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## Research Article

**Keywords:** rheumatic heart disease, mortality, age-period-cohort analysis, JoinPoint, China

**Posted Date:** June 23rd, 2022

**DOI:** <https://doi.org/10.21203/rs.3.rs-1759369/v1>

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## RESEARCH

# Analysis of rheumatic heart disease mortality in the Chinese population: A JoinPoint and age-period-cohort study

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## Abstract

**Background:** The aim of this study was to analyze rheumatic heart disease (RHD) mortality trends in China's urban and rural areas and to determine the roles of age, period, and cohort effects.

**Methods:** Based on mortality data extracted from the Chinese Health Statistics Yearbook, we calculated the crude mortality rate of RHD in China. Age-adjusted rates were computed by the direct method using the 2020 census as the standard population. The annual percentage change (APC) and average annual percentage change (AAPC) were determined by the JoinPoint regression model. The age-period-cohort model and the intrinsic estimator (IE) algorithm were used to estimate the effects of age, period, and cohort.

**Results:** From 2006 to 2020, the general trend in RHD standardized mortality declined. The RHD mortality rate was higher in rural than in urban areas and among females than males. JoinPoint regression showed that the elderly (over 60 years old) were at high risk for RHD deaths in China. The age effect increased with age, and the cohort effect showed an overall declining trend as chronology grew, but the period effect was not significant.

**Conclusions:** China has achieved great success in RHD, but RHD mortality may increase with age. We should focus on publicity and education about RHD among the elderly. Compared with the period effect, age and cohort effects dominated the risk of RHD deaths.

**Keywords:** rheumatic heart disease; mortality; age-period-cohort analysis; JoinPoint; China

## Background

Rheumatic heart disease (RHD) is one of the sequelae of acute rheumatic fever[1]. Upon progression, RHD can result in cardiac calcification and even heart failure, and can have a severe negative impact on health and quality of life[2]. Global RHD morbidity and mortality declined in the 21st century, along with improvements in housing congestion and environmental pollution[3]. RHD morbidity and mortality rates in developed countries are almost 0, and RHD is currently concentrated in low-income countries and poverty groups of high-income countries[4, 5]. In 2015, the three countries with the most deaths due to RHD were estimated to be India, China, and Pakistan[6]. By 2020, the Chinese RHD death rate was still high, at 3.18/100,000 in urban areas and 3.81/100,000 in rural areas, far above the rates of common malignant tumors, such as nasopharyngeal carcinoma[7]. The aging soci-

ety and the shifting medical environment are affecting the prevalence of RHD in China. However, there is little available literature providing evaluation and guidance on public health interventions for RHD in China. Sun's research focused solely on overall trends in cardiovascular disease mortality and years of life lost[8], and the trends in RHD mortality in China were vague. Therefore, it is critical to understand the integrated role of causative agents and sanitary measures and to propose targeted policies.

Using data from only one cross-section tends to confound the relationship between age, period, and cohort. For example, when interpreting the effect of age on RHD, period and birth cohort differences must be considered. However, the JoinPoint Regression Model can independently assess the pattern of changes in RHD mortality, and the Age-Period-Cohort model (APC model) can decompose the effects of age, period, and birth cohort factors on the risk of RHD death.

The goal of this study was to provide a reference base for investigating the RHD mortality trend and performing precise sanitary work. We applied the JoinPoint Regression Model to explore trends in RHD mortality by sex and area from 2006 to 2020. We also used the APC model to quantify the effect coefficients.

## Methods

Between 2006 and 2020, this study collected age, sex, and regional (urban, rural) RHD mortality data from the Disease Surveillance Points system (DSPs) of China. The system is administered by the National Health Commission (previously the National Health and Family Planning Commission) Center of Health Information and Statistics (CHIS). China contained 522 surveillance points (361 counties and 161 districts) in 2020, covering 31 provinces, and these points submitted monthly reports to CHIS via electronic file transfer. Hence, the data represent China well. We adopted the 10th revision of the International Classification of Diseases to code for chronic rheumatic heart disease [ICD10:I05-I09].

The crude mortality rate for RHD was calculated separately for urban and rural areas, as well as for males and females. Using the 7th census data in 2020 as the standard population, age-adjusted mortality rates in all subgroups were calculated. Since the mortality rate of RHD under 30 years old was virtually 0, and the cause of death was more complicated in patients aged 80 years and above, we considered the population aged 30–79 years in China as participants.

To determine the magnitude of the secular trends for the RHD mortality rate, the JoinPoint Regression Program 4.9.0.0 (available through the National Cancer Institute's Surveillance Research Program) was applied to fit the trend of RHD mortality and compute the annual percentage change (APC) and average annual percentage change (AAPC). The model truncated and divided age into five-year intervals (30–34, 35–39, ... , 75–79), with up to three turning points based on the incorporated data. In this model, the mortality rates were also log-transformed, and the 95% confidence intervals (95% CIs) were set to 0.05 by the Monte Carlo permutation method.

Based on a Poisson distribution, the age-period-cohort model (APC model) is frequently employed in studies of chronic noncommunicable disease morbidity and mortality[9]. Because there is a linear relationship between age, period, and cohort

(cohort = period – age), the APC model cannot identify the unique estimates of the three effect parameters. To address this issue, Fu proposed the intrinsic estimator (IE) method over the estimation function method[10]; subsequently, IE was later demonstrated by Yang et al. to produce convergent and exclusive estimates[11]. Therefore, in this study, the APC model combined with IE was performed to roughly calculate the risk parameter of RHD death. We appropriately divided the data into ten age groups and three period groups, with five-year group intervals. The birth cohort was grouped into twelve cohort groups based on the linear relationship between birth cohort, period, and age. We also used the years 2008, 2013, and 2018 to substitute for the three period groups in the APC model to avoid data overlap between adjacent cohorts. Finally, our study implemented the APC model with Stata 14.0.

## Results

During the period 2006–2020, the RHD death rate in urban men/women and rural men/women declined. Rural regions had a higher average standardized mortality rate (4.2/100,000) than urban areas (2.7/100,000). As shown in Figure 1, males and females in urban areas showed consistently higher age-adjusted death rates than males and females in rural areas.

From 2006 to 2020, the JoinPoint analysis found a significant decrease in RHD standardized and crude mortality rates. When comparing the JoinPoint regression results for standardized and gross mortality rates, the age-adjusted and crude mortality rates for urban men and women indicated no difference. Between 2006 and 2012, the age-adjusted mortality rate for rural males and females did not present a statistically significant change. After 2012, APC fell by 6.0% and 7.3%, respectively. While the crude mortality rate continued to decline by 2.0% and 3.2% per year from 2006 to 2020 (Additional file 1 and Additional file 2).

The age-specific mortality rates of the four subgroups showed a marked decreasing trend year by year. However, the decline was significantly smaller in the elderly (60 years and older), and it even grew at an annual rate of 0.2% and 2.0% in the age groups of 70–74 and 75–79 urban males, respectively ( $P > 0.05$ ). In particular, RHD mortality fell annually ( $P < 0.05$ ) in most age groups of urban men (30–69 years) and all age groups of urban women, and most middle-aged rural women (35–39, 40–44, 45–49, and 55–59 years) showed a decrease of 10% or more in the annual percentage change (Additional file 3 and Additional file 4).

The APC model results demonstrated that age and birth cohort were the main risks for RHD death (Figure 2). The age effect increased with age, and period-specific mortality was plotted with age to assess the age effect more visually (Figure 3). This result indicated that, during the three periods of 2008, 2013, and 2018, age-specific mortality rates for urban and rural populations of different sexes and age subgroups were relatively low and stable up to age 50. Then, they consistently grew in the 50–75 age range and peaked at 75–79 years old. After controlling for age and cohort effects, the period effect coefficient fluctuated inconspicuously and fell overall. Variations in cohort effect were more complex, showing a slow change followed by a decline before the 1963 birth cohort. The 1964–1968 birth cohort groups generally illustrated a slight upward trend, with a more distinct downward

trend after 1969. In summary, the whole coefficient of the cohort effect dropped from 1931 to 1990. Undeniably, in the same birth cohort, mortality rates for urban males and rural males/females showed an upward and then a downward trend at ages 65–69 and 75–79 years, respectively (Figure 4). Young adults had a lower risk of death from RHD than older people.

## Discussion

To the best of our knowledge, this is the first study to exclusively utilize JoinPoint regression model to analyze trends in RHD mortality in China and to decompose the effects of age, period, and cohort by the APC model for urban and rural areas and men and women. The findings indicated a downward trend in the RHD standardized mortality rate from 2006 to 2020, with obvious regional differences. In the same years, the rural standardized rate was higher than the urban rate, and the female rate was higher than the male rate; however, the discrepancies between urban and rural areas gradually shrank. In the early 20th century, the timely use of antibiotics, such as penicillin, helped avoid subsequent rheumatic fever and rheumatic heart disease. It also dramatically reduced the prevalence and severity of RHD in China and improved the patients' quality of life, with approximately 70% of acute rheumatic fever patients recovering within 2–3 months[12]. Sex differences in RHD mortality may be associated with female autoimmune susceptibility and the intensity of streptococcal exposure[13, 14]. In addition, improving health awareness and education has kept people away from risk factors. From 1993 to 1995, the Chinese government conducted regular surveys on the prevalence of RHD, as well as improved health education for children and adolescents with streptococcal pharyngitis and rheumatic fever[15]. Meanwhile, urban and rural schooling levels improved dramatically from 2006 to 2020, particularly in rural schooling[16]. All of these factors contributed to a better quality of health services for Chinese residents regarding RHD. To some extent, RHD prevention and control measures have achieved some success.

We gathered national data on RHD aged 30–79 years from China's largest and best-accessible program. The massive sample size made the data more representative and allowed us to describe trends in RHD in urban and rural areas by gender from 2006 to 2020. By comparing the results of the JoinPoint analysis of standardized and crude mortality, we concluded that there were no differences between urban males and urban females. The standardized mortality rates for rural males and rural females changed slowly from 2006 to 2012 and decreased by 6.0% and 7.3% per year after 2012, respectively. The crude mortality rates of rural areas showed a linear downward trend, with the standardized mortality rates declining more than the crude mortality rates. Consistent with the findings of Cheng, the mortality distribution may be related to age composition[17]. Our study also found that the age-specific mortality rates decreased year by year in the four subgroups, but the percentage reduction was less for the elderly and even indicated an increasing trend for urban males over 70 years old. In particular, China is facing rapid population aging. The number of people over 65 years old is expected to exceed 200 million in 2022, and China will enter a "deeply aging society"[18]. Older adults face a rapid decline in physical function and a significant drop in social status as well as a high

prevalence of chronic diseases. Thus, the key population for RHD prevention and control in China is elderly individuals, and health promotion efforts for this group should be bolstered. Additionally, unlike in developed countries, rheumatic heart disease has not been effectively controlled in China. Therefore, it is still necessary to monitor the trend of the RHD epidemic in the long term and continue to improve prevention and control efforts.

The APC model discovered that age, period, and cohort effects affected all four subgroups, with age and birth cohort effects being the most severe. The risk of RHD death increased with age in both urban and rural areas and in both sexes, peaking at 75–79 years old. Part of this may be due to the lack of early RHD symptoms, which led to treatment neglect. As patients age, the risk of death increases significantly as RHD develops into heart failure[19, 20]. The period effect of RHD deaths among urban and rural residents in China from 2006 to 2020 was not apparent and might indicate that the growth of RHD mortality has stopped. The three successive Medicare systems established after the 1990s appear to explain the overall slow decline in the period effect coefficient. The cohort effect, referring to changes in risk factor exposure caused by experiencing different historical events, has greater public health significance than the age and period effects[21, 22]. The risk varied by birth cohort, and we argue that there was an overall downward trend in the cohort effect, with the later birth cohort having a lower risk of RHD death. On the one hand, RHD is heavily influenced by socioeconomic status[23]. The population's education rate is gradually increasing, and its socioeconomic status is improving, thus growing the health reserves of the younger generation and reducing the risk of RHD death[24]. On the other hand, it is associated with a rapidly developing national economy and daily improvements in living conditions. Because RHD is a disease of poverty, overcrowding, and poor sanitation, studies have demonstrated a correlation between the Gini coefficient and RHD prevalence[25, 26]. Reducing exposure to pathogenic factors early in embryonic development will substantially lower the adverse effects of future life[27, 28]. It has also been shown that the consumption of soybean oil and eggs can inhibit rheumatic processes[29]. Most RHD patients are malnourished with a low BMI and a mid-upper arm circumference[23, 30].

In short, improving living conditions, conducting public education, and receiving early antibiotic treatment may help lay a solid foundation for public health efforts in Chinese RHD. However, without sustained, intensive, and targeted public health interventions, it is challenging to ensure that rheumatic heart disease mortality will continue to fall and that the aim of rheumatic heart disease eradication will be met. Unlike the global disease burden of RHD, which is concentrated in girls and women[3, 31], JoinPoint analysis and APC model results implied that the elderly were a high-risk group for RHD in China. This might be because the sickness was already established before economic improvement and antibiotic administration. As a result, considering our country's circumstances, the focus of RHD prevention and treatment might be appropriately shifted to the elderly. At the same time, the prevalence of asymptomatic RHD is distinctly higher than that of symptomatic RHD. Our study suggested that echocardiographic screening combined with health checkups should be conducted in high-risk groups, and a registry with regular follow-up should be established [32, 33].

However, this study still has some limitations. First, the period effect was not distinct due to the short data year span. Second, this study was subject to data quality control. Although the data source was reliable, remote areas inevitably have incomplete reporting and other situations[34]. In the future, the RHD burden in China should be further explored in the context of the prevalence of RHD.

## Conclusion

Although rheumatic heart disease mortality showed an overall downward trend from 2006 to 2020 years, rheumatic heart disease has not ever disappeared. Some effective measures focusing on patients with rheumatic heart disease need to be taken to protect them and prevent the occurrence of rheumatic heart disease.

## Appendix

### Acknowledgements

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of Chinese Center for Disease Control and Prevention. Use of trade names and commercial sources is for identification only and does not imply endorsement by National Health Commission.

### Funding

This research received no specific grant from any funding agency or from commercial or not-for-profit sectors.

### Abbreviations

RHD:rheumatic heart disease; APC:annual percentage change; AAPC: average annual percentage change; IE: intrinsic estimator; APC model:age-period-cohort model; DSPs:Disease Surveillance Points system; CHIS: Center of Health Information and Statistics; 95 % CIs: 95% confidence intervals;

### Availability of data and materials

Rheumatic heart disease mortality data from the Disease Surveillance Points system (DSPs) of China. The system is administered by the National Health Commission (previously the National Health and Family Planning Commission) Center of Health Information and Statistics (CHIS).

### Ethics approval and consent to participate

Because the data is de-identified and public, the Jilin University IRB exempted this study from review.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publication

Not applicable.

### Authors' contributions

Conception and Design: Changgui Kou Analysis and interpretation of data: Jiameng Cui, Xinru Guo, Xin Yuan, Hao Wu, Ge Yu Drafting the manuscript: Jiameng Cui, Xinru Guo, Xin Yuan, Hao Wu, Ge Yu, Biao Li Critical revision of the manuscript: Changgui Kou Final approval of the manuscript: All authors

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#### Figures

**Figure 1** Changes in the standardized mortality rate of RHD in urban and rural areas by sex in China (1/100,000).

**Figure 2** Multivariable age-period-cohort analysis of RHD mortality rates by region and sex in China from 2006 to 2020. For the 3 line graphs, the left lines represent age effect, the middle lines are the estimated birth cohort effect, and the short lines refer to the period effects (risk ratio). The shaded areas surrounding the lines represent the 95% confidence intervals. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]

**Figure 3** Mortality rates of RHD in China from 2006 to 2020. Mortality data were collected from the Disease Surveillance Points system of China. Age analyses were from 30 to 79, with every 5-year interval as one age. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]

**Figure 4** Mortality rates of RHD in China among those aged 30 to 79 years. Mortality data were collected from the Disease Surveillance Points system of China. Birth cohorts analyses were from 1931 to 1990, with every 5-year interval as one cohort. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]

**Additional Files**

Additional file 1 — AAPC and APC of standardized mortality rate of RHD by area and gender in China.

APC (annual percentage change); AAPC (average annual percentage change); \* indicates statistically significant ( $P < 0.05$ ).

Additional file 2 — AAPC and APC of crude mortality rate of RHD by area and gender in China.

APC (annual percentage change); AAPC (average annual percentage change); \* indicates statistically significant ( $P < 0.05$ ).

Additional file 3 — Temporal trend analysis of age-specific mortality rates for RHD in urban Chinese residents.

APC (annual percentage change); AAPC (average annual percentage change); \* indicates statistically significant ( $P < 0.05$ ).

Additional file 4 — Temporal trend analysis of age-specific mortality rates for RHD in rural Chinese residents.

APC (annual percentage change); AAPC (average annual percentage change); \* indicates statistically significant ( $P < 0.05$ ).

## Figures

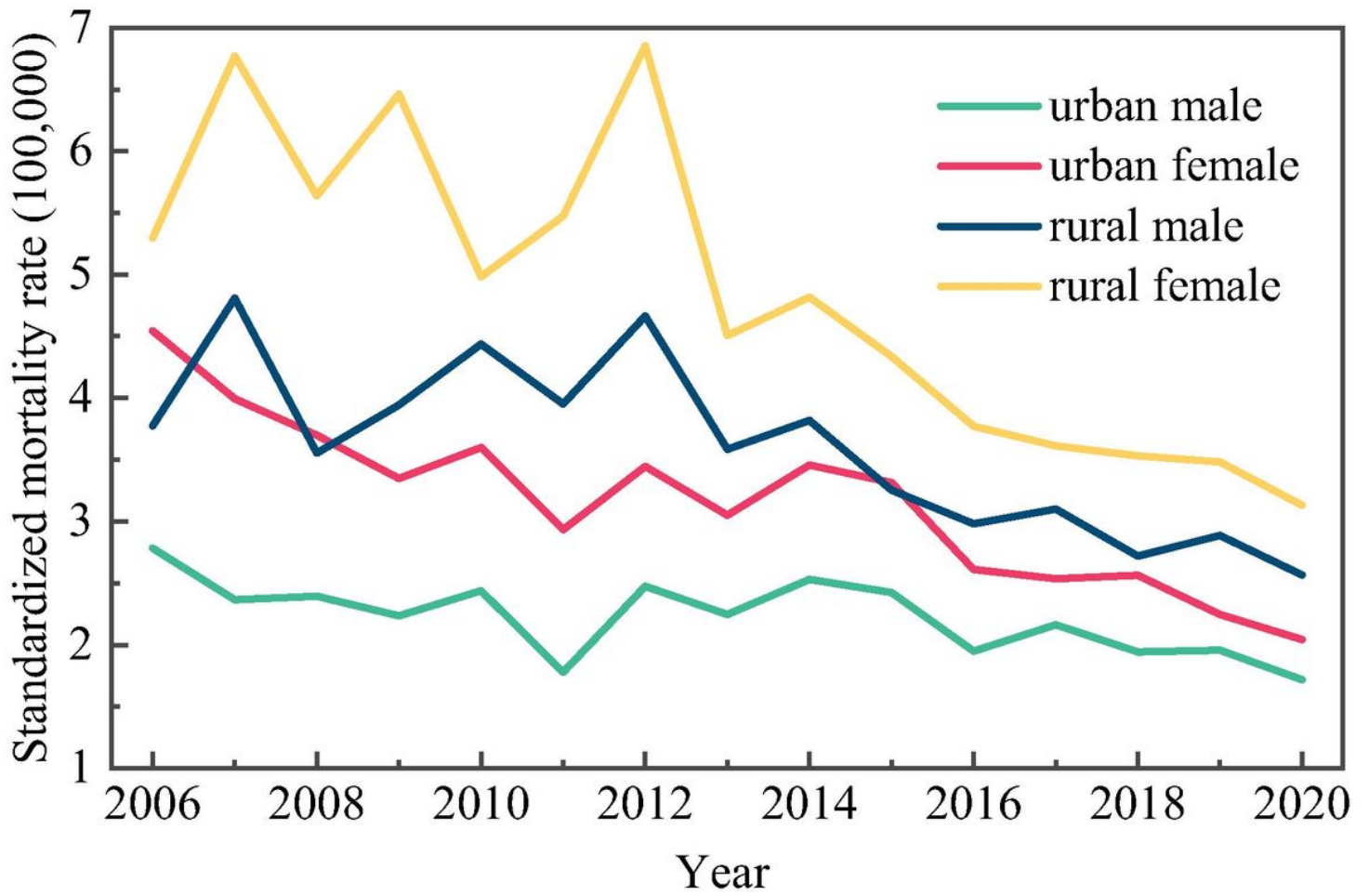
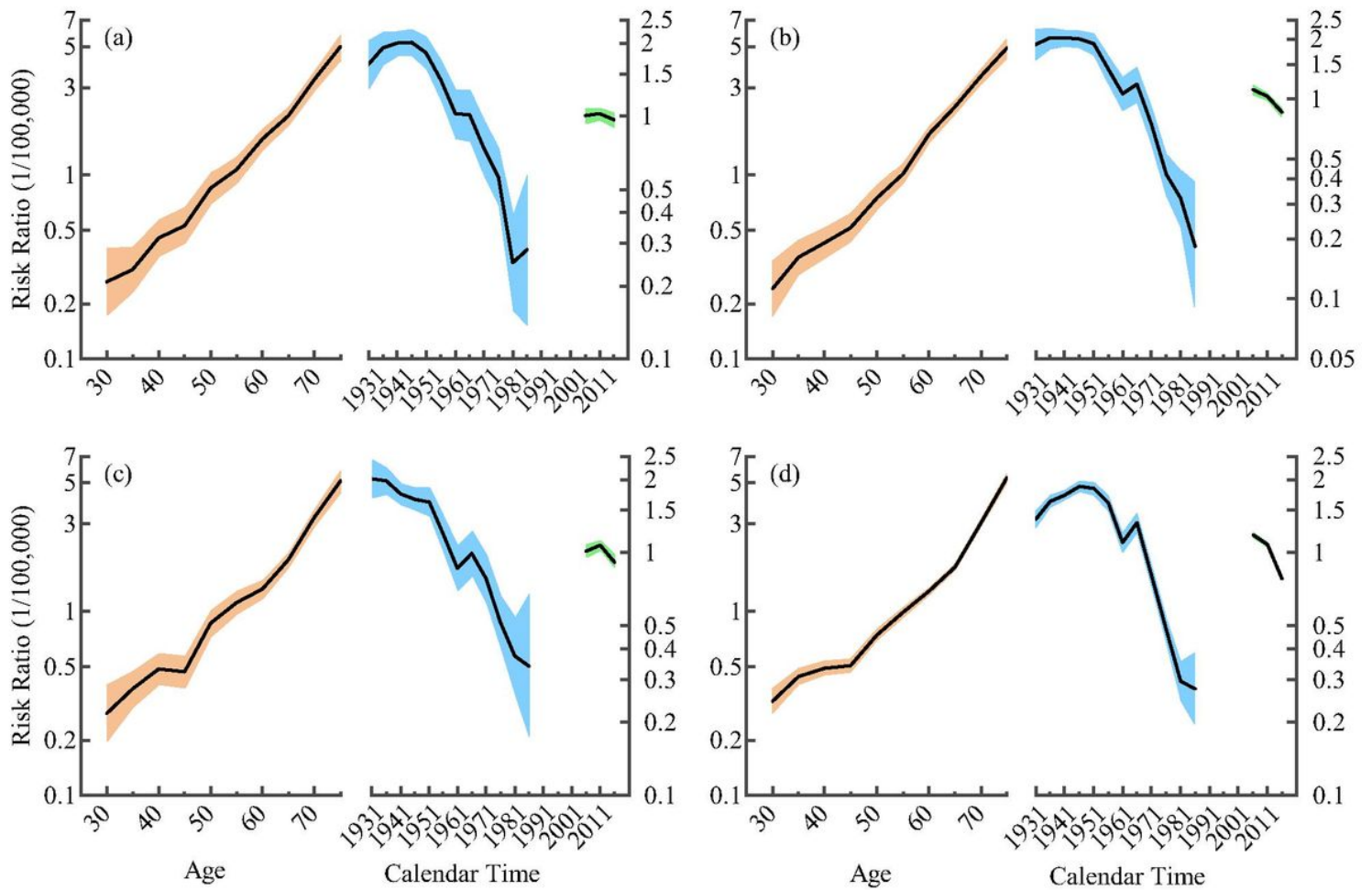


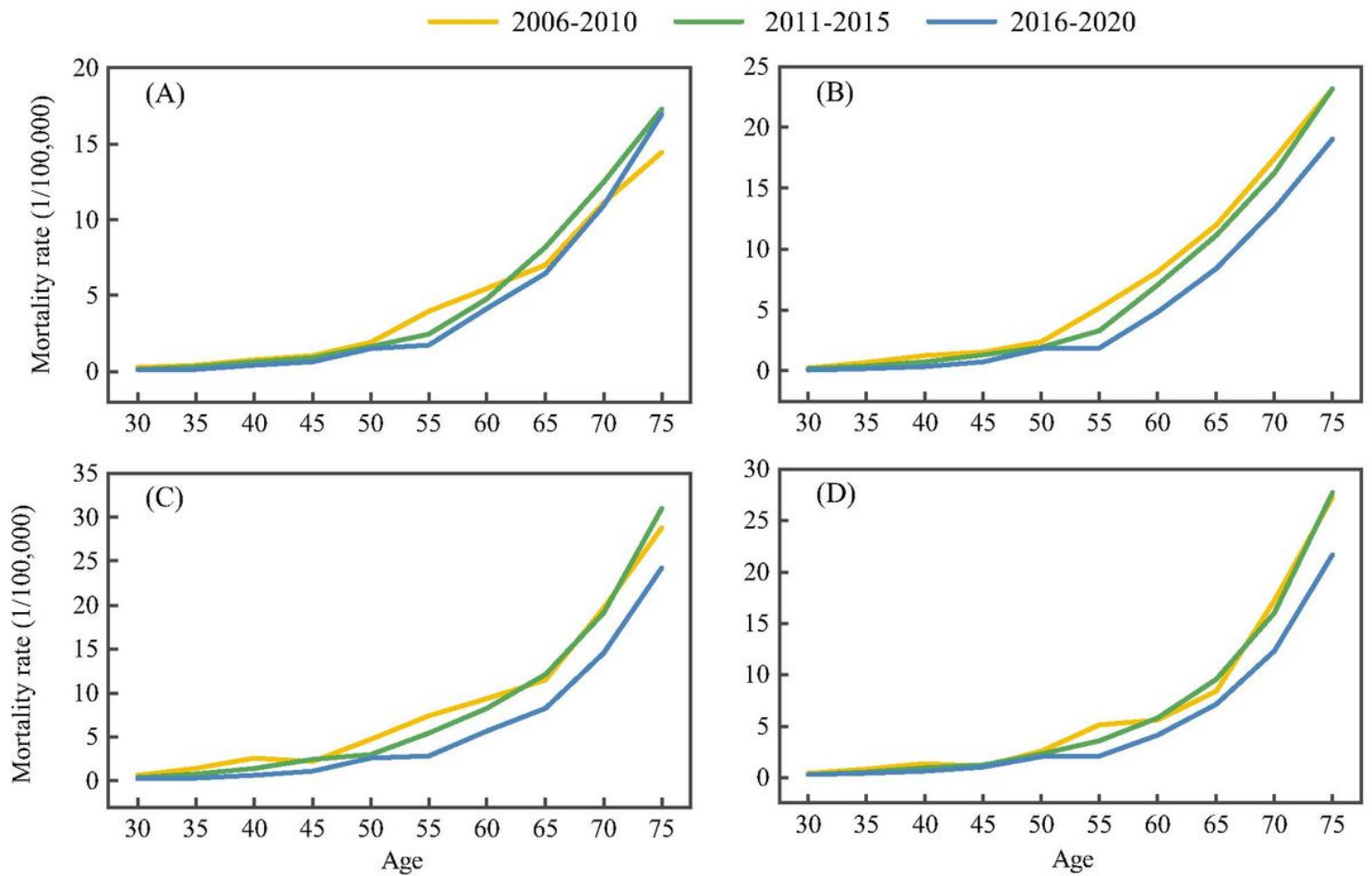
Figure 1

Changes in the standardized mortality rate of RHD in urban and rural areas by sex in China (1/100,000).



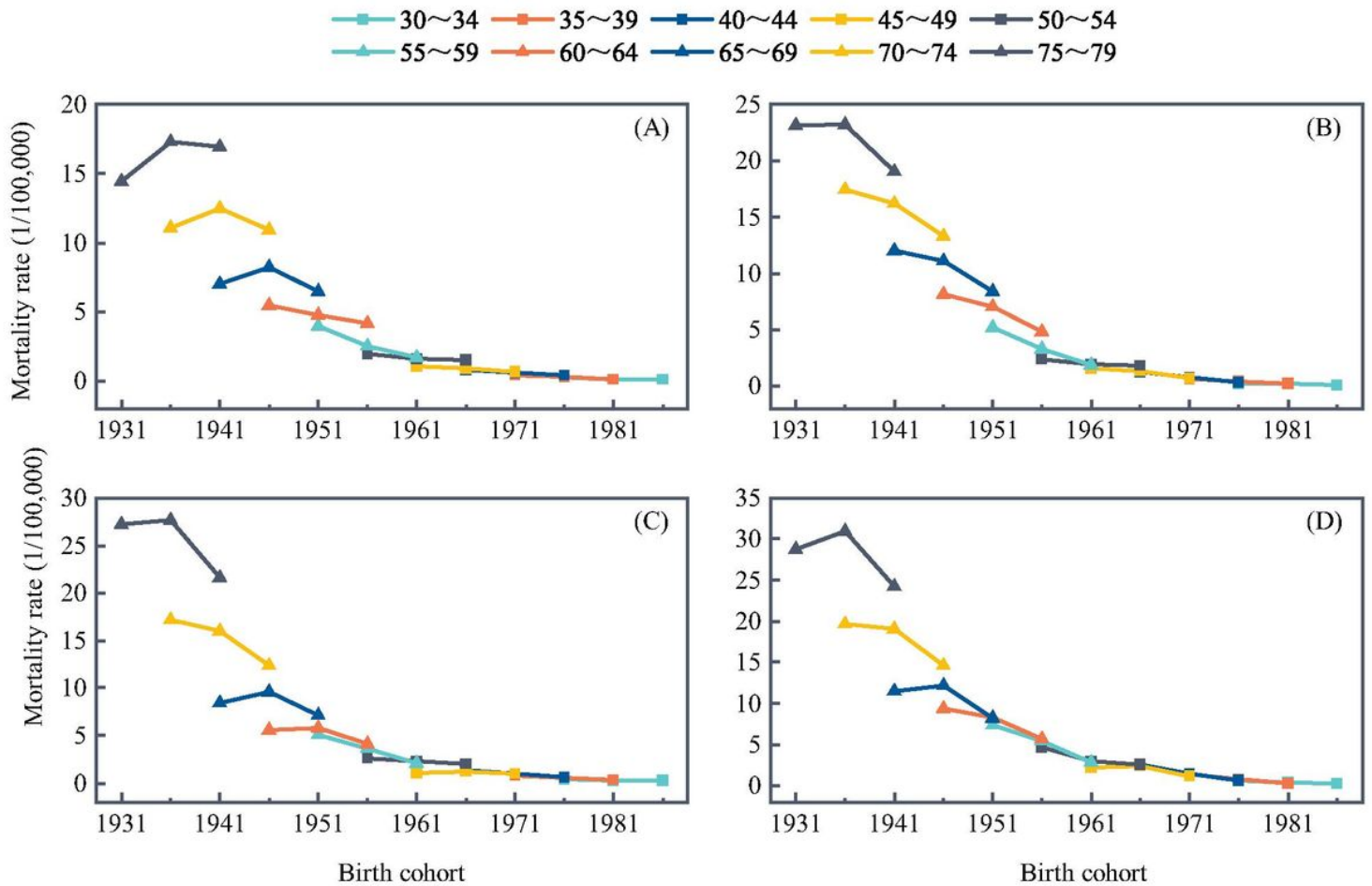
**Figure 2**

Multivariable age-period-cohort analysis of RHD mortality rates by region and sex in China from 2006 to 2020. For the 3 line graphs, the left lines represent age effect, the middle lines are the estimated birth cohort effect, and the short lines refer to the period effects (risk ratio). The shaded areas surrounding the lines represent the 95% confidence intervals. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]



**Figure 3**

Mortality rates of RHD in China from 2006 to 2020. Mortality data were collected from the Disease Surveillance Points system of China. Age analyses were from 30 to 79, with every 5-year interval as one age. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]



**Figure 4**

Mortality rates of RHD in China among those aged 30 to 79 years. Mortality data were collected from the Disease Surveillance Points system of China. Birth cohorts analyses were from 1931 to 1990, with every 5-year interval as one cohort. [(a) urban male, (b) urban female, (c) rural male, (d) rural female]

## Supplementary Files

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