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Trends in the Incidence and Mortality Rates of Myocarditis in the Chinese Population During 1990-2019: Joinpoint Regression and Age–Period–Cohort Analysis

ORIGINAL INVESTIGATION

ABSTRACT

Background: This study aimed to analyze trends in the burden of myocarditis in the Chinese population during 1990-2019.

Methods: The Global Burden of Disease (GBD) database aims to assess the burden of various diseases and injuries on a global scale, and the contribution of relevant risk factors to the burden of disease was also included. In this study, we collected age-standardized incidence and mortality rates for myocarditis in China from 1990 to 2019 using GBD 2019. The age–period–cohort model was utilized to calculate local drift, longitudinal age patterns, as well as the ratios of period and cohort.

Results: The age-standardized incidence and mortality rates of myocarditis in both men and women presented a decreasing trend during 1990-2019 [average annual percentage change (AAPC) of men = −0.202 (95% CI: −0.213 to −0.191); AAPC of women = −0.263 (95% CI: −0.27 to −0.256) for incidence; AAPC of men = −0.233 (95% CI: −0.371 to −0.094); AAPC of women = −0.872 (95% CI: −1.112 to −0.631) for mortality]. Longitudinal age curves showed that myocarditis incidence and mortality rates elevated with age among individuals aged 15-95+ years, with a higher growth rate in men than in women. The period and cohort ratios for both men and women showed similar decreasing trends. Local drift values for the incidence and mortality rates of myocarditis showed an increasing trend among individuals aged 70-75 years and above.

Conclusion: Although the overall burden of myocarditis in China presented a decreasing trend during 1990-2019, the male and elderly populations still have a higher risk of incidence and mortality. Therefore, it is essential for the health-care system to introduce effective prevention and treatment measures for myocarditis.

Keywords: Myocarditis, China, age-standardized incidence rate, age-standardized mortality rate, age–period–cohort analysis

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INTRODUCTION

Myocarditis is a major inflammatory heart disease, primarily induced by viruses but can also be triggered by drugs and systemic immune-mediated diseases, leading to severe cardiac damage and acute heart failure.[1,2] Myocarditis affects people of all ages, and its clinical manifestations are diverse, making diagnosis challenging.[3] Patients suspected of acute myocarditis are typically assessed in the emergency department with chest pain, shortness of breath, fatigue, palpitations, or syncope.[4] According to large registry studies, chest pain is the predominant symptom of myocarditis (85%-95% of cases), followed by fever (about 65% of cases) and shortness of breath (19%-49% of cases).[5-8] Most myocarditis patients can spontaneously recover, but patients with persistent ventricular dysfunction have a 20% annual mortality rate.[9] Therefore, accurately assessing the epidemiology of myocarditis is crucial for its prevention and treatment.

According to discharge records from 1990 to 2013, Global Burden of Disease (GBD) study estimated an annual incidence of approximately 22 cases of myocarditis per 100 000 patients worldwide.[10] All data on myocarditis hospitalizations in the

National Health Service (NHS) of England from 1998 to 2017 showed that during the 19 years, 12 927 hospitalizations with myocarditis as the primary diagnosis accounted for 0.04% (36.5/100 000) of all NHS hospitalizations, with about 2/3 of patients being male, and a median age of 33 years for males and 46 years for females, and a median hospital stay of 4.2 days. Over the study period, hospitalizations due to myocarditis increased by 88% (57% increase in all cardiac hospitalizations),[11] suggesting an added burden of hospitalizations from myocarditis. However, there is limited accurate information on the incidence and mortality trends of myocarditis for the entire Chinese population. A recent study based on GBD 2016 data reported an age-standardized incidence rate (ASIR) of 32.8 (per 100 000 individuals) for myocardial disease and myocarditis in China in 2016, an increase of 23.1% compared to 1990.[12] To our knowledge, there is currently no study that has applied age–period–cohort model to delineate the incidence and mortality trends of myocarditis in China. This study intended to use GBD 2019 data and age–period–cohort model to analyze the trends in the burden of myocarditis in China. This may lay the groundwork for public health policies, resource allocation, and the design of intervention plans.

METHODS

Data Sources

All anonymous incidence and mortality data related to myocarditis in China during 1990-2019 were downloaded from the latest GBD database (GBD 2019, https://www.healthdata.org/gbd) from the Institute for Health Metrics and Evaluation. Global Burden of Disease has created a unique platform for comparing the severity of health losses caused by different diseases, injuries, and risk factors across different ages, sexes, and geographic locations. This study downloaded age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) data for myocarditis in China from GHDx (https://vizhub.healthdata.org/gbd-results/). Age-standardized incidence rate and ASMR are methods used to compare disease incidence and mortality rates among different populations or regions, taking into account variations in population age structure. These methods standardize the incidence or mortality rates of different age groups, enabling a more accurate comparison of disease incidence or mortality rates among different populations while eliminating differences caused by variations in age distribution. These standardized rates are typically expressed as the number of cases or deaths per 100 000 population per year.

HIGHLIGHTS

- The burden of myocarditis in China was analyzed for the first time using an age–period–cohort model.
- From 1990 to 2019, the burden of myocarditis in China showed an overall decreasing trend.
- Myocarditis posed a significant risk to Chinese men and the elderly population.

Statistical Analysis

Joinpoint Regression Analysis

To evaluate trends in the disease burden attributable to myocarditis over time, we conducted Joinpoint regression analysis. The calculation method of this model used the least squares method to estimate changing patterns of disease rates, avoiding subjectivity of typical trend analysis on the basis of linear trends. The sum of squares of residuals between estimated and true values can be used to identify the inflection point of a shifting trend. We utilized Joinpoint software (version 4.9.1.0; National Cancer Institute, Rockville, Md, USA) to calculate the annual percentage change (APC) and average annual percentage change (AAPC), along with their corresponding 95% CI, to determine the trends in disease burden. We assessed the fluctuation trends in different sections by comparing APC/AAPC with 0 to determine statistical significance ($P < .05$). An APC/AAPC >0 indicates an upward trend, while the APC/AAPC <0 signifies a downward trend. If APC/AAPC equals 0, it suggests a stable trend (Supplementary Table 1 & 2).

Age–Period–Cohort Analysis

The age–period–cohort model was utilized to explain effects of age, period, and cohort on the incidence and mortality rates of myocarditis, with data analysis performed by APC online web tool (https://analystools.cancer.gov/apc/). We estimated rate ratios (RRs) of myocarditis incidence and mortality relative to a reference point for varying periods (period effects) and cohorts (cohort effects). The term "period effect," which was used to describe changes in incidence and death rates brought on by artificial variables, such as the advancement of diagnostic technology, early screening and diagnosis, modifications to illness classification and registration, and advancements in therapy, was represented by the period RRs. Period effects can occur as a result of these artificial elements' potential to change the incidence rate over time. Cohort effect was represented by cohort RR, which referred to the deviations in mortality rates between different generations resulting from changes in lifestyles or exposure to different risk factors. We calculated net drift, local drift, and longitudinal age curve of the incidence and mortality rates of myocarditis. Net drift represented the overall APC in age-adjusted incidence and mortality rates of myocarditis over time, which represented total linear trend of logarithmic incidence and mortality rates divided by period and cohort. Local drift indicated a particular logarithmic trend of myocarditis incidence and death rates divided by period and cohort, as well as APC in incidence and mortality rates of myocarditis for a certain age group over time. The reference cohort's longitudinal age curve represented predicted age-specific ratios that had been period effects-adjusted.

We coded age, period, and cohort into data with continuous 5-year intervals. Age was divided into 17 groups. Due to the absence of relevant data in the GBD 2019 database for age groups below 15 years old, our study's data start from 15 to 9 years, 20 to 24 years, and so on, up to 95+ years (where individuals aged 95 and above were grouped together). Period was divided into 6 groups (1990-1994, 1995-1999, ..., 2015-2019). Twenty-two birth cohorts (1895-1899, 1900-1904, ..., 1995-2000) were obtained based on age and period. The logarithmic linear model for the APC model is as follows:[13,14]

$$Y = \log(M) = \mu + \alpha(\text{age})_i + \beta(\text{period})_j + \gamma(\text{cohort})_k + \mathcal{E}$$

where, M represents the incidence/mortality rate of myocarditis, μ and ε represent intercept error and random error, respectively. α_i represents the age group effect, and β and γ represent period and cohort effects.

GraphPad (Prism 9.1.0) and R software (version 3.5.1) were used to conduct the statistical analysis. $P < .05$ was considered as statistically significant.

RESULTS

Trends in Age-Standardized Incidence Rate and Age-Standardized Mortality Rate of Myocarditis in China over Time

During 1990-2019, the ASIR of myocarditis in Chinese males and females remained relatively stable, with a slight decrease in 2006-2009, followed by stabilizing. The incidence was consistently higher in males than in females, and this trend remained consistent (Figure 1A).

During 1990-2019, ASMR of myocarditis in Chinese males and females elevated annually from 1990 to 2005, peaked in 2005 and then decreased annually. Age-standardized mortality rate was generally higher in males than in females (Figure 1B).

Joinpoint Regression Analysis of Age-Standardized Incidence Rate and Age-Standardized Mortality Rate of Myocarditis in Chinese Males and Females During 1990-2019

Table 1 showed AAPC of ASIR of myocarditis in both genders over the past 3 decades. The results showed that during 1990-2019, ASIR of myocarditis in Chinese males and females decreased by −0.202 (95% CI: −0.213 to −0.191) and −0.263 (95% CI: −0.27 to −0.256), respectively. Average annual percentage change of incidence rates was higher in males than in females. From 2006 to 2009, the incidence of myocarditis significantly decreased in both males (APC = −1.287, 95% CI: −1.391 to −1.183) and females (APC = −1.996, 95% CI: −2.062 to −1.93); however, the decreasing trend of incidence rates in both genders slowed down after 2009.

Table 2 showed the AAPC of ASMR of myocarditis in Chinese males and females over the past 3 decades. During 1990-2019, ASMR of myocarditis in Chinese males and females reduced by 0.233 (95% CI: −0.371 to −0.094) and 0.872 (95% CI: −1.112 to −0.631), respectively. From 1998 to 2005, ASMR in females substantially elevated (APC = 2.519), while from 2005 to 2019, they significantly decreased (APC = −2.341 from 2005 to 2014 and APC = −3.695 from 2014 to 2019). Similarly, from 1999 to 2005, the ASMR in males significantly increased (APC = 2.537), and from 2009 to 2019, they significantly decreased (APC = −1.49 from 2009 to 2015 and APC = −3.301 from 2015 to 2019).

Effects of Age, Period, and Cohort on Age-Standardized Incidence Rate and Age-Standardized Mortality Rate of Myocarditis in China

Longitudinal Age-Specific Incidence and Mortality Curves of Myocarditis in Chinese Males and Females

We then observed the expected age-specific incidence rates in the reference cohort after adjusting for period effects. For the same birth cohort, the incidence rate of myocarditis in Chinese females increased exponentially with age and peaked in the 95+ age group. Age-standardized incidence rate was higher in males than in females in all age groups, and

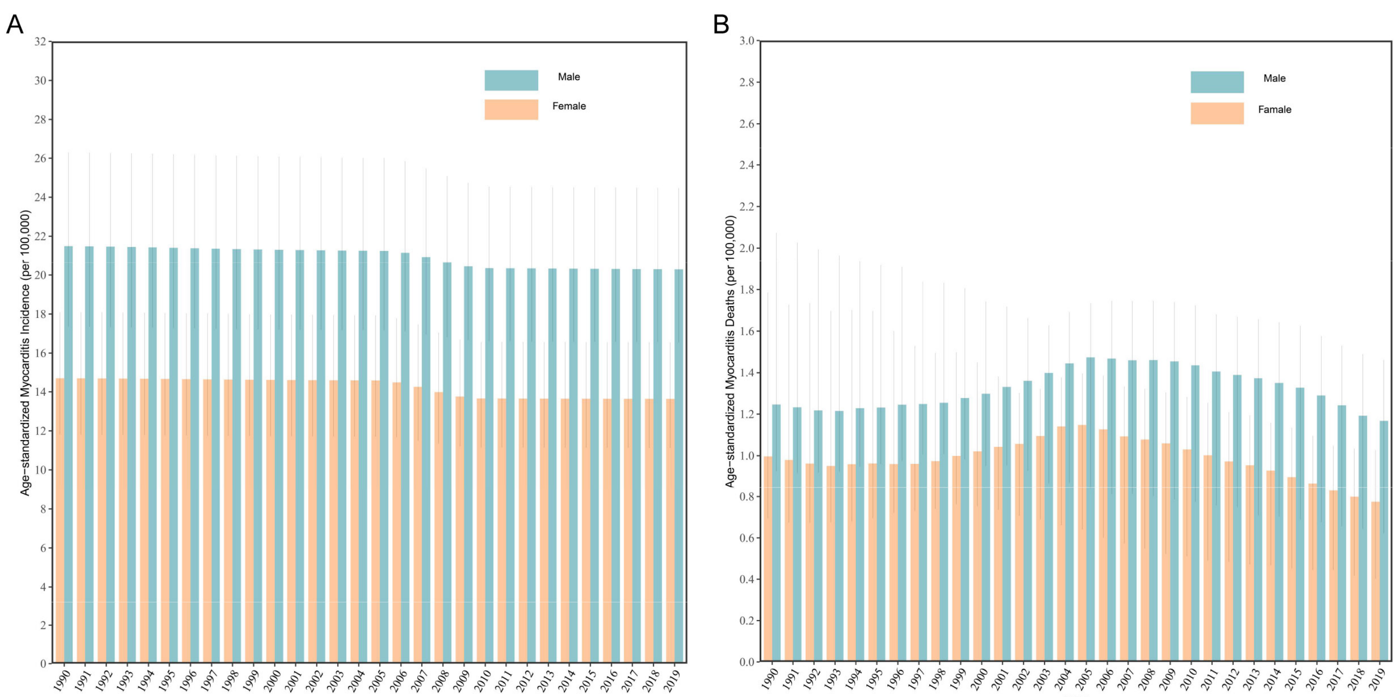

Figure 1. Trends in ASIR and ASMR of myocarditis in China over time. (A) Trends in ASIR of myocarditis by gender in China during 1990-2019. (B) Trends in ASMR of myocarditis by gender in China during 1990-2019.

Table 1. Joinpoint Regression Analysis: Trends in ASIR (per 100 000 Population) for Males and Females in China from 1990 to 2019

Female				Male			
Segment	**Period**	**APC**	***P***	**Segment**	**Period**	**APC**	***P***
1	1990-2006	−0.068 (−0.07 to −0.065)	<.001	1	1990-2006	−0.088 (−0.093 to −0.084)	<.001
2	2006-2009	−1.996 (−2.062 to −1.93)	<.001	2	2006-2009	−1.287 (−1.391 to −1.183)	<.001
3	2009-2019	−0.051 (−0.056 to −0.046)	<.001	3	2009-2019	−0.055 (−0.063 to −0.047)	<.001
AAPC	1990-2019	−0.263 (−0.27 to −0.256)	<.001	AAPC	1990-2019	−0.202 (−0.213 to −0.191)	<.001

age-specific incidence in males decreased in the 20-40 age group (Figure 2A). For mortality rates, myocarditis mortality was quite low in the 15-65 age group (RR <1), and it increased rapidly with age in patients over 65 years old. The change trend was consistent in males and females (Figure 2B).

Period Rate Ratios of Incidence and Mortality Rates of Myocarditis in Chinese Males and Females

During 1990-2019, the impact of the period on the incidence of myocarditis in China showed a decreasing trend, with similar trends in both genders. The RR in males reduced from 1.004 (95% CI: 0.992-1.016) to 0.976 (95% CI: 0.963-0.989), and RR in females reduced from 1.014 (95% CI: 1.003-1.025) to 0.959 (95% CI: 0.950-0.969) over the entire study period (Figure 3A). The influence of the period on the mortality of myocarditis in China also showed a decreasing trend, with a more significant decrease in females than in males. However, between 1995 and 2005, the influence of the period on the mortality of myocarditis in China showed an increasing trend, with similar trends in both genders (Figure 3B).

Cohort Rate Ratios of Incidence and Mortality Rates of Myocarditis in Chinese Males and Females

Myocarditis incidence in Chinese males and females born between 1895 and 2000 showed an overall decreasing trend. The RR in the entire male cohort decreased from 0.979 (95% CI: 0.530-1.811) to 0.893 (95% CI: 0.860-0.927), and RR in females reduced from 0.985 (95% CI: 0.780-1.243) to 0.739 (95% CI: 0.706-0.774) (Figure 4A). The mortality rates of myocarditis in people born before 1930 gradually increased, while those born after 1930 gradually decreased, with similar trends observed in both genders (Figure 4B).

Local Drifts in Incidence and Mortality Rates of Myocarditis in Chinese Males and Females

The local drift curves of the incidence rates of myocarditis in Chinese males during 1990-2019 presented a decreasing trend in the 20-60 age group and an increasing trend in other age groups. Incidence rates of myocarditis in Chinese females showed a decreasing trend in the 15-75 age group and an increasing trend in the over-75 age group (Figure 5A). As for mortality rates, local drift values were less than 0 in males under 70 years old and females under 75 years old, indicating a decreasing trend in ASMR. However, in males aged older than 70 and females aged older than 75, ASMR presented an increasing trend (Figure 5B).

DISCUSSION

This study investigated changes in myocarditis burden in China over the past 3 decades, focusing on gender and age. We found that during 1990-2019, myocarditis incidence in China remained stable, with no discernible decrease, while the mortality rate decreased annually from 2005 onward. This suggests that the burden of myocarditis in China is still high, and it is necessary for us to have a more comprehensive understanding of the differences in myocarditis by gender and age and to increase our focus on its prevention and treatment.

Regarding gender, this study showed that myocarditis incidence and mortality were generally higher in males than in females. This is highly consistent with the findings of Yu et al[15] in their study on myocarditis burden in China. Moreover, several other studies have shown that incidence rate of myocarditis is significantly higher in males than in females, accounting for 71%-86% of total cases.[16,17] Additionally, this study demonstrates that from 2005 to 2019, the decline in ASMR for myocarditis in females was greater than in males, potentially due to the higher demand for healthcare services among women compared to men. This can be attributed to several factors. Firstly, women have specific health needs such as reproductive health, maternal care, family planning, and gynecological services, which require regular screening, consultations,

Table 2. Joinpoint Regression Analysis: Trends in ASMR (per 100 000 Population) for Males and Females in China from 1990 to 2019

Female				Male			
Segment	**Period**	**APC**	***P***	**Segment**	**Period**	**APC**	***P***
1	1990-1993	−1.477 (−3.039 to 0.111)	.066	1	1990-1993	−0.747 (−1.513 to 0.026)	.057
2	1993-1998	0.363 (−0.508 to 1.242)	.391	2	1993-1999	0.704 (0.422- 0.986)	<.001
3	1998-2005	2.519 (2.185- 2.854)	<.001	3	1999-2005	2.537 (2.308- 2.767)	<.001
4	2005-2014	−2.341 (−2.566 to −2.116)	<.001	4	2005-2009	−0.327 (−0.874 to 0.223)	.221
5	2014-2019	−3.695 (−4.182 to −3.207)	<.001	5	2009-2015	−1.49 (−1.746 to −1.233)	<.001
				6	2015-2019	−3.301 (−3.673 to −2.928)	<.001
AAPC	1990-2019	−0.872 (−1.112 to −0.631)	<.001	AAPC	1990-2019	−0.233 (−0.371 to −0.094)	<.001

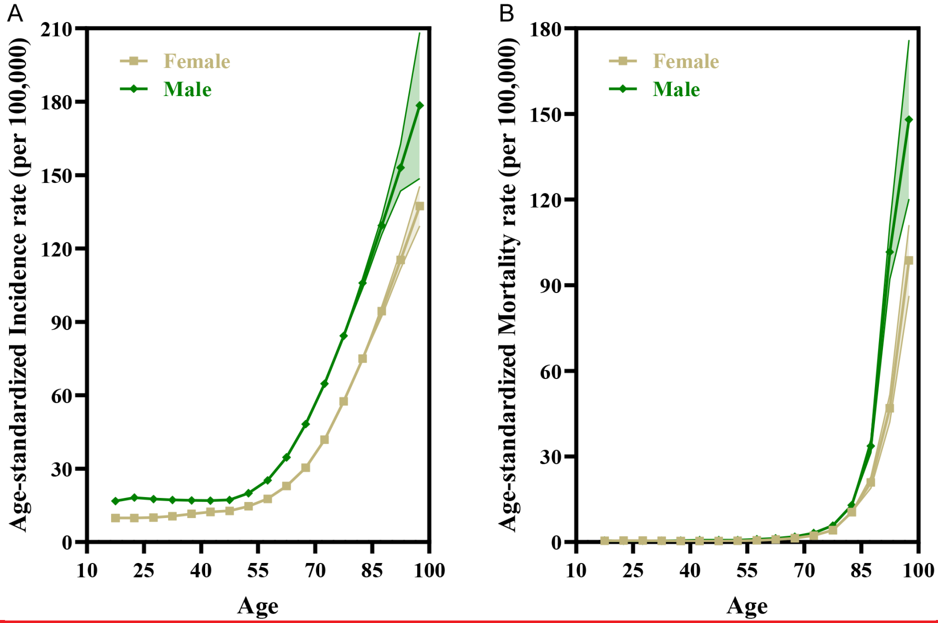

Figure 2. Longitudinal age curves of ASIR and ASMR of myocarditis in China. (A) Longitudinal age curve of ASIR of myocarditis in Chinese men and women during 1990-2019. (B) Longitudinal age curve of ASMR of myocarditis in Chinese men and women during 1990-2019. The solid line represents the age-specific rates (per 100 000 persons per year) of incidence and mortality of myocarditis, and the shaded area represents the corresponding 95% CI.

and appropriate medical interventions, hence leading to a higher demand for healthcare services. Secondly, women often take on multiple roles within the family and community, including caring for children, the elderly, and other family members. These responsibilities prompt them to seek healthcare services, increasing their overall demand for healthcare. Moreover, there is a higher societal focus on women's health issues, early detection of diseases, and health screenings. Awareness campaigns and educational initiatives about various health issues for women have also contributed to an increased understanding of health matters and reinforced their awareness to seek medical care. Furthermore, research also suggests that men are more prone to get severe myocarditis, whereas women are much

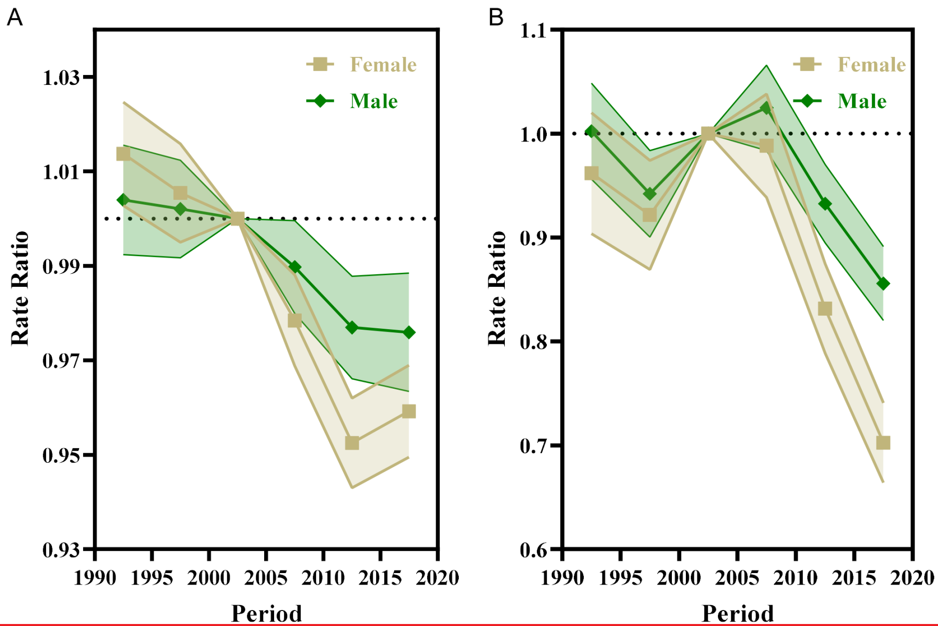

Figure 3. Period RR of incidence and mortality rates of myocarditis in Chinese men and women. (A) Period RR of incidence rates of myocarditis by gender in China during 1990-2019. (B) Period RR of mortality rates of myocarditis by gender in China during 1990-2019. Compared with the reference period (2000-2004). The relative risks of each period were adjusted for age and nonlinear cohort effects, along with the corresponding 95% CI.

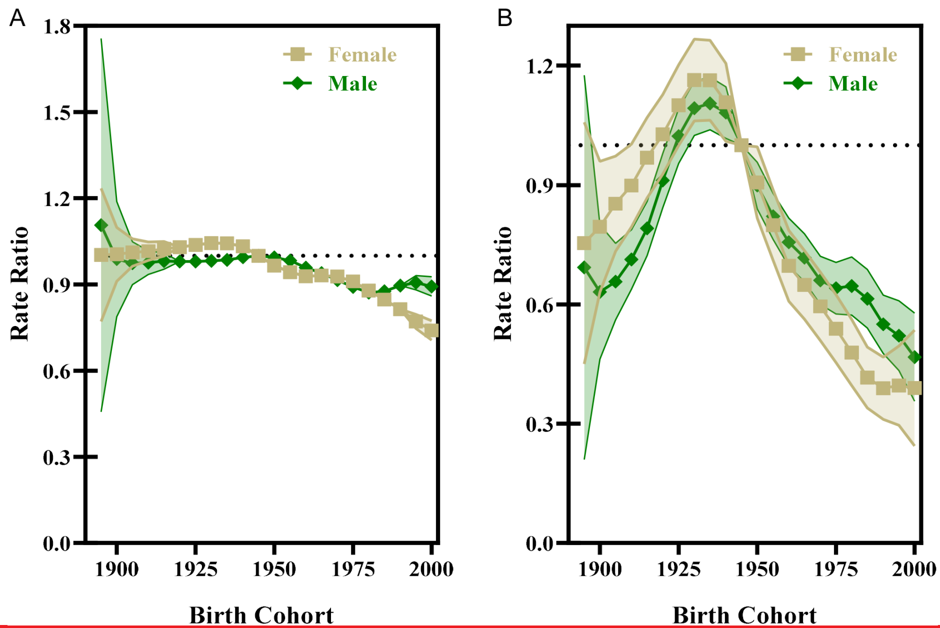

Figure 4. Cohort RR of incidence and mortality rates of myocarditis in Chinese men and women. (A) Cohort RR of incidence rates of myocarditis in Chinese men and women born from 1895 to 2000. (B) Cohort RR of mortality rates of myocarditis in Chinese men and women born from 1895 to 2000. The vertical axis represents the relative risks of each cohort compared with the reference cohort (1945), adjusted for age and nonlinear period effects, along with the corresponding 95% CI.

less likely to pass away or need a heart transplant.[18] In a mouse model experiment, CVB3, a predominant pathogen in viral myocarditis patients, induced a higher incidence and more severe clinical course of myocarditis in male mice.[19] Testosterone promotes susceptibility to myocarditis in male mice, as castrated male mice are protected, and exogenous testosterone administration can restore susceptibility.[20] Treatment with male E2 provides a protective effect since ovariectomized female mice have higher myocarditis compared to intact female mice.[21] The reason for this may be related to the ability of sex hormones to influence innate and adaptive immune responses. CVB3-infected male and

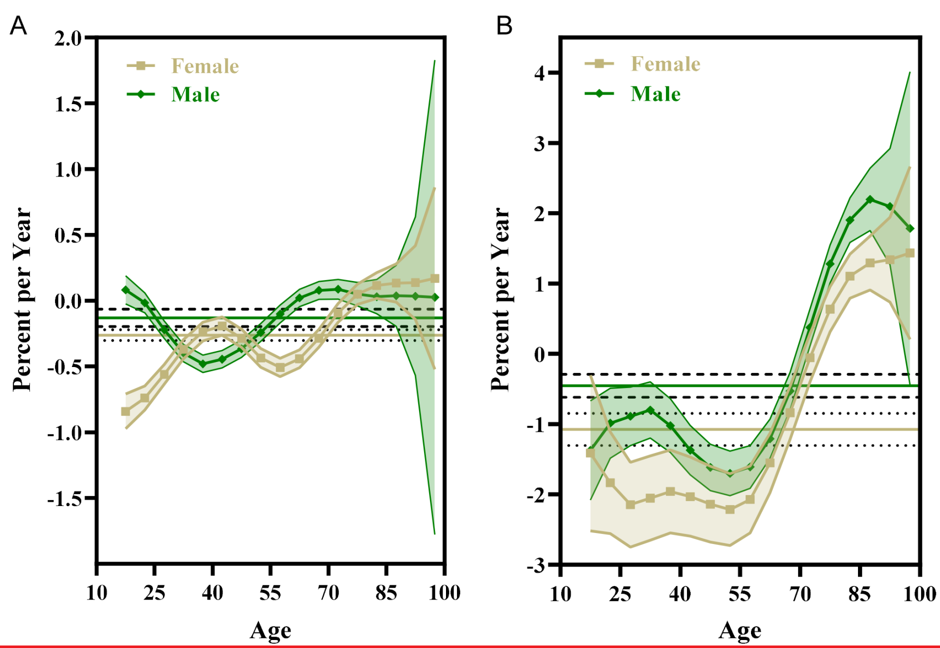

Figure 5. Local drifts in incidence and mortality rates of myocarditis in Chinese men and women. (A) Net and local drifts in incidence rates of myocarditis in Chinese men and women during 1990-2019. (B) Net and local drifts in mortality rates of myocarditis in Chinese men and women during 1990-2019. The solid line represents the net drift value, and the dashed line represents the corresponding 95% CI. The local drift value is represented by the dotted line, and the shaded area represents the corresponding 95% CI.

female mice produce different T-cell responses, with males producing a pro-inflammatory response, while females produce an anti-inflammatory or immune-suppressive response.[22,23]

To our knowledge, this study is the first to examine the trend of myocarditis in China using an age–period–cohort model. Age effects refer to changes in disease rates with age and are important determinants of disease occurrence. Myocarditis occurs in all age groups, with median age of onset being 30-45 years.[6,7,24] In the US COVID-19 Vaccine Adverse Event Reporting System, as of August 31, 2021, there were 1991 cases of myocarditis recorded, with a median age of 21 years.[25] However, this study found that myocarditis incidence and mortality in China elevated rapidly with age following adjusting for period and cohort biases using age–period–cohort model. Local drift curves also showed that individuals over 70 had a higher incidence and risk of death from myocarditis. Currently, the Chinese population is rapidly aging, and various diseases, especially cardiovascular diseases, are prevalent among the elderly.[26] Furthermore, it has been reported that female myocarditis patients often exhibit more severe disease manifestations (worsening of ventricular tachycardia, ventricular fibrillation) in old age.[27] These results indicate that the aging trend of the burden of myocarditis needs to be taken seriously, and further attention should be paid to myocarditis patients in the elderly population.

This study revealed a general trend toward a lessening influence of period and cohort effects on the incidence and death rates of myocarditis in China. Several factors, including measures to improve the timely diagnosis and treatment of myocarditis, may be a contributing factor to the decrease in the burden of myocarditis disease. The mortality rate is showing a downward trend, partly due to improvements in myocarditis treatment and an increase in the level of medical intervention.[28,29] Clinical signs and symptoms of myocarditis might range from minor chest pain to cardiogenic shock, and there are no specific diagnostic tests, making it difficult to diagnose clinically. Electrocardiography is used to test for myocarditis, but its sensitivity is only 47%.[30] Over the years, with the development of various diagnostic technologies, myocarditis patients have been more accurately identified, and diagnostic methods include clinical, laboratory, imaging, and histological parameters.[31,32] In recent years, utilization of cardiac magnetic resonance imaging for noninvasive assessment of suspected myocarditis patients has become more frequent,[33] with unique tissue characterization potential that can assess 3 markers of tissue damage, including intracellular and interstitial edema, congestion and capillary leak age, and necrosis and fibrosis.[28] We are better able to comprehend the actual prevalence and different patient types of myocarditis thanks to these new diagnostic tools and algorithms. Moreover, to increase the accessibility, affordability, and availability of medical care, the Chinese government is working to increase urbanization and basic health insurance. The improvement in medical technology and the abundance of medical resources may also be one of the reasons for the decreasing incidence and mortality rates of myocarditis.

Study Limitations

In spite of the progress, there are still several limitations. First off, biases resulting from missing data may be challenging to prevent, even though GBD 2019 has modified and adjusted data sources and collection evaluation methods to increase data quality. Due to different diagnostic criteria, statistical errors in the data appear to be unavoidable within the standards for including cases. Secondly, this study did not classify the burden of myocarditis according to etiology, such as viral myocarditis or immunotherapy-related myocarditis. Finally, we should also take other factors like environmental exposure, economic development level, and educational attainment into account in addition to the impacts of age, period, cohort, and gender.

CONCLUSION

In summary, the burden of myocarditis in China generally demonstrated a declining trend between 1990 and 2019, but the incidence rate remained high, posing a threat to people's health and lives. In addition, the burden of myocarditis in male and elderly populations needs more attention. Therefore, relevant departments should take more proactive measures to reduce the burden of myocarditis, such as unifying diagnostic standards and exploring effective specific treatment methods.

Data Availability Statement: The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics Committee Approval: The Institutional Ethics Committee exempted the study, which did not require approval because the 2019 GBD data is publicly available. The study followed guidelines for accurate and transparent health assessment reporting.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.B., Y.W.; Design – L.S., C.B., Y.W., G.Y.; Supervision – G.Y., X.L.; Resource – X.L., Y.W., L.S.; Materials – Y.W.; Data Collection and/or Processing – C.B., Y.W., G.Y.; Analysis and/or Interpretation – X.L., G.Y., Y.W.; Literature Search – L.S., C.B., Y.W., G.Y.; Writing – C.B., Y.W.; Critical Review – C.B., Y.W., X.L., L.S., G.Y.

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GLOBAL BURDEN OF DISEASE (GBD):

The GBD (Global Burden of Disease) database, abbreviated from the Global Burden of Disease, is a database created and maintained by the Institute for Health Metrics and Evaluation (IHME). The purpose of this database is to assess the burden on human health caused by diseases, injuries, and risk factors on a global scale.

GLOBAL HEALTH DATA EXCHANGE (GHDX):

Global Health Data Exchange (GHDx) is a health data exchange platform maintained and operated by the Institute for Health Metrics and Evaluation (IHME). The purpose of GHDx is to provide a wide range of global health data and statistical information to researchers, policymakers, healthcare professionals, and the public to support global health research, policy formulation, and public health decision-making.

ANNUAL PERCENT CHANGE (APC):

APC refers to the average annual percentage change of a variable (such as disease incidence, mortality rate) within a specified time period. APC helps us understand the annual percentage change in the variable, indicating whether it is increasing or decreasing.

AVERAGE ANNUAL PERCENT CHANGE (AAPC):

AAPC refers to the average annual percentage change of a variable over the entire time series, taking into account multiple time periods. It provides an overall estimate of the annual percentage change in the variable. AAPC is typically calculated by taking a weighted average of the APCs, where the weights are based on the lengths of each time period.

AGE-STANDARDIZED INCIDENCE RATE (ASIR):

ASIR (Age-Standardized Incidence Rate) is the age-standardized incidence rate, which is a method used to compare disease incidence rates among different populations or regions. It takes into account the population structure differences among different age groups by standardizing the incidence rates of each age group. This enables a more accurate comparison of disease incidence rates among different populations and eliminates differences caused by variations in age distribution.

AGE-STANDARDIZED MORTALITY RATE (ASMR):

ASMR (Age-Standardized Mortality Rate) is the age-standardized mortality rate used to compare mortality rates among different populations or regions. Similar to ASIR, it considers population structure differences among different age groups by standardizing the mortality rates of each age group. This allows for a more accurate comparison of mortality rates among different populations and eliminates differences caused by variations in age distribution.

These two indicators are commonly used in epidemiological research and health statistics to compare disease incidence and mortality rates among different regions, countries, or populations, while accounting for the impact of age structure. Standardized rates enable researchers to gain a more accurate understanding of health disparities among different populations and facilitate more meaningful comparisons.

Abbreviations	Full title
GBD	Global burden of disease
GHDx	Global Health Data Exchange
RR	Relative Risk
95% CI	95% Confidence Interval
APC	Annual Percent Change
AAPC	Average Annual Percent Change
ASIR	Age-Standardized Incidence Rate
ASMR	Age-Standardized Mortality Rate

Supplementary Table 1.

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Estimated Joinpoints								
Cohort	Joinpoint	Estimate	Lower CI	Upper CI				
Female	1	2006	2005	2007				
Female	2	2009	2008	2010				
Annual Percent Change (APC)								
Cohort	Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
Female	1	1990	2006	-0.068*	-0.070	-0.065	-52.815	< 0.001
Female	2	2006	2009	-1.996*	-2.062	-1.930	-62.484	< 0.001
Female	3	2009	2019	-0.051*	-0.056	-0.046	-21.156	< 0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level								
Average Annual Percent Change (AAPC)								
Cohort	Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Female	Full Range	1990	2019	-0.263*	-0.270	-0.256	-75.030	< 0.001

* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.
~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More

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Estimated Joinpoints								
Cohort	Joinpoint	Estimate	Lower CI	Upper CI				
Male	1	2006	2005	2007				
Male	2	2009	2008	2010				
Annual Percent Change (APC)								
Cohort	Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
Male	1	1990	2006	-0.088*	-0.093	-0.084	-44.097	< 0.001
Male	2	2006	2009	-1.287*	-1.391	-1.183	-25.527	< 0.001
Male	3	2009	2019	-0.055*	-0.063	-0.047	-14.521	< 0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level								
Average Annual Percent Change (AAPC)								
Cohort	Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Male	Full Range	1990	2019	-0.202*	-0.213	-0.191	-36.551	< 0.001

* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.
~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More

Supplementary Table 2.

Graph | Data | Model Estimates | Trends | Model Selection

Estimated Joinpoints

Cohort	Joinpoint	Estimate	Lower CI	Upper CI				
Female	1	1993	1992	1998				
Female	2	1998	1996	2006				
Female	3	2005	2004	2014				
Female	4	2014	2010	2017				

Annual Percent Change (APC)

Cohort	Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
Female	1	1990	1993	-1.477	-3.039	0.111	-1.973	0.066
Female	2	1993	1998	0.363	-0.508	1.242	0.882	0.391
Female	3	1998	2005	2.519*	2.185	2.854	16.175	< 0.001
Female	4	2005	2014	-2.341*	-2.566	-2.116	-21.814	< 0.001
Female	5	2014	2019	-3.695*	-4.182	-3.207	-15.768	< 0.001

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level

Average Annual Percent Change (AAPC)

Cohort	Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Female	Full Range	1990	2019	-0.872*	-1.112	-0.631	-7.072	< 0.001

* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.
~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More

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Estimated Joinpoints

Cohort	Joinpoint	Estimate	Lower CI	Upper CI				
Male	1	1993	1992	1996				
Male	2	1999	1997	2001				
Male	3	2005	2004	2006				
Male	4	2009	2007	2011				
Male	5	2015	2013	2017				

Annual Percent Change (APC)

Cohort	Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
Male	1	1990	1993	-0.747	-1.513	0.026	-2.089	0.057
Male	2	1993	1999	0.704*	0.422	0.986	5.412	< 0.001
Male	3	1999	2005	2.537*	2.308	2.767	24.175	< 0.001
Male	4	2005	2009	-0.327	-0.874	0.223	-1.285	0.221
Male	5	2009	2015	-1.490*	-1.746	-1.233	-12.460	< 0.001
Male	6	2015	2019	-3.301*	-3.673	-2.928	-18.839	< 0.001

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level

Average Annual Percent Change (AAPC)

Cohort	Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Male	Full Range	1990	2019	-0.233*	-0.371	-0.094	-3.288	0.001

* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level.
~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More