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Original Article

Trends and Age-Period-Cohort Effects on Gastric Cancer Mortality in the Iranian Population (1990–2023)

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Abstract

Introduction: Gastric cancer (GC) remains a major cause of cancer mortality in Iran, with clear disparities between males and females. This study provides a comprehensive evaluation of GC mortality patterns from 1990 to 2023 in Iran, focusing on how age, period, and birth cohort have shaped these trends through advanced statistical analyses.

Methods: Age-specific and age-standardized GC mortality rates for the Iranian population, stratified by gender, were extracted from the Global Burden of Disease (GBD) Study 2023 for the years 1990 to 2023. Joinpoint regression and the Age-Period-Cohort (APC) model were applied to estimate the Average Annual Percentage Change (AAPC) and the Relative Risks (RRs), respectively.

Results: The findings showed a significant decrease in GC mortality rates, with average annual percent changes of -2.26, -2.41, and -2.07 per 100,000 population for the total, female, and male populations, respectively. Additionally, the APC model revealed an upward trend in age and period effects, and a decreasing trend in cohort effect for both males and females. In the total population, the age effect increased, except for the 90-94-year group (RR = 5.47, 95% CI: 5.37, 5.64, $P < 0.001$). The period effect showed an increase from 1994 (RR = 0.90; 95% CI: 0.89, 0.90) to 2023 (RR = 1.20; 95% CI: 1.17, 1.21). The cohort effect showed a consistent decrease in mortality from earlier to later birth cohorts (RR = 3.86 for the < 1903 cohort vs. RR = 0.19 for the 2004-2008 cohort).

Conclusion: Gastric cancer mortality in Iran has declined over the past three decades; however, it remains higher among older individuals and men. The recent increase observed during 2014–2023 underscores the need for continued surveillance of temporal trends.

Keywords: Age-Period-Cohort analysis, Gastric cancer, Iran, Joinpoint regression, Mortality, Sex differences, Temporal trend

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Introduction

Gastric cancer (GC), commonly referred to as stomach cancer, ranks among the most prevalent malignancies worldwide and remains a major contributor to cancer-related mortality. Despite substantial global efforts to reduce its incidence, this disease continues to pose a significant challenge for public health systems. According to the most recent Global Cancer Observatory (GLOBOCAN) 2022 estimates, GC accounted for approximately 968,000 new cases and around 660,000 deaths globally, ranking fifth in both incidence and mortality among all cancers.[1]

Marked geographical variation persists, with the highest age-standardized incidence rates observed in East Asia and Eastern Europe, while the lowest rates are reported in Africa. Furthermore, GC remains one of the deadliest malignancies across several regions in Central and Western Asia, including Iran, where it represents a major cause of cancer-related mortality.[2] The incidence of the disease is highly dependent on geography and sex.[3-5]

Gastric cancer is considered one of the most significant public health challenges in Iran.[6,7] In recent years, the high prevalence of factors such as *Helicobacter pylori* infection, tobacco use, gastroesophageal reflux disease, and excessive dietary salt intake has been reported as major environmental contributors to the increasing incidence of gastric cancer in the Iranian population.[8] In addition, gastric cancer is the most frequent cancer among men and the second most common cancer among women (after breast cancer) in Iran,[9] and it is also the leading cause of cancer-related mortality in both sexes.[9] Epidemiological investigations indicate that the distribution of gastric cancer in Iran is heterogeneous, exhibiting a distinct pattern across different geographic regions of the country.[10] The highest prevalence is observed in the northwestern and northern regions, which are considered part of the "Asian esophageal–gastric cancer belt." This belt, which originates in East Asia and extends through Central Asia to the Middle East, is characterized by elevated rates of gastric and esophageal cancers, and the location of northern and northwestern Iran along this pathway may explain the higher incidence in these areas.[11] In contrast, the southern regions of Iran report the lowest incidence of gastric cancer.[11] The central and western regions demonstrate moderate levels of incidence;[12] however, certain densely

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populated urban areas (such as the Tehran metropolitan region) show relatively higher rates.[13]

Patient age is one of the most important and influential prognostic factors in gastric cancer, with older age at diagnosis being consistently associated with significantly poorer outcomes. Furthermore, demographic shifts and the increasing mean age of the Iranian population may affect both the burden and prognosis of the disease over time. Another persistent challenge is that a substantial proportion of patients in Iran are diagnosed at advanced stages, which limits effective treatment and substantially reduces survival 9. In addition, notable differences in mortality between men and women highlight the importance of sex-specific analyses in understanding the epidemiology of gastric cancer.[14-16] Given the rising trend of gastric cancer mortality in Iran [17] and the influence of demographic, age, and sex-related dynamics, the use of advanced analytical approaches capable of disentangling these effects is essential.

Therefore, the present study addresses these gaps by conducting a comprehensive, nationwide analysis of gastric cancer mortality in Iran from 1990 to 2023, using Joinpoint regression and Age-Period-Cohort (APC) modeling to examine temporal trends, identify significant shifts, and explore the impact of age and sex on mortality patterns. This approach provides novel insights into the dynamics of gastric cancer mortality and informs more effective, targeted strategies for disease control and prevention.

Materials and Methods

Study Data

The Global Burden of Disease (GBD) 2023 Study, coordinated by the Institute for Health Metrics and Evaluation (IHME), is an ongoing, comprehensive research initiative designed to quantify the impact of diseases, injuries, and risk factors on global health. It offers a systematic and comparable assessment of health metrics across 204 countries and territories, broken down by sex and age group, spanning from 1990 to 2023. The study focuses on the burden of disease in terms of incidence, prevalence, mortality, years of life lost (YLL), years lived with disability (YLD), and disability-adjusted life years (DALY). The findings from the GBD study provide valuable insights that decision-makers at global, regional, national, and local levels can use to set health priorities and assess the effectiveness of interventions. In this ecological study, we extracted the age-specific and age-standardized GC mortality rates per 100,000 people for Iranian males, females, and the total population from the GBD 2023 dataset, covering the period from 1990 to 2023.[18] In terms of sample size, as this was an ecological study using nationally aggregated data from the GBD 2023 database, no sample selection or formal sample size calculation was required. The data covered the entire Iranian population, stratified by sex and age group, from 1990 to 2023.

Statistical Analysis

Joinpoint Regression Model

First, joinpoint regression analysis was employed to describe the trend and identify changes in the pattern of GC mortality rates in Iran. For the observations (t_1, y_1), (t_2, y_2), …, (t_n, y_n) where $t_1 < t_2 < \ldots < t_n$, the joinpoint regression model is defined as follows:

$$y_i = \beta_0 + \beta_1 t_i + \gamma_1 (t_i - \tau_1)^+ + \ldots + \gamma_k (t_i - \tau_k)^+ + \varepsilon_i$$

In the above model, t_i corresponds to the time points (1990, 1991, …, 2023), while y_i represents the mortality rates for GC. The variable τ_k (for k = 1, 2, …, K) marks the locations of the change points, K denotes the total number of change points, and β_0, β_1, and γ_1 … … γ_k are the regression coefficients. Lastly, ε_i stands for the model's error term.

The notation $(t_i - \tau_k)^+$ is defined as $t_i - \tau_k$ when $t_i - \tau_k > 0$, and 0 otherwise. Joinpoint regression models are fitted to aggregate annual rates on the log scale using ordinary least squares, assuming normally distributed random errors with constant variance (homoscedasticity). This corresponds to an identity link on the log scale and yields piecewise linear trends in log rates, from which annual percent changes (APCs) were derived.[19] The APC from year τ_j to year τ_{j+1} is calculated as follows:

$$\text{APC} = \left(e^{(\beta_0 + \gamma_1 + \ldots + \gamma_j)} - 1\right) * 100$$

A positive APC indicates an increasing trend, while a negative APC indicates a decreasing trend over time. For each fitted joinpoint regression model, the Average Annual Percent Change (AAPC) is calculated as the weighted mean of the APCs, where the segment lengths (the time intervals between change points) are used as the weights.[20] Additionally, the 95% confidence intervals for both the APCs and AAPCs were computed. The joinpoint regression analysis was performed using Joinpoint software version 5.2.0.0. The software fits the simplest model supported by the data, beginning with 0 joinpoints (a straight line), and sequentially tests whether additional joinpoints significantly improve model fit up to the maximum number allowed according to the number of data points in the time series. The statistical significance of adding joinpoints is evaluated using the Monte-Carlo permutation test, in which a simpler null model with fewer joinpoints is compared with a more complex alternative model. Residuals from the null model are repeatedly permuted to generate permutation datasets, and a test statistic based on the ratio of the sums of squared errors between the two models is calculated. A *P*-value is then estimated from the proportion of permutation datasets producing a test statistic as extreme as that observed in the original data; a small *P*-value indicates that the model with additional joinpoint(s) provides a significantly better fit.[21] To check the assumptions of the linear regression model, diagnostic checks were performed on the log scale using residual-versus-fitted, residual-versus-time, and Q–Q plots, which did not show any substantial violations of linearity (on the log scale), normality of residuals, or homogeneity of variance. Diagnostic plots are provided

in Supplementary Figure S1. The analysis was conducted under the constant variance (homoscedasticity) option, a standard specification in Joinpoint analyses based on two-field input data that assumes constant variance of regression errors across time points. No autocorrelated error structure was specified.[22]

Age-Period-Cohort Analysis

Next, the Age-Period-Cohort (APC) analysis was employed to examine the effects of age, period, and cohort on the trend of GC mortality during the study period. The APC regression model assumes a Poisson distribution for the mortality rates and is represented by the following equation:

$$g\left(\frac{Y_j}{\mu}\right) = \log\left(\lambda_j\right) = u + \alpha * age_j + \beta * period_j + \gamma * cohort_j$$

In this formulation, λ_j represents the modeled outcome, capturing the net influence on GC mortality for group j, while Y_j denotes the observed number of deaths and μ refers to the corresponding population at risk. The parameters α, β, and γ quantify the contributions of age, period, and birth cohort within the APC framework, respectively, with u serving as the intercept term. To resolve the inherent identification problem in APC analysis, we applied the Intrinsic Estimator (IE), a method widely acknowledged for its stability and superior model performance relative to other estimation techniques.[23] In addition, the variance assumption of the Poisson model was evaluated by examining the deviance-to-degrees-of-freedom and Pearson chi-square–to–degrees-of-freedom ratios, both of which were close to 1, indicating no meaningful overdispersion.

In this study, the data spans birth cohorts from < 1903 to 2004–2008, divided into 22 distinct groups. For the calendar periods, a 6-year interval was used, ranging from 1994–1998 to 2019–2023. Additionally, age groups were categorized into 17-year intervals, starting from 15–19 years to those over 95 years.

The exact linear relationship among age, period, and cohort (Cohort = Period – Age) results in complete collinearity, a well-known issue referred to as the identification problem. This problem makes it impossible to uniquely estimate the individual effects of age, period, and cohort using conventional regression models. To address this challenge, we employed the Intrinsic Estimator (IE) method, which is designed to handle this issue effectively.[24] The IE method utilizes a principal component approach that allows for simultaneous, unbiased, and statistically efficient estimation of the three effects (age, period, and cohort) while overcoming collinearity. For conducting this analysis, we used the "apc-ie" command in the STATA 17 (StataCorp, 2021) software, which implements the IE method specifically for age-period-cohort models.

It should be noted that the influence of these factors (age, period, and cohort) on the GC mortality rate is reported based on relative risk (RR), where $RR = e^{Coefficient}$. The RR indicates the likelihood of mortality for a specific age, period, or birth cohort relative to the average level. An RR greater than 1 indicates an increased risk, while an RR less than 1 indicates a decreased risk. The model coefficients and overall effects were considered statistically significant at the 5% level ($P < 0.05$).

Results

In this study, we examined the mortality rates for GC in Iran from 1990 to 2023. To model the trend of GC mortality over this period, we applied three joinpoint regression models to mortality rates per 100,000 population for the total population, women, and men. Table 1 presents the estimates obtained from fitting the joinpoint regression models to mortality rates, stratified by gender. For the female data, the analysis revealed five joinpoints in 1997, 2003, 2006, 2013, and 2018, resulting in six distinct time intervals, each with different trends. The estimated APCs in mortality rates for women were -2.96, -0.90, -5.44, -2.44, -0.34, and -3.59 in the time intervals 1990-1997, 1997-2003, 2003-2006, 2006-2013, 2013-2018, and 2018-2023, respectively. For the male population, the fitted model yielded three joinpoints and four-time intervals. The estimated APCs for men were -3.39, -1.97, -0.47, and -3.27 in the periods 1990-1995, 1995-2013, 2013-2019, and 2019-2023, respectively. For the total population, the fitted model resulted in four joinpoints and five-time intervals.

The estimated APCs for the total population were -3.13, -1.41, -2.97, -0.76, and -3.54 in the time intervals 1990-1997, 1997-2003, 2003-2011, 2011-2019, and 2019-2023, respectively. In females, the reduction in mortality during the time intervals of 1997-2003 and 2013-2018 was not statistically significant ($P = 0.08$, $P = 0.48$). In males, the

Table 1. Results of Joinpoint Regression Models for Trend Analysis of Mortality Rates in Female, Male, and Total Populations from 1990 to 2023

Gender	Segments	Time interval	APC (95%CI)	*P* value
Female	Trend 1	1990-1997	-2.96 (-3.54, -2.54)	<0.001
	Trend 2	1997-2003	-0.90 (-1.39, 0.22)	0.08
	Trend3	2003-2006	-5.44 (-6.15, -4.06)	<0.001
	Trend4	2006-2013	-2.44 (-2.97, -1.85)	<0.001
	Trend5	2013-2018	-0.34 (-1.03, 0.92)	0.48
	Trend6	2018-2023	-3.59 (-4.46, -2.99)	<0.001
	AAPC (95%CI)	1990-2023	-2.41 (-2.49, -2.34)	<0.001
Male	Trend 1	1990-1995	-3.39 (-4.74, -2.77)	<0.001
	Trend 2	1995-2013	-1.97 (-2.10, -1.83)	<0.001
	Trend3	2013-2019	-0.47 (-0.99, 1.00)	0.32
	Trend4	2019-2023	-3.27 (-4.95, -2.42)	<0.001
	AAPC (95%CI)	1990-2023	-2.07 (-2.17, -2.00)	<0.001
Both	Trend 1	1990-1997	-3.13 (-3.88, -2.72)	<0.001
	Trend 2	1997-2003	-1.41 (-1.94, -0.09)	0.03
	Trend3	2003-2011	-2.97 (-3.95, -2.62)	<0.001
	Trend4	2011-2019	-0.76 (-1.14, -0.03)	0.04
	Trend5	2019-2023	-3.54 (-4.99, -2.65)	<0.001
	AAPC (95%CI)	1990-2023	-2.26 (-2.34, -2.18)	<0.001

reduction in mortality during the time interval 2013-2019 was also not significant ($P = 0.32$). However, reductions in other time intervals were significant ($P < 0.001$). The estimated AAPCs provide a clear overview of the trends in GC mortality for the total population as well as for men and women in Iran. The total, female, and male populations experienced average annual decreases of -2.26 (95%CI: -2.34, -2.18, $P < 0.001$), -2.41 (95%CI: -2.49, -2.34, $P < 0.001$), and -2.07 (95%CI: -2.17, -2.00, $P < 0.001$) per 100,000 in mortality rates, respectively, from 1990 to 2023. Figure 1 illustrates the estimated trends in mortality rates, based on the fitted joinpoint regression models, stratified by gender, over the period from 1990 to 2023.

Additionally, the description of cohort trends in GC mortality across different age groups, stratified by gender and the total population, is presented in Figure 2. This figure reveals a general decline in mortality rates over time for both genders and the total population. Among females, older cohorts, particularly those aged 80 years or above, exhibited higher mortality rates compared to younger cohorts. In other words, a significant decline in mortality was observed in the most recent cohort across all age groups. For males and the total population, the trend in mortality followed a similar pattern to that of females, with the key difference being that older cohorts, especially those aged 95 and above, demonstrated significantly higher mortality rates compared to the older age groups in subsequent cohorts.

In the following step, we applied the APC model with the IE method to estimate the coefficients for age, period, and cohort effects for males, females, and the overall population. In females, after adjusting for period and cohort effects, the age effect displayed an upward trend (Figure 3). For instance, as shown in Table 2, the estimated RR for the age effect in the 15-19-year age group was 0.08 (95% CI: 0.08, 0.09 $P < 0.001$), while for those aged ≥ 95 years, it was 5.87 (95% CI: 5.70, 6.07, $P < 0.001$). The ratio of these RRs showed that, after controlling for period and cohort effects, the GC mortality rate in the ≥ 95-year group was about 73.37 times higher than in the 15-19-year group. Furthermore, the period effect demonstrated an increasing trend from 1994 (RR = 0.95; 95% CI: 0.93, 0.96, $P < 0.001$) to 2023 (RR = 1.09; 95% CI: 1.08, 1.12, $P < 0.001$) (Table 2, Figure 3). Additionally, as shown in Table 2, and Figure 3, the cohort effect revealed a consistent reduction in mortality rates across earlier birth cohorts compared to later birth cohorts, after adjusting for age and period effects (RR = 3.42, $P < 0.001$ in the < 1903 cohort to RR = 0.19, $P < 0.001$ in the 2004–2008 cohort).

In males, the results of the APC model, after controlling for period and cohort effects, revealed a clear and significant upward trend in the age effect, with increasing age leading to higher mortality from GC. For example, the RR for the 15-19-year age group was 0.05 (95% CI: 0.05, 0.06, $P < 0.001$), while it was 7.69 (95% CI: 7.46, 7.85 $P < 0.001$) for the ≥ 95-year age group. The ratio of these RRs showed that, after adjusting for period and cohort effects, the GC mortality rate in the ≥ 95-year group was approximately 153.80 times higher than in the 15-19-year group. Regarding the period and cohort effects, a similar increasing trend over time was observed, as seen in females (Table 3, Figure 4).

In the total population, with adjusting for period and cohort effects, the age effect showed an increasing trend, except in the 90-94-year age group (Figure 5). The estimated age effect RR for the 85-89-year age group was 5.64 (95% CI: 5.53, 5.75, $P < 0.001$), while it was 5.47 (95% CI: 5.37, 5.64, $P < 0.001$) for the 90–94-year age group. This slight decline in the 90-94-year group suggests a deviation from the otherwise consistent increase in mortality with age. Additionally, the period and cohort effects displayed increasing and decreasing trends over time, respectively,

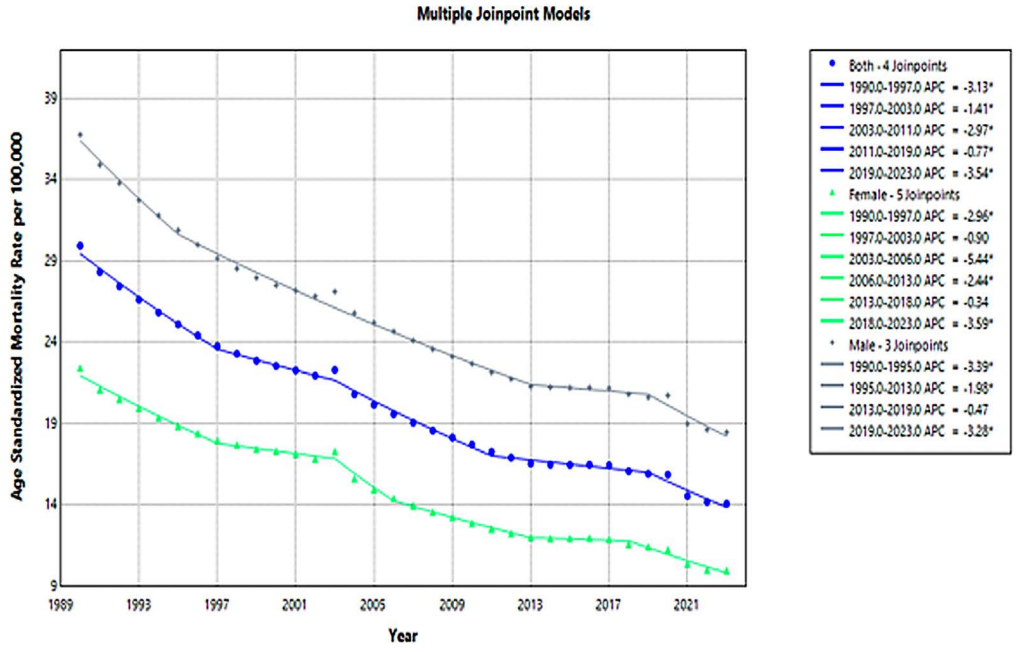

Figure 1. Results of Joinpoint Regression Models for Analyzing the Mortality Trend of Stomach Cancer by Gender and Total Population from 1990 to 2023

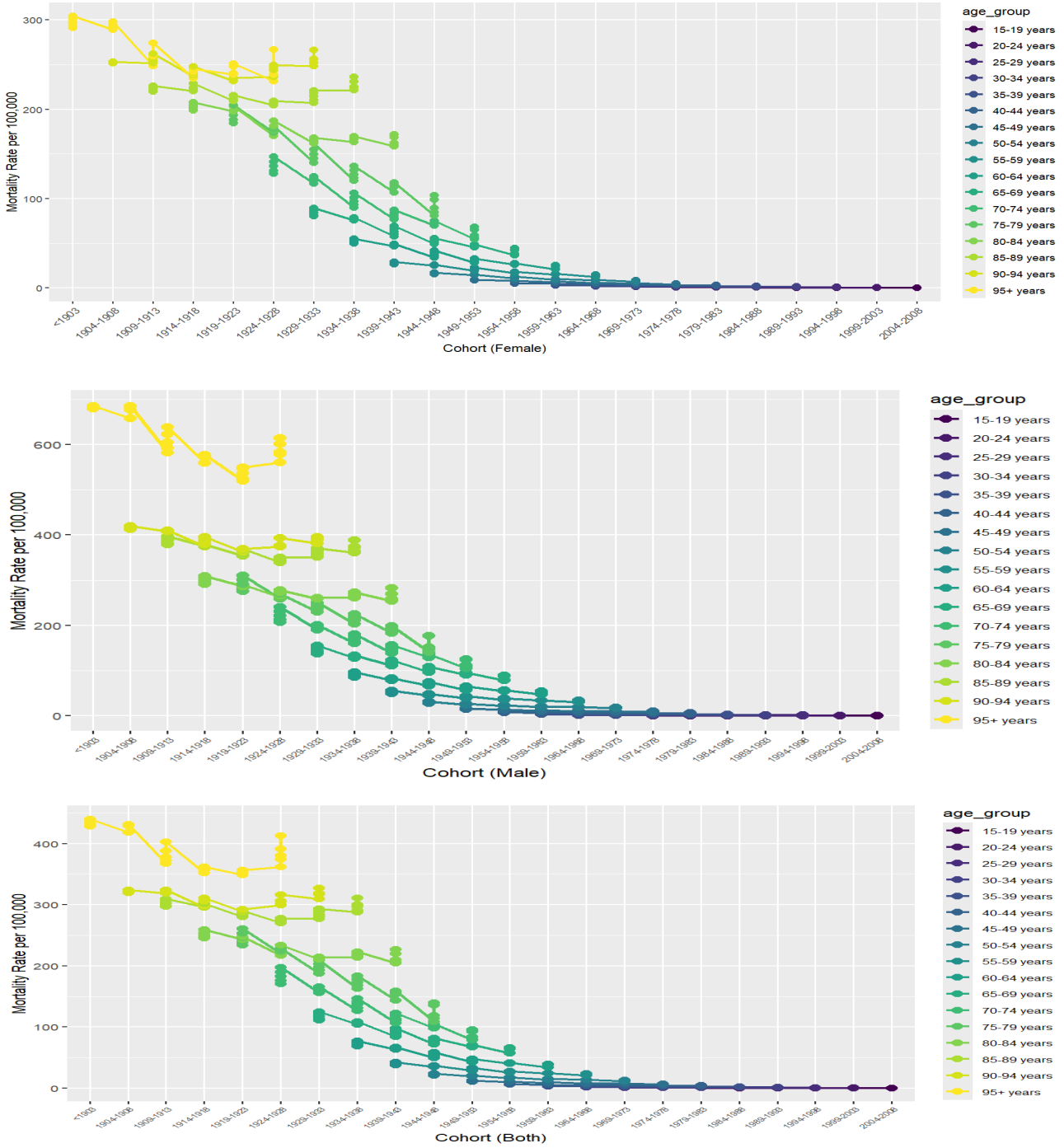

Figure 2. Cohort Trends in Stomach Cancer Mortality by Age Group, Gender, and Total Population (1990-2023)

reflecting changes in mortality patterns and the impact of different birth cohorts (Table 4, Figure 5).

Discussion

GC is a malignant disease of the stomach lining and constitutes one of the most common cancers of the digestive system globally. It remains a major public health challenge due to its high mortality and substantial burden on healthcare systems, particularly in developing countries.[25] In 2020, approximately 1.09 million new cases and 0.77 million deaths from GC were reported globally, highlighting its significant contribution to cancer-related morbidity and mortality.[26] In Iran, GC is among the most prevalent malignancies, with an age-standardized incidence rate of about 22.4 per 100,000 in men and 12.5 per 100,000 in women, emphasizing its persistent impact on public health.[27] To examine trends in GC mortality in Iran from 1990 to 2023, we employed two complementary statistical approaches: Joinpoint Regression, which allows identification of significant change-points and calculation of annual percent changes, and an APC analysis, which enables estimation of the independent effects of age, period, and birth cohort on mortality. Together, these methods provide a comprehensive understanding of temporal trends and the demographic determinants of GC mortality.

The joinpoint regression analysis revealed distinct trends in GC mortality in Iran from 1990 to 2023 for the total

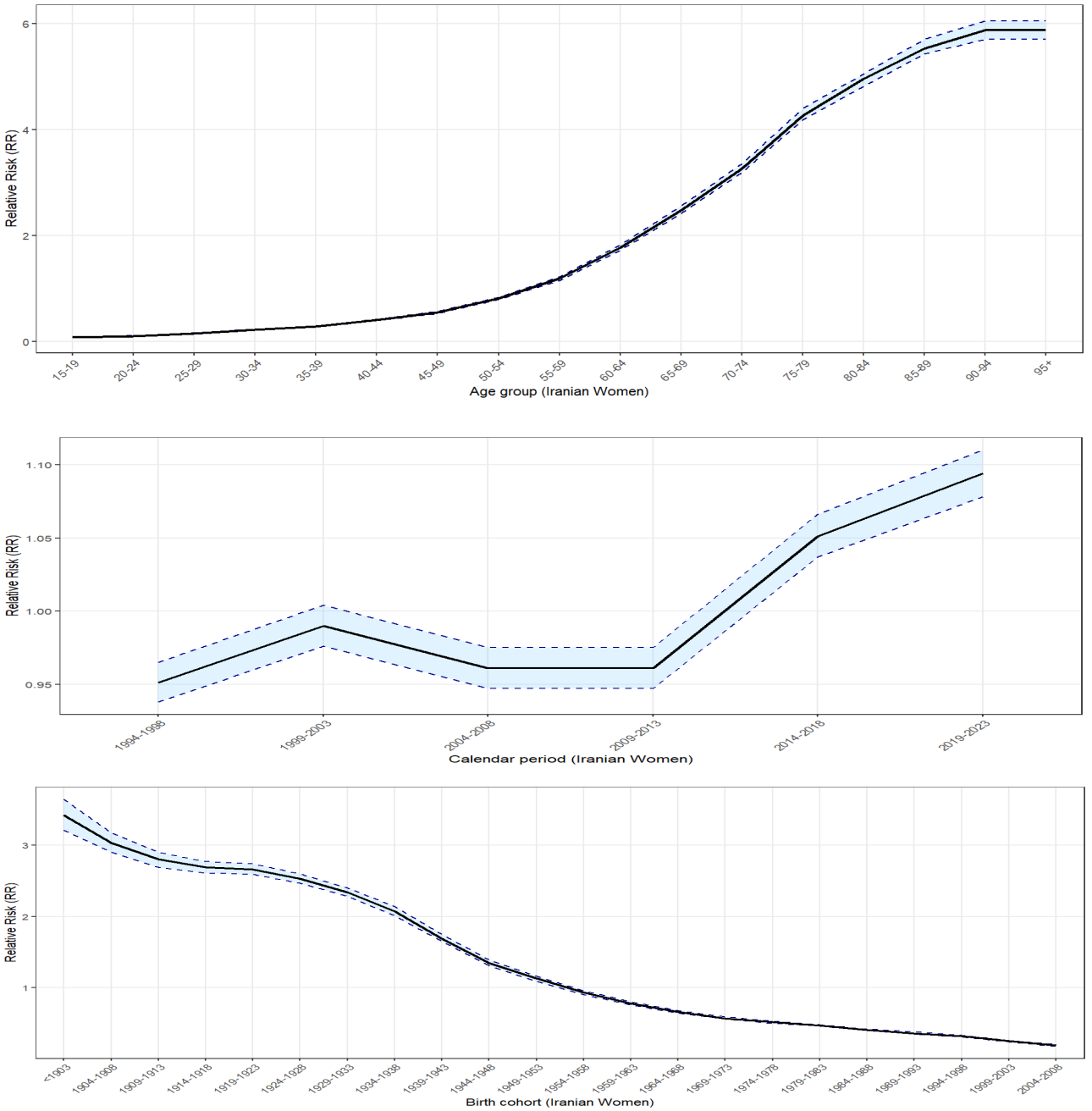

Figure 3. Stomach Cancer Mortality of Iranian Women Relative Risks Due to Age; Period; and Cohort Effects

population, as well as separately for men and women. While there has been an overall decline in mortality across all groups, the trends were not consistent throughout the study period. For both women and men, certain time intervals showed more pronounced decreases in mortality, while others indicated slower or non-significant changes. Notably, the mortality rate for men has consistently been higher than for women, which is consistent with global patterns, where men are generally at greater risk of developing and dying from GC 3. This gender disparity may be attributed to a combination of biological, environmental, and lifestyle factors. Looking at the broader context, many developing regions have experienced a slower decline in gastric cancer mortality. For example, in Eastern European countries such as Romania and Russia, reductions in mortality have been more gradual compared to high-income countries like Japan and South Korea, where structured screening and early detection programs have contributed to steeper declines.[28] Similarly, in parts of South America, including Argentina and Brazil, GC remains a significant cause of death, with improvements in mortality rates being less pronounced than in other regions.[5] These trends underscore the continuing challenges faced by these regions, such as limited healthcare access, lower rates of early detection, and fewer resources for treatment and prevention programs. In comparison, Iran has experienced a consistent and notable decline in GC mortality over the past few decades. The trend appears somewhat more favorable than in some middle-income countries with historically high mortality, but still less pronounced than in high-income countries with advanced screening and prevention programs. Periods of slower or

Table 2. APC Model Analysis Results for Stomach Cancer Mortality Among Iranian Women

Variable	RR	95% CI	*P* value
Age (Years)			
15-19	0.08	(0.08, 0.09)	<0.001
20-24	0.10	(0.10, 0.11)	<0.001
25-29	0.15	(0.15, 0.16)	<0.001
30-34	0.22	(0.22, 0.23)	<0.001
35-39	0.28	(0.27, 0.29)	<0.001
40-44	0.40	(0.39, 0.41)	<0.001
45-49	0.55	(0.53, 0.57)	<0.001
50-54	0.81	(0.79, 0.83)	<0.001
55-59	1.19	(1.15, 1.22)	<0.001
60-64	1.77	(1.72, 1.82)	<0.001
65-69	2.48	(2.41, 2.56)	<0.001
70-74	3.26	(3.19, 3.35)	<0.001
75-79	4.26	(4.18, 4.39)	<0.001
80-84	4.95	(4.81, 5.05)	<0.001
85-89	5.53	(5.42, 5.70)	<0.001
90-94	5.87	(5.70, 6.05)	<0.001
95+	5.87	(5.70, 6.07)	<0.001
Period			
1994-1998	0.95	(0.94, 0.96)	<0.001
1999-2003	0.99	(0.98, 1.01)	0.36
2004-2008	0.96	(0.95, 0.97)	<0.001
2009-2013	0.96	(0.95, 0.97)	<0.001
2014-2018	1.05	(1.04, 1.07)	<0.001
2019-2023	1.09	(1.08, 1.11)	<0.001
Cohort			
<1903	3.42	(3.21, 3.64)	<0.001
1904-1908	3.03	(2.90, 3.17)	<0.001
1909-1913	2.80	(2.69, 2.90)	<0.001
1914-1918	2.69	(2.61, 2.77)	<0.001
1919-1923	2.66	(2.59, 2.74)	<0.001
1924-1928	2.53	(2.47, 2.60)	<0.001
1929-1933	2.34	(2.28, 2.40)	<0.001
1934-1938	2.07	(2.01, 2.14)	<0.001
1939-1943	1.69	(1.65, 1.75)	<0.001
1944-1948	1.35	(1.31, 1.39)	<0.001
1949-1953	1.13	(1.09, 1.163)	<0.001
1954-1958	0.93	(0.90, 0.96)	<0.001
1959-1963	0.78	(0.76, 0.80)	<0.001
1964-1968	0.66	(0.64, 0.68)	<0.001
1969-1973	0.57	(0.56, 0.59)	<0.001
1974-1978	0.52	(0.50, 0.53)	<0.001
1979-1983	0.47	(0.46, 0.48)	<0.001
1984-1988	0.41	(0.40, 0.42)	<0.001
1989-1993	0.36	(0.35, 0.38)	<0.001
1994-1998	0.32	(0.31, 0.33)	<0.001
1999-2003	0.25	(0.24, 0.26)	<0.001
2004-2008	0.19	(0.18, 0.20)	<0.001

Table 3. APC Model Analysis Results for Stomach Cancer Mortality Among Iranian Men

Variable	RR	95% CI	*P* value
Age (Years)			
15-19	0.05	(0.05, 0.05)	<0.001
20-24	0.06	(0.06, 0.06)	<0.001
25-29	0.09	(0.09, 0.09)	<0.001
30-34	0.15	(0.14, 0.15)	<0.001
35-39	0.25	(0.24, 0.25)	<0.001
40-44	0.43	(0.42, 0.44)	<0.001
45-49	0.71	(0.70, 0.73)	<0.001
50-54	1.14	(1.12, 1.16)	<0.001
55-59	1.72	(1.68, 1.75)	<0.001
60-64	2.36	(2.32, 2.41)	<0.001
65-69	3.22	(3.16, 3.29)	<0.001
70-74	3.89	(3.82, 3.97)	<0.001
75-79	4.62	(4.53, 4.71)	<0.001
80-84	4.90	(4.81, 5.00)	<0.001
85-89	5.75	(5.64, 5.93)	<0.001
90-94	5.47	(5.37, 5.58)	<0.001
95+	7.69	(7.46, 7.85)	<0.001
Period			
1994-1998	0.85	(0.84, 0.86)	<0.001
1999-2003	0.89	(0.88, 0.90)	<0.001
2004-2008	0.93	(0.92, 0.94)	<0.001
2009-2013	0.99	(0.98, 1.00)	0.08
2014-2018	1.13	(1.12, 1.14)	<0.001
2019-2023	1.27	(1.26, 1.28)	<0.001
Cohort			
<1903	4.44	(4.22, 4.67)	<0.001
1904-1908	3.97	(3.86, 4.09)	<0.001
1909-1913	3.49	(3.38, 3.61)	<0.001
1914-1918	3.13	(3.06, 3.21)	<0.001
1919-1923	2.86	(2.79, 2.93)	<0.001
1924-1928	2.64	(2.57, 2.71)	<0.001
1929-1933	2.34	(2.27, 2.41)	<0.001
1934-1938	1.99	(1.94, 2.05)	<0.001
1939-1943	1.63	(1.58, 1.69)	<0.001
1944-1948	1.28	(1.25, 1.32)	<0.001
1949-1953	1.06	(1.04, 1.08)	<0.001
1954-1958	0.88	(0.86, 0.89)	<0.001
1959-1963	0.73	(0.71, 0.74)	<0.001
1964-1968	0.62	(0.60, 0.64)	<0.001
1969-1973	0.52	(0.51, 0.54)	<0.001
1974-1978	0.46	(0.44, 0.48)	<0.001
1979-1983	0.41	(0.40, 0.43)	<0.001
1984-1988	0.37	(0.36, 0.38)	<0.001
1989-1993	0.33	(0.32, 0.34)	<0.001
1994-1998	0.29	(0.28, 0.30)	<0.001
1999-2003	0.25	(0.23, 0.26)	<0.001
2004-2008	0.20	(0.19, 0.21)	<0.001

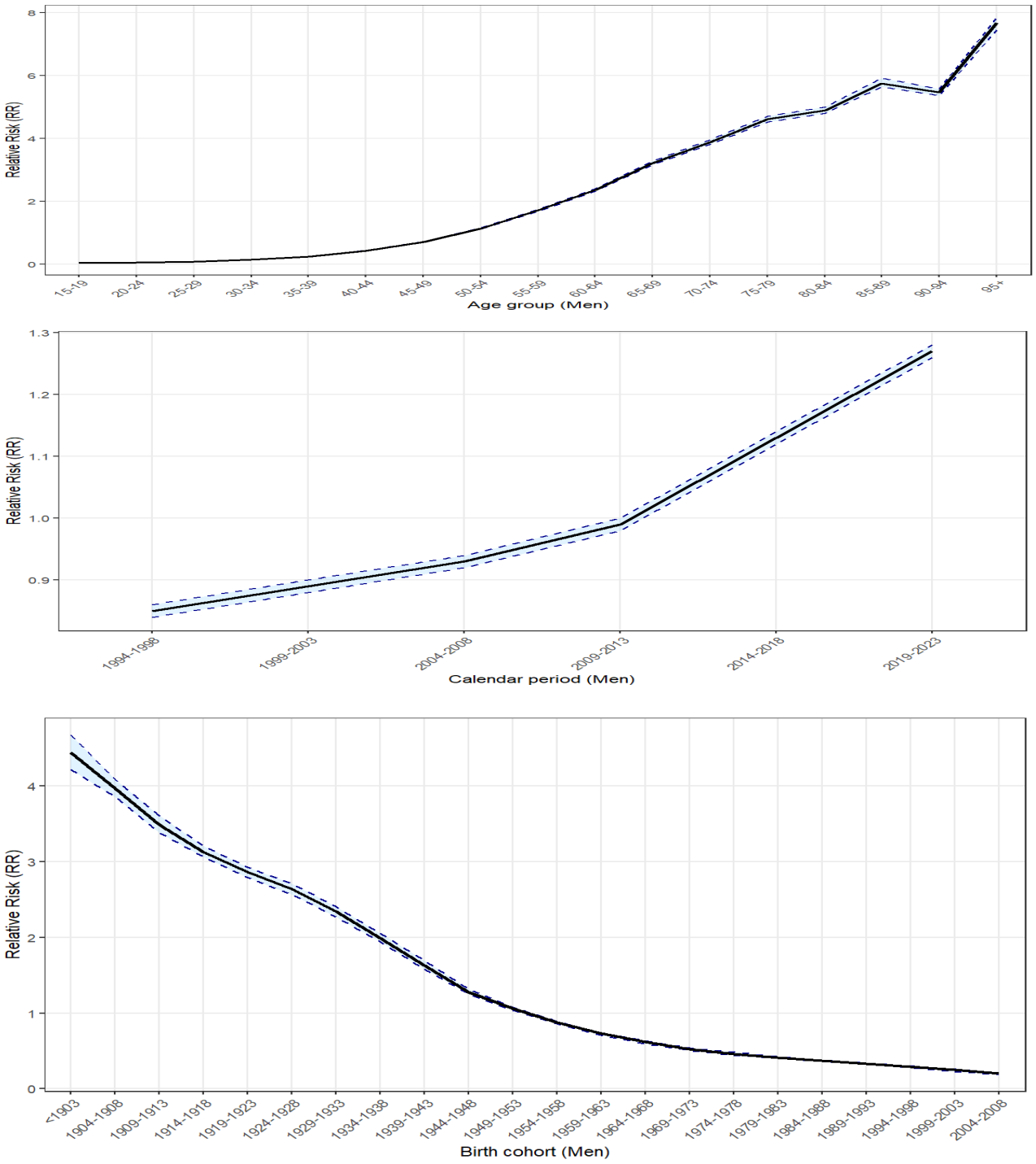

Figure 4. Stomach Cancer Mortality of Iranian Men Relative Risks Due to Age; Period; and Cohort Effects

non-significant decline, along with persistently higher mortality among men, underscore the ongoing need for public health interventions, including expanded access to early detection and the implementation of comprehensive prevention strategies to reduce the burden of gastric cancer.

The APC analysis demonstrates a strong age effect on GC mortality in Iran among women, men, and the total population. Mortality rates are lowest in the youngest age groups (15-19 years) and progressively increase with advancing age, with the highest levels observed among the oldest populations. The increase in mortality with age is more pronounced among men, reflecting a persistent gender disparity, with consistently higher mortality rates compared to women. The population-level analysis further confirms that older adults bear the greatest burden of GC mortality.

These age-related patterns are consistent with international observations. For example, studies in Japan and South Korea report a sharp increase in gastric cancer mortality among individuals aged over 60, reflecting cumulative exposure to risk factors and the impact of age-related physiological changes.[29,30] In a population-based study from one of the highest gastric cancer risk regions in China, Niu et al. examined registry-based data from 2010 to

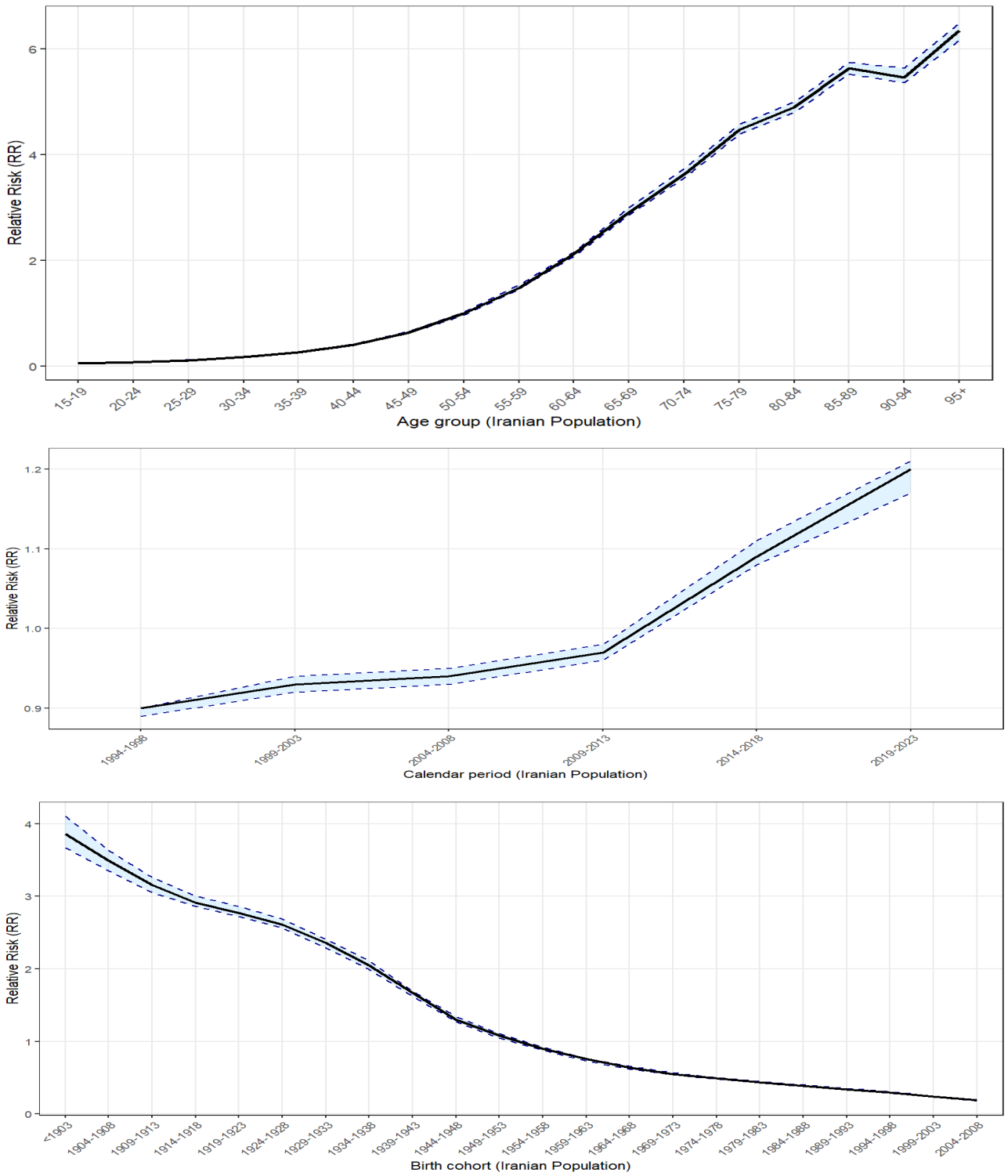

Figure 5. Stomach Cancer Mortality of Iranian Population Relative Risks Due to Age; Period; and Cohort Effects

2019 and demonstrated that disease burden and mortality were substantially higher among older adults, highlighting the significant impact of increasing age on gastric cancer outcomes.[31] Similarly, Wang et al. demonstrated that increasing age independently contributes to higher gastric cancer mortality, even after simultaneous adjustment for age, period, cohort effects, and declining *Helicobacter pylori* prevalence.[9] The consistency of these trends highlights aging as a major determinant of gastric cancer mortality globally.[10,11] The marked increase in mortality from middle age onwards underscores the importance of age-targeted interventions in Iran, including early detection strategies, screening programs, and preventive measures aimed at modifiable lifestyle factors and gastric disease management. Implementing such interventions across the life course is likely to play a critical role in reducing the burden of gastric cancer in older populations.

After adjusting for age and cohort effects in the APC model, the period effect demonstrated an increasing trend in the most recent intervals for both men and women, with

Table 4. APC Model Analysis Results for Stomach Cancer Mortality Among the Iranian Population

Variable	RR	95% CI	*P* value
Age (Years)			
15-19	0.06	(0.06, 0.07)	<0.001
20-24	0.08	(0.08, 0.08)	<0.001
25-29	0.11	(0.11, 0.12)	<0.001
30-34	0.18	(0.17, 0.18)	<0.001
35-39	0.26	(0.25, 0.26)	<0.001
40-44	0.41	(0.40, 0.42)	<0.001
45-49	0.64	(0.63, 0.66)	<0.001
50-54	1.00	(0.97, 1.02)	0.89
55-59	1.49	(1.46, 1.54)	<0.001
60-64	2.12	(2.08, 2.16)	<0.001
65-69	2.91	(2.86, 3.00)	<0.001
70-74	3.63	(3.56, 3.74)	<0.001
75-79	4.48	(4.39, 4.57)	<0.001
80-84	4.90	(4.81, 5.00)	<0.001
85-89	5.64	(5.53, 5.75)	<0.001
90-94	5.47	(5.37, 5.64)	<0.001
95+	6.36	(6.17, 6.49)	<0.001
Period			
1994-1998	0.90	(0.89, 0.90)	<0.001
1999-2003	0.93	(0.92, 0.94)	<0.001
2004-2008	0.94	(0.93, 0.95)	<0.001
2009-2013	0.97	(0.96, 0.98)	<0.001
2014-2018	1.09	(1.08, 1.11)	<0.001
2019-2023	1.20	(1.17, 1.21)	<0.001
Cohort			
<1903	3.86	(3.67, 4.10)	<0.001
1904-1908	3.49	(3.35, 3.63)	<0.001
1909-1913	3.16	(3.05, 3.26)	<0.001
1914-1918	2.91	(2.86, 3.00)	<0.001
1919-1923	2.77	(2.72, 2.86)	<0.001
1924-1928	2.61	(2.56, 2.69)	<0.001
1929-1933	2.36	(2.29, 2.41)	<0.001
1934-1938	2.05	(1.99, 2.11)	<0.001
1939-1943	1.67	(1.62, 1.69)	<0.001
1944-1948	1.30	(1.27, 1.34)	<0.001
1949-1953	1.08	(1.05, 1.11)	<0.001
1954-1958	0.90	(0.88, 0.92)	<0.001
1959-1963	0.76	(0.73, 0.77)	<0.001
1964-1968	0.64	(0.62, 0.66)	<0.001
1969-1973	0.55	(0.54, 0.57)	<0.001
1974-1978	0.49	(0.48, 0.50)	<0.001
1979-1983	0.44	(0.43, 0.45)	<0.001
1984-1988	0.39	(0.38, 0.40)	<0.001
1989-1993	0.34	(0.34, 0.35)	<0.001
1994-1998	0.30	(0.29, 0.31)	<0.001
1999-2003	0.24	(0.24, 0.25)	<0.001
2004-2008	0.19	(0.18, 0.20)	<0.001

a greater magnitude observed among men. Earlier periods were associated with declining GC mortality across both sexes, whereas later periods, particularly 2014-2018 and 2019-2023, indicated a reversal toward increasing risk. This temporal pattern may reflect changes in diagnostic practices, healthcare system factors, or population-level exposure to risk factors over time. This pattern is consistent with findings from East Asian countries such as Japan and South Korea, where long-term declines in gastric cancer mortality have been widely attributed to improvements in food preservation, hygiene, reduced *Helicobacter pylori* prevalence, and advances in early diagnosis and treatment.[32-34] Similar period-related declines have also been reported in regional analyses from China and population-based studies in high-incidence settings, supporting the notion that public health interventions and healthcare improvements exert measurable effects on population-level mortality rates over time.[35] Consistent with these findings, an age-period-cohort analysis from the Golestan Province (a recognized high-risk area in Iran) reported a decreasing trend in gastric cancer incidence from 2004 to 2018, although the decline was not statistically significant.[36] However, several recent studies have reported either stabilization or renewed increases in gastric cancer burden in specific populations and time periods, particularly in the last decade. In high-risk regions of China, recent surveillance data have indicated that mortality among older adults has plateaued rather than continued to decline, suggesting that earlier gains in disease control may be weakening.[31] Moreover, emerging evidence has reported rising trends in early-onset gastric cancer among younger cohorts, further challenging the assumption of a uniformly declining temporal pattern.[37] The recent increase in gastric cancer risk in Iran may be linked to population-level changes, including diet, obesity, antibiotic resistance affecting *H. pylori* treatment, or delayed diagnosis and care. These findings suggest that although period effects were previously protective, recent environmental, behavioral, and healthcare shifts may have reduced or reversed earlier gains, highlighting the need for renewed prevention strategies and stronger health system responses.

Cohort effects reflect variations in risk among individuals of similar age who were born in different years and experienced distinct social, environmental, and health-related conditions throughout life. In the present study, although the crude cohort-specific mortality trends appeared to increase in some of the more recent birth cohorts, the results of the APC-IE model demonstrated a clear and significant decline in the relative risk of GC mortality across successive birth cohorts after adjustment for age and period effects. Specifically, individuals born in earlier cohorts, particularly those born before 1903, exhibited the highest mortality risks, whereas those born in later cohorts, especially after 2000, had the lowest risks in both sexes and in the total population. This declining cohort pattern suggests a substantial improvement in risk profiles among younger generations, likely attributable

to advances in healthcare systems, improved access to diagnostic and treatment services, changes in dietary patterns, reduced exposure to environmental risk factors, and enhanced awareness of disease prevention and health-promoting behaviors. Moreover, the stronger cohort effect observed in men compared with women may reflect historical differences in lifestyle factors such as smoking patterns, occupational exposures, and dietary habits.[29,38-41] The observed cohort-related decline in mortality risk is consistent with findings from other Asian populations. For example, a population-based study in rural China using APC analysis reported that total cancer mortality risk declined markedly in more recent birth cohorts compared with earlier ones.[42] Similarly, in Taiwan, the incidence and mortality of gastric cancer showed a steady decrease over recent decades; birth-cohort analyses demonstrated that more recent cohorts had lower gastric cancer incidence than older cohorts within the same age group.[43]

Conclusion

Although gastric cancer mortality in Iran has declined over the past three decades, significant disparities persist across age groups and between sexes, reflecting the ongoing burden of the disease. The APC analysis revealed a marked increase in mortality with advancing age, a rising trend in period effects during recent years (2014–2023), and a consistent decline in risk among more recent birth cohorts. These patterns highlight the complex interplay between demographic changes and temporal trends in mortality. The findings underscore the importance of continued efforts in prevention and early detection, particularly for older populations and high-risk groups. By applying advanced statistical approaches, this study provides comprehensive and methodologically robust evidence to inform national cancer control policies and support effective decision-making.

Authors' Contribution

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Supervision: Fatemeh Masaebi
Validation: Fatemeh Masaebi, Maryam Karimi Ghahfarokhi
Visualization: Fatemeh Masaebi, Maryam Karimi Ghahfarokhi
Writing-Original Draft: Maryam Karimi Ghahfarokhi
Writing-Review & Editing: Maryam Karimi Ghahfarokhi, Fatemeh Masaebi, Majid Aminzare

Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

All data analyzed in this study are publicly available from the Global Burden of Disease results tool (http://ghdx.healthdata.org/gbd-results-tool).

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Supplementary Files

Supplementary file 1 contains Figure S1.

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