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A trend analysis of tuberculosis mortality among rural people in China from 2006 to 2020: a joinpoint and age-period-cohort analysis

shuaihu ni
Lanzhou University
Ke Sun
Lanzhou University
Xiaofeng Luo (luoxiaof@lzu.edu.cn)
Lanzhou University
Yan Qu
Chinese Center for Disease Control and Prevention

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Abstract

Objective

To investigate the mortality trends of tuberculosis among rural people in China from 2006 to 2020, and to provide a basis for formulating scientific tuberculosis prevention and control strategies.

Methods

According to the data of Chinese Disease Surveillance Points, taking rural people aged 5 ~ 84 years in China from 2006 to 2020 as the research subjects, the Joinpoint regression model was used to explore the overall trend of tuberculosis mortality, and the age-period-cohort model was used to estimate the age effect, period effect and birth cohort effect.

Results

From 2006 to 2020, the standardized mortality rate of tuberculosis among rural people in China showed a downward trend. The age effect of tuberculosis deaths in the population was on the rise, with the age of men aged 35 ~ 84 and women aged 60 ~ 84 as risk factors; The period effect showed a downward trend, the rate of decline gradually slowed down, and the risk of death in males increased from 2016 to 2020; The birth cohort effect generally declined, and birth cohorts turned into protective factors after 1969 ~ 1973. Males had an increased risk of death in the birth cohorts 1964 ~ 1968, 1984 ~ 1988, 1994 ~ 1998, and 2004 ~ 2008. Females also had an increased risk of death in the birth cohort 1989 ~ 2003.

Conclusions

Rural males aged 35 ~ 84 years old and females aged 60 ~ 84 years old had a higher risk of tuberculosis death. The risk of TB death for rural people decreased overall over time, with the risk of TB death increasing for rural males from 2016 to 2020. In general, the risk of TB death is lower in late birth cohorts, However, it is alarming that the risk of TB death increased in some birth cohorts in recent years, both males and females.

Introduction

Tuberculosis is a chronic infectious disease caused by mycobacterium tuberculosis, the leading cause of death from a single source of infection, and the 13th leading cause of death worldwide, with early features such as cough, fatigue, and fever. Over the past two centuries, approximately 1 billion people have died from TB[1–3]. TB morbidity and mortality have declined over the past few years, but the COVID-19 pandemic has changed this trend[4–7]. As a result of the COVID-19 pandemic, access to TB testing and treatment has rapidly decreased, with the number of TB deaths among HIV-negative people worldwide increasing from 1.21 million in 2019 to 1.28 million in 2020, and the death rate rising from 16 to 17 per 100,000, the first increase in TB deaths since 2005[8].

An estimated 10.6 million new TB cases were reported globally in 2021, with an incidence of 134 per 100,000, an increase of 4.5% from 10.1 million cases in 2020[9]. Among them, adult males accounted for the largest proportion, accounting for 56.5% of all cases. Geographically, the majority of TB patients are located in South-East Asia (45%), Africa (23%) and the Western Pacific (18%), with the five countries with the highest burden of TB being India (28%), Indonesia (9.2%), China (7.4%), Philippines (7.0%), and Pakistan (5.8%).

In 2021, the number of new TB cases in China was estimated at 780,000, with an incidence rate of 55 per 100,000 and a mortality rate of 2.1 per 100 000. Among the 30 countries with a high burden of TB, China ranks third in the number of estimated TB cases, lower than Indonesia (969,000) and India (2.95 million) [9].

Previous TB-related studies have mostly been on pathogenesis, diagnosis and treatment, with studies of global trends less common[10–14]. Trend studies, on the other hand, focus on all inhabitants of a single country or different countries, and less often involve people of different regions and genders within a country[15–18]. However, about 500 million people live in rural areas in China, and 80% of TB patients are rural people[19],[20]. In 2020, the mortality rate of tuberculosis in rural China was 1.99 per 100,000 for men and 0.53 per 100,000 for women[21].Therefore, analysis of gender-specific rural populations in China, a country with a high burden of tuberculosis, is necessary.

Materials and Methods

Data Sources

All data comes from the Chinese Disease Surveillance Points (DSP) released annually by the Chinese Center for Disease Control and Prevention, which includes age-specific death rates, causes of death, the structure of the population covered (all aggregated at the regional level), the list of surveillance points of the national cause of death surveillance system, standard population table and coding comparison table.

Chinese Disease Surveillance Points was founded in 1978, over the years, the national disease surveillance system has undertaken the important task of collecting basic information on the health status of the population, and its routine surveillance data has provided a scientific basis for the formulation of disease prevention and control strategies and relevant policies and has also undertaken several important national scientific research and thematic investigation tasks. After two adjustments in 1990 and 2005, the national disease surveillance system includes 161 surveillance points in 31 provinces (autonomous regions and municipalities directly under the central government), with a total surveillance population of more than 73 million, covering 6% of the national population. The study collated and used information on age-specific deaths and mortality rates by sex in rural areas from 2006 to 2020.

Statistical analysis

Joinpoint regression analysis

The joinpoint model describes trends in the data by assuming segment points that connect the trend lines of different age-adjusted mortality rates, that is, "joinpoint" points.In this study, in Joinpoint Regression Program[22], the model was constructed by grid search method, and the model was optimized using Monte Carlo permutation test to evaluate the long-term trend of tuberculosis mortality among people of different sexes in rural areas from 2006 to 2020 by annual percentage change (APC) and averag annual percentage change (AAPC) and their 95% CI[15].

Age-period-cohort analysis

The age-period-cohort model is essentially based on the Poisson distribution, which decomposes the three dimensions of age, period and birth cohort, and then analyzes the influence of these three factors on the dependent variable [15]. Age effects are changes related to biological and social processes of aging specific to an individual, period effects are the results of external factors affecting all age groups equally at a given calendar time, and birth cohort effects are changes in people with different levels of exposure in different birth years. Due to the collinearity of age, period, and cohort, this study uses the IE algorithm to process the data. IE algorithms have proven effective in solving collinearity and other problems[23].

In this study, the age group was divided into 16 groups (5~, 10~ …, 80~). According to the requirements of the model, the period group distance should be the same as the age group distance [16], so the period was divided into three groups: 2006 ~ 2010, 2011 ~ 2015 and 2016 ~ 2020, and the data of the period group in 2008, 2013 and 2018 were used instead of the average data of the 5-year period group for analysis. The birth cohort was given by subtracting age from the period to obtain 18 groups (1924 ~ 1928, 1929 ~ 1933, 1934 ~ 1938 ..., 2009 ~ 2013). The associated risk (RR) is the exponential value of the coefficient. The statistical analysis is done in the Stata software. The study uses Wald's chi-square test to calculate the significance of estimable parameters and functions. All statistical tests were 2-sided and considered a significance level of 5%. Model fit is evaluated by bias, SE coefficient, Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC).

Results

This study collated the mortality data of rural people in China from 2006 to 2020, using the Joinpoint to analyze the overall trend of mortality changes, and using the APC model to analyze the age effect, period effect, and birth cohort effect of mortality changes.

Mortality trends

Mortality trends of tuberculosis in each year

Figure 1 shows the trend of age-standardized mortality from tuberculosis among rural people in China from 2006 to 2020. From 2006 to 2020, except for a slight increase in mortality in 2015, TB mortality continued to decline in other years. Mortality increased in 2009 and 2015 for rural males, and continued to decrease in the remaining years, with both male mortality rates being higher than female mortality; Rural females increased their mortality rates in 2010, 2012 and 2015, and decreased in the remaining years.

Mortality trends of tuberculosis by age

Figure 2 shows the trend of tuberculosis mortality among rural people of all ages in China from 2006 to 2020. With increasing age, the mortality rate of rural people and rural people of different sexes was increasing, with the exception of 10 ~ 14 years and 15 ~ 19 years of age, the mortality rate of males was higher than that of females in all ages.

Mortality trends of tuberculosis by birth cohort

Figures 3 shows the trend in tuberculosis mortality by total and sex among rural people in different birth cohorts in China from 2006 to 2020. The later the birth of inhabitants of all ages, the lower the mortality rate, which was always higher for males than for females.

Overall trend of tuberculosis mortality in rural China from 2006 to 2020

Table 1 shows trends in standardized mortality rates from tuberculosis among rural people in China in general and by sex. The tuberculosis mortality rate of rural people decreased from 3.76 per 100,000 in 2006 to 1.11 per 100,000 in 2020, showing a downward trend (AAPC=-8.9, 95% CI=-10.0~-7.8); the tuberculosis mortality rate of rural females decreased from 2.19 per 100,000 in 2006 to 1.47 per 100,000 in 2020, showing a downward trend (AAPC=-11.0, 95%CI=-12.5~-9.5);the tuberculosis mortality rate of rural males decreased from 5.43 per 100,000 in 2006 to 1.79 per 100,000 in 2020, showing a downward trend (AAPC=-7.4, 95%CI=-9.6~-5.1), among which, the decline rate was obvious from 2011 to 2014 (APC=-14.9, 95%CI=-24.8~-3.7).

Table.1 Trends in standardized tuberculosis mortality among rural people in China from 2006 to 2020

Gender	Year	APC			AAPC		
		95%CI	T value	P value	95%CI	T value	P value
male	2006-2010	-6.1（-8.7～-3.5）	-5.4	0.001			
	2011-2013	-14.9（-24.8～-3.7）	-3.1	0.018	-7.4(-9.6～-5.1)	-6.1	<0.001
	2014-2020	-4.5(-6.5～-2.5）	-5.3	0.001			
female	2006-2020	-11.0(-12.5～-9.5）	-14.7	<0.001	-11.0(-12.5～-9.5)	-14.7	<0.001
overall	2006-2020	-8.9(-10.0～-7.8)	-17.2	<0.001	-8.9(-10.0～-7.8)	-17.2	<0.001

Effects of age, period, and birth cohort on tuberculosis mortality

Age effect

Figure 4 shows the age RRs of TB mortality for total and gender-specific people in rural China (Table S1). The risk of death from the age effect of tuberculosis in rural people aged 5 ~ 39 years increased slowly, and RRs < 1, age after 40 years of age changed to risk factor (RR > 1), and the risk of death began to rise rapidly, peaking at 75 ~ 79 years. The relative risk of rural males and females aged 5 ~ 34 years was less than 1, and the risk was higher for females than for males; After the age of 35, the risk of death among males increased rapidly, and age changed to a risk factor, peaking at 70 ~ 74 years. The risk of death in females aged 35 ~ 49 years declined slowly, rose after age 50, became a risk factor at age 60 ~ 64, and peaked at age 75 ~ 79.

Period effect

Figure 5 shows the period RRs of TB mortality for total and gender-specific people in rural China (Table S1). The RRs of the period effect of rural people showed an overall downward trend, and the period effect of both males and females turned to a protective factor (RR < 1) after 2011 ~ 2015. From 2006 to 2020, the RRs value of rural people decreased from 1.340 to 0.890 and then to 0.839, and the rate of decline tended to be slow; the RRs value of males decreased from 1.223 to 0.903 and then rose to 0.905; and the RRs value of females decreased from 1.654 to 0.862 and then to 0.702, and the rate of decline tended to be slow.

Birth cohort effect

Figure 6 shows the birth cohort RRs of TB mortality for total and gender-specific people in rural China (Table S1). The RRs value of the birth cohort effect in rural people generally decreased between 1926 and 2010, and the birth cohort changed to a protective factor after 1969 ~ 1973. The RRs value of rural male birth cohorts also showed an overall downward trend between 1926 and 2010, and the birth cohort changed to a protective factor after 1959 ~ 1963, but increased slightly in the birth cohort 1964 ~ 1968, 1984 ~ 1988, 1994 ~ 1998, and 2004 ~ 2008. The RRs value of females first increased and then decreased in the birth cohort 1924 ~ 1938, continued to rise in the birth cohort from 1939 to 1953, showed an overall downward trend in the birth cohort from 1953 to 2013, and turned into a protective factor in the birth cohort after 1969 ~ 1973, but there was a small upward trend in the birth cohort from 1989 to 2003.

Discussion

Due to poor sanitation in rural and weak health awareness among rural people, 80% of the patients are rural people and migrants, and rural areas are areas with a high incidence of tuberculosis in China[19], [20]. However, previous studies have focused on TB deaths across the population of China, while ignoring trends in TB deaths among rural people[15–18]. This study analyzes the mortality rate of tuberculosis among rural people in China and discusses the high-risk groups of tuberculosis in rural China and the effectiveness of prevention and control measures.

The mortality rate of tuberculosis among rural people in China from 2006 to 2020 showed a downward trend, indicating that a series of policies introduced by the government were effective. Since 2006, China has introduced and implemented a number of international cooperation projects, carried out baseline investigation of drug resistance, and fully implemented the Modern Tuberculosis Control Strategy (DOTS Strategy)[24, 25]. In 2016, the government issued the "Healthy China 2030" plan, exploring new management models for tuberculosis patients, conducting research on the treatment of tuberculosis and AIDS co-infection, carrying out the prevention and treatment of drug-resistant tuberculosis, and implementing a new tuberculosis prevention and treatment service model of "trinity" of the Center for Disease Control and Prevention, hospitals and township health centers[26–28]. In 2017, the Chinese government proposed the 13th Five-Year Plan for National Tuberculosis Prevention and Control, which mentioned that it is necessary to increase pathogenic examination and drug resistance screening, strengthen the construction of tuberculosis prevention and control informatization, and gradually realize the whole process of information management of tuberculosis patients[15, 29].

Age effects are related to the biological and social processes of aging specific to an individual, including physiological changes and accumulation of social experiences associated with aging[30–32]. The relative risk of TB death among rural people increased with age, and the risk increased significantly faster in rural females from age after 60 years, mainly due to the high incidence of atypical symptoms and complications and adverse reactions after onset. On the one hand, elderly tuberculosis patients have hidden clinical symptoms, and the proportion of fever, hemoptysis, chest pain and other symptoms is lower than that of young patients[33]. It is easy to misdiagnose chronic bronchitis, lung infection and emphysema in the clinical diagnosis process, and if the patient itself is accompanied by respiratory diseases, it is easy to be misdiagnosed as recurrence of respiratory diseases or aggravation of symptoms, thereby delaying the treatment of tuberculosis[34]. On the other hand, the elderly are prone to other respiratory diseases, especially lung infections and respiratory failure, the proportion is significantly higher than that of young and middle-aged patients, because the elderly patients have poor immune function and most of them are more serious, which makes the chance of nosocomial infection significantly increased[35]. Pulmonary infection can precipitate or exacerbate underlying lung disease in older people, leading to respiratory failure. Finally, adverse reactions may occur due to reduced liver blood flow, decreased liver enzyme activity, reduced rate of drug biotransformation and synthesis reaction in the elderly, and prolonged drug half-life[36]. The plasma protein synthesis of the elderly decreases, reduces the protein binding rate of the drug, and increases the free part to increase the adverse drug reactions, which affects the patient's treatment compliance and the completion of the course of treatment, thereby reducing the cure rate[35].Rural males became a risk factor from age after age 35, and the risk of death rose rapidly, which may be due to the need for work and the need for rural males to continue to move, coupled with increased living pressure, age after age 35 becomes a risk factor.

Period effects are the result of external factors affecting all age groups equally at a given calendar time, and may result from a range of environmental, social and economic factors[30–32]. The risk of death decreased for both rural males and females, and the period effect shifted to a protective factor from 2011 to 2015. This may be related to the reform of the TB service system. China's tuberculosis treatment service system changed from being provided by CDC or specialized pharmacies to designated general hospitals [37]. Doctors in hospitals are more professional than CDC staff, able to provide better medical services, and better able to meet the needs of patients. This is consistent with previous studies [37, 38]. In addition, this study found a gradual slowdown in the decline in the risk of death, which may be related to the slow progress of new TB tests, treatment regimens, and vaccines at the same time as the service system was transformed [39]. risk of death among rural men increased between 2016 and 2020, which may be related to the outbreak of the new crown epidemic [40]. On the one hand, the outbreak of the COVID-19, medical services and resources that originally belonged to tuberculosis gave way to COVID-19 prevention and control, resulting in insufficient basic tuberculosis services[41, 42]. COVID-19 and tuberculosis are both respiratory diseases, and there are certain similarities in diagnosis and treatment, and some anti-tuberculosis drugs coincide with drugs for the treatment of COVID-19, resulting in drug shortages and price increases, which in turn makes patients stop taking drugs[43]. On the other hand, the isolation measures adopted for the COVID-19 have made it more difficult for tuberculosis patients to be detected and treated in time[44].

The birth cohort effect is the sum of all exposures that the cohort experiences from birth[30–32]. From 1924 to 1949, China was at its highest risk of death from birth sequence during the War of Resistance Against Japan and the War of Liberation, when the war made tuberculosis spread more widely and rapidly, the health system was destroyed and patients could not receive adequate treatment[16]. In the early days of the war, due to the influence of traditional Chinese thinking, men mostly worked outside the home, and women were mostly active at home or not far from home, so men were more likely to get sick and then have a higher risk of death due to poor medical services[45]. As the war progressed, many male patients died in the war as a result of being drafted as soldiers, so the risk of death from tuberculosis in the birth cohort was reduced, and the risk of death increased for women, mostly at home, due to lack of medical care due to poverty or the collapse of the health system[46]. From 1952 to 1978, China launched a patriotic health campaign and initially established a relatively complete health system [47], and the cooperative medical system was implemented in rural areas, which fully guaranteed the health of rural people, and the risk of death in the tuberculosis birth cohort for both men and women continued to decrease, and the birth cohort of rural people was no longer a risk factor. After 1978, China entered the period of reform and opening up, began to actively study foreign health policies, combined with its own patriotic health campaign, carried out a number of national tuberculosis epidemiological sample surveys, carried out exploratory health reform and explored the possibility of trying to adapt to China's medical system[48–50]. Due to the transition from a planned economy to a market economy, new rural cooperative medical care was set up in rural areas, and the cost of personal medical care continued to increase, resulting in an overall downward trend in the birth queue of rural people, but in some years it increased[51].

Limitations

This study has some limitations. First, because tuberculosis patients are often combined with other diseases, such as chronic obstructive pulmonary disease, asthma, pneumoconiosis, etc., when tuberculosis patients die, it is difficult to determine whether the cause of death is tuberculosis or other combined diseases. Therefore, when CDC counts tuberculosis mortality data, it may include some patients who died from other diseases in tuberculosis mortality data, making tuberculosis mortality data biased. Second, due to the lack of public data on tuberculosis mortality in rural areas, this study used the mortality data of Chinese rural people from 2006 to 2020, with a short time span, and the results may have limitations. Thirdly, although the IE algorithm used in this study does not require model assumptions and has excellent results, the principle of the method is relatively complex, and the practical significance of parameter estimation needs further research. Fourth, because the number of deaths from tuberculosis other than pulmonary tuberculosis in the data is small, it is impossible to analyze each tuberculosis separately.

Conclusions

Rural males aged 35 ~ 84 years old and females aged 60 ~ 84 years old had a higher risk of tuberculosis death. The risk of TB death for rural people decreased overall over time, with the risk of TB death increasing for rural males from 2016 to 2020. In general, the risk of TB death is lower in late birth cohorts, However, it is alarming that the risk of TB death increased in some birth cohorts in recent years, both males and females.

Abbreviations

APC model Age–period–cohort model

APC Annual Percentage Change

AAPC Averag Annual Percentage Change

CI Confidence interval

TB Tuberculosis

RR Relative risk

DSP Disease Surveillance Points

IE Intrinsic estimator

DOTS Directly observed treatment short-course

Declarations

Ethics approval and consent to participate

No humans were directly involved in the study. It was determined by the National Health Commission of China that the collection of data on notifiable infectious diseases was part of continuing public health surveillance of infectious diseases and was exempt from Institutional Review Board assessment. All the data of cases used in this study were anonymized and personal identification information is not included in the data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author contributions

SHN and KS wrote this manuscript; XFL and YQ oversaw the conception, writing, formatting and editing. All authors read and approved the final manuscript.

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Availability of data and materials

The data from 2008 to 2020 are publicly available data (https://ncncd.chinacdc.cn/xzzq_1/202101/t20210111_223706.htm). The datasets for 2006 and 2007 are available from the corresponding author upon reasonable request.

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Footnotes

Shuaihu Ni and Ke Sun contributed equally to this study.

Contributor Information

Xiaofeng Luo, Email: luoxiaof@lzu.edu.cn

Yan Qu, Email: quyan@chinacdc.cn

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Figures

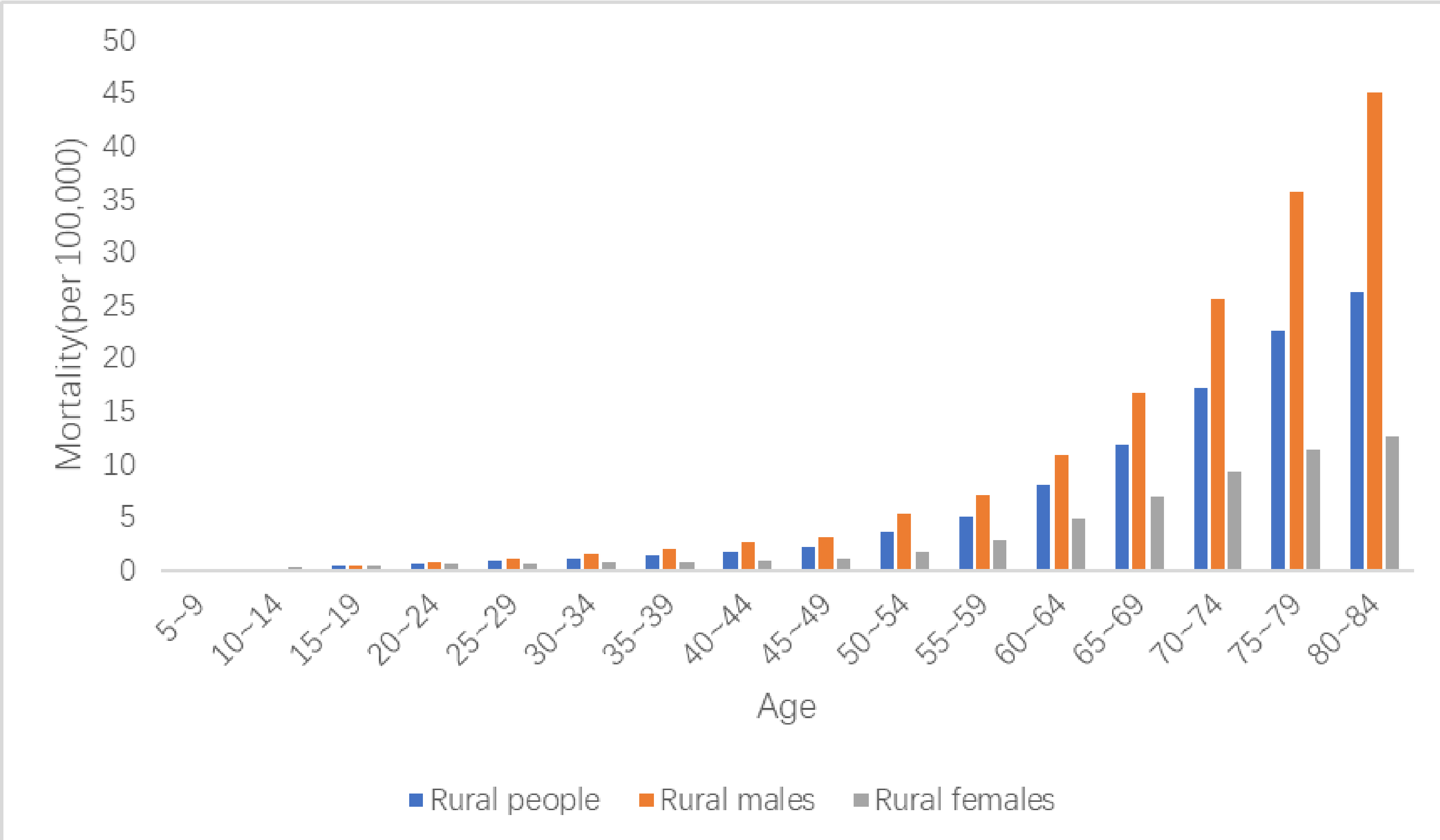

Figure 1

Age-standardized mortality trends of total and gender-specific people in rural China, 2006~2020

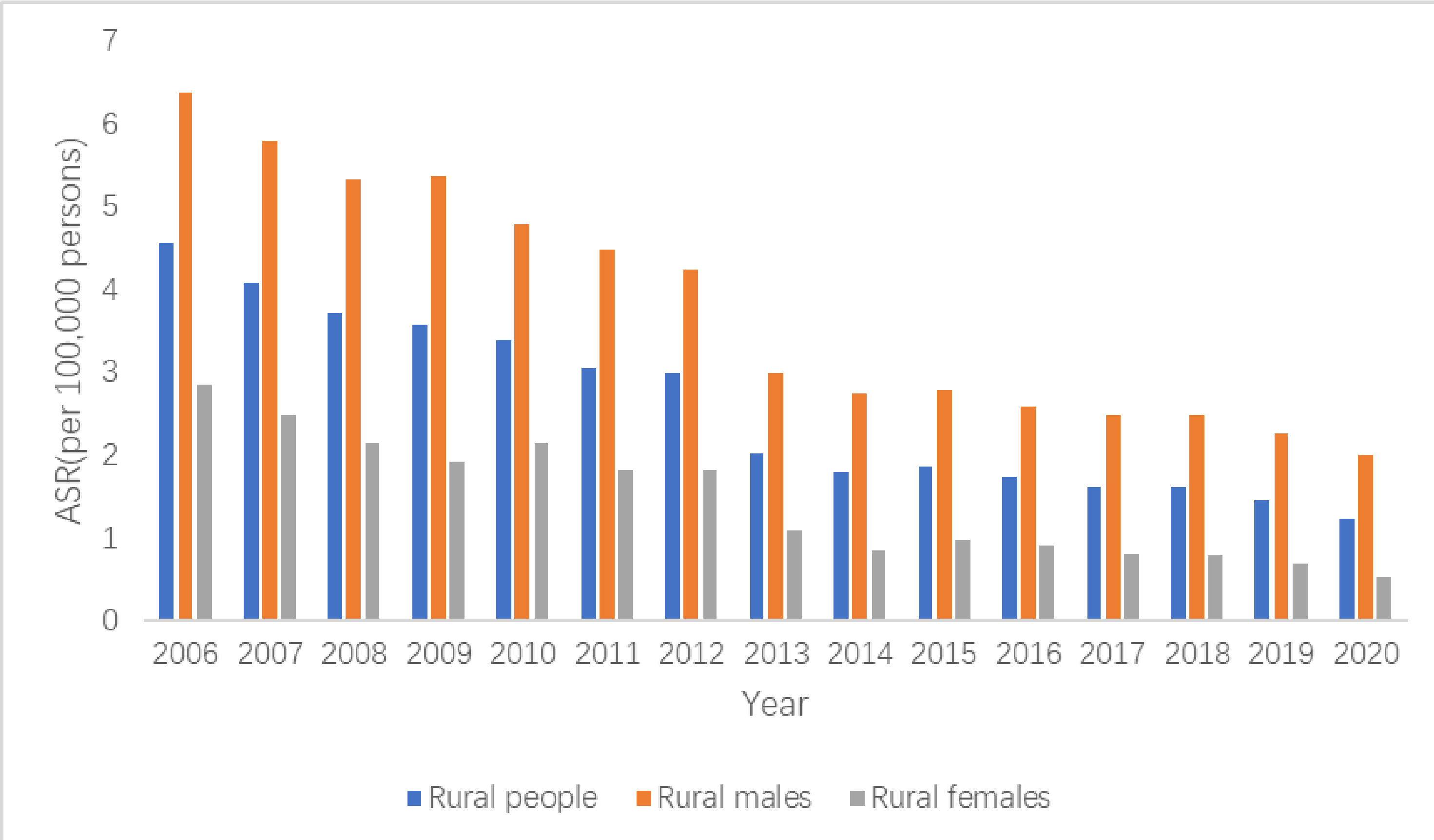

Figure 2

Trends in age-specific tuberculosis mortality among total and gender-specific people in rural China, 2006~2020

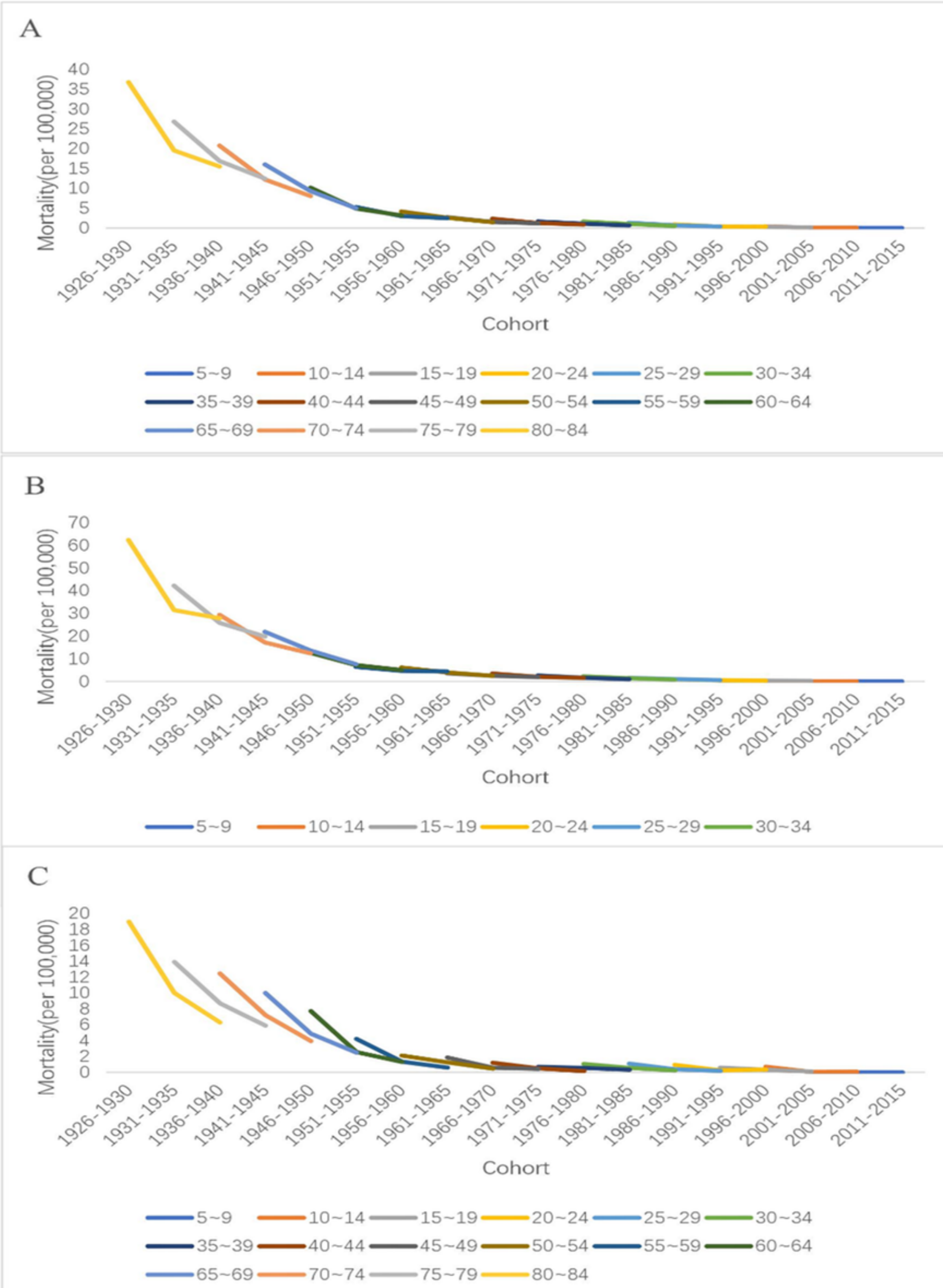

Figure 3

Trends in tuberculosis mortality among different birth cohorts of A rural people, B rural males and C rural females in China

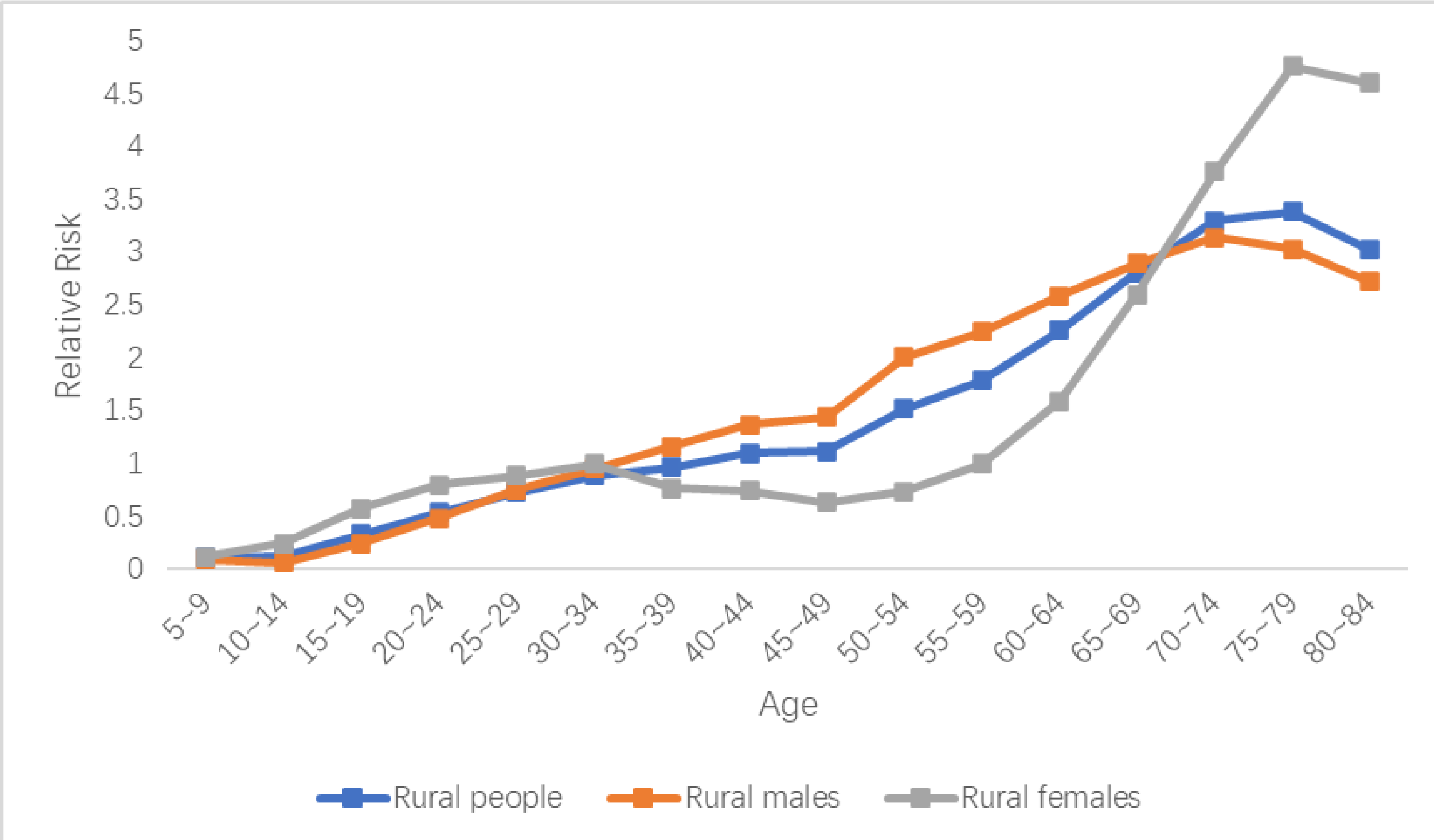

Figure 4

Age effects of tuberculosis mortality rates in rural people in general and by sex

Figure 5

Period effects of tuberculosis mortality rates in rural people in general and by sex

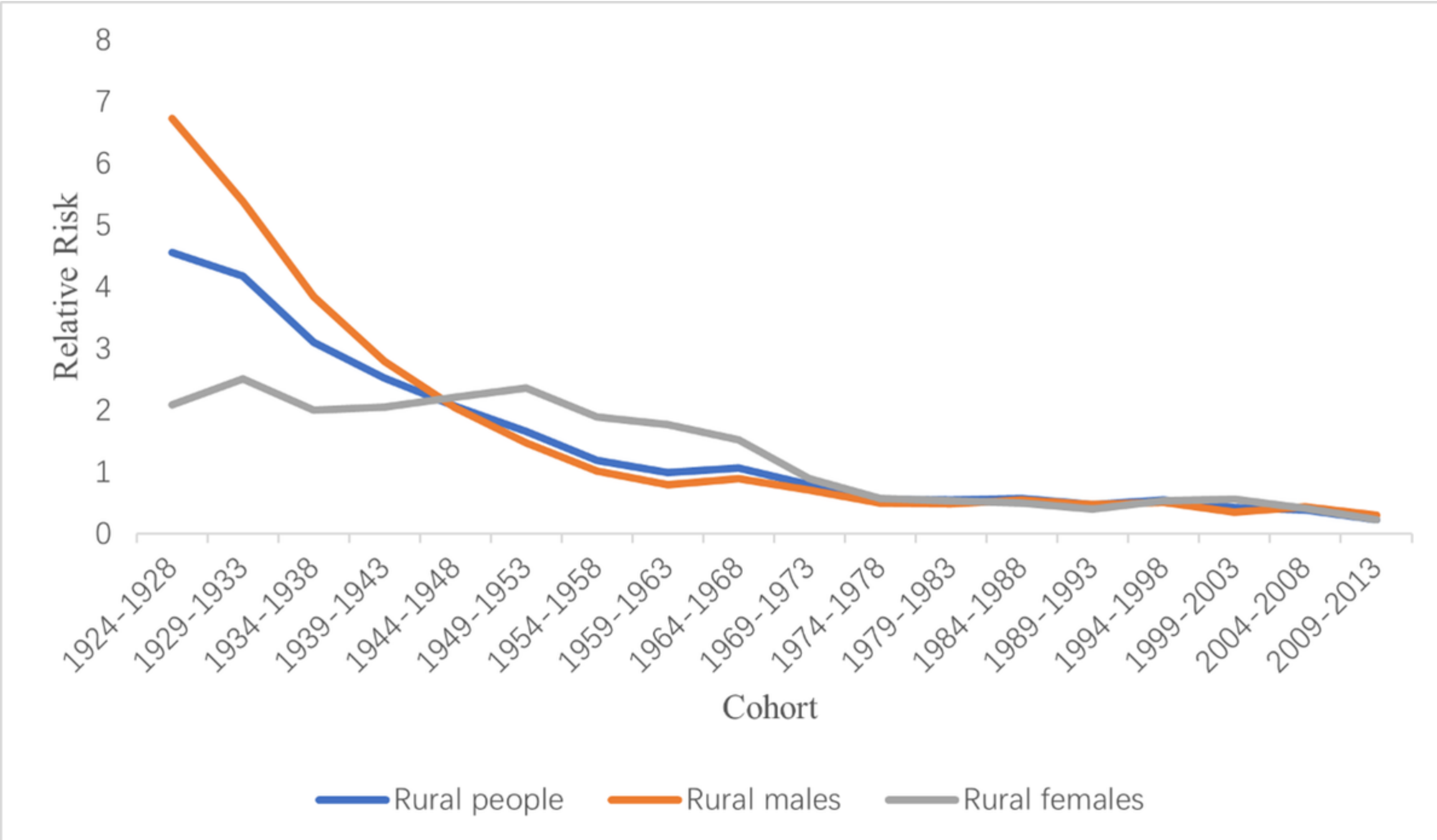

Figure 6

Birth cohort of tuberculosis mortality rates in rural people in general and by sex

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