reduce mortality and enhance prognosis[44]. Third, policy measures, including tobacco product taxes and dietary salt regulations, can mitigate the impact of these risk factors at the population level[45]. Finally, in low-SDI areas, international collaboration is crucial for improving healthcare services and infrastructure, ensuring vulnerable populations have access to early diagnosis and treatment. For example, successful interventions in high-SDI countries can help bridge gaps in healthcare delivery[46].

Primary prevention of smoking initiation is equally critical as cessation efforts. Three evidence-based strategies have demonstrated particular promise for EOGC prevention. First, community-based education programs have shown significant success[47]. The "Done with Menthol" campaign in Los Angeles serves as an exemplary model, specifically targeting menthol cigarette use reduction among African American and Latino populations. This initiative employed culturally-tailored strategies, compelling visual materials, and informative messages to highlight health risks while providing accessible cessation resources. The campaign's effectiveness was demonstrated through increased quit attempts and heightened utilization of cessation support services. Second, regulatory measures have proven effective[48] with studies showing that plain-packaged tobacco products are disliked by > 50% of young people. Third, economic disincentives[49], such as increased cigarette excise taxes in Poland, have shown promise in reducing youth smoking initiation. The success in Japan in reducing GC incidence and mortality provides a comprehensive model for prevention. The approach in Japan combined large-scale screening programs, including endoscopic examinations, standardized treatment protocols, and the promotion of traditional, fiber-rich, low-salt diets[50,51]. Cost-effectiveness analyses have supported these interventions with endoscopic screening showing favorable results compared to no screening. The lowest calculated incremental cost-effectiveness ratio was 1,230 USD per life-year gained and 1,500 USD per quality-adjusted life-year[52]. Furthermore, research has identified sodium intake as a crucial mediator in GC development, accounting for 52.4%–100% of the association. These findings provide valuable guidance for developing targeted preventive strategies and public health interventions for EOGC[53].

This study had several limitations associated with the analysis of GBD data on the EOGC burden. The accuracy of GBD data is impacted by the quality of cancer registry data across various countries, which may include underreporting and diagnostic deficiencies[54]. Although GBD data limitations exist, emerging methodologies, such as environmental DNA mapping for *H. pylori* strain surveillance and health-based salt intake and smoke monitoring may enhance future estimates. Additionally, GBD integrates system dynamics models with statistical models, potentially introducing methodologic constraints. The study depends on GBD data, which lack detailed provincial or city-level breakdowns, thereby limiting regional analyses within countries. Clinical staging and pathologic subtypes of GC were not comprehensively gathered, hindering the assessment of the impact of polygenic risk scores (PRs) on various gastric cancer subtypes or early-onset risk. Furthermore, some samples lack data on tumor sites and the small number of cardia cancer cases may decrease the accuracy of PRs analyses for this subtype. Additionally, this analysis did not include

the DALY burden attributable to *H. pylori*, despite its well-established role as a major gastric carcinogen. This omission was explicitly due to limitations inherent in the GBD 2021 dataset, which currently lacks comprehensive, pathogen-specific attributable burden estimates for EOGC. This constitutes a significant limitation of the current study. Given the critical public health implications of *H. pylori* infection in gastric carcinogenesis, future research should prioritize integrating detailed and high-quality data on pathogen-specific contributions to the EOGC burden, thereby enabling more targeted prevention and intervention strategies.

These limitations caution against overgeneralizing GBD findings and emphasize the need for future research to enhance data collection and analytical methods. A more thorough understanding of the interaction between genetic, environmental, and lifestyle factors in EOGC is crucial for improving prevention and treatment strategies.

Conclusions

This study highlighted notable progress in reducing the global EOGC burden, while revealing ongoing disparities across regions, genders, age groups, and economic levels. The impact of modifiable risk factors, such as smoking and high-salt diets, remains significant. The findings stress the urgent need for targeted public health interventions to address these risk factors and tackle healthcare inequities in low-SDI regions. Future efforts should prioritize enhancing data quality, advancing early detection, and implementing context-specific strategies to alleviate the global burden of EOGC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Contributed data or analysis tools: Xueyang Zhang, Boao Gao.
Performed the analysis: Xueyang Zhang, Boao Gao, Wei Wang.
Wrote the paper: Xueyang Zhang, Boao Gao, Wei Wang.

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