Age-Period-Cohort Analysis of Ischemic Heart Disease Morbidity and Mortality in China, 1990–2019

Danmei Wei, BSc; Wenbo Xiao, BSc; Lihui Zhou, MD; Jian Guo, MD; Wenli Lu, PhD; Yuan Wang, PhD

**Background:** The disease burden of ischemic heart disease (IHD) continues to increase. This study aimed to assess the age, period, and cohort effects on the long-term trends of IHD incidence and mortality in China from 1990 to 2019.

**Methods and Results:** The data were obtained from the Global Burden of Disease Study (GBD) 2019, and the age-standardized incidence/mortality rate (ASIR/ASMR) was calculated. The age-period-cohort (APC) model, which is a generalized linear model revealing the correlation of disease rate and attained age, period, and cohort, was applied to estimate the net drift (estimated annual percentage change [EAPC]), the local drifts (age-specific EAPCs), the age, period, and cohort effects. The analyses elucidated that the ASIR and ASMR of IHD declined after 2013. The net drift of incidence was 0.212% in females, and the net drift of mortality was 0.371% in males. The local drifts of mortality were above 0 in males aged 20–84 years and in females aged 65–84 years. The age effects showed elevated trends during the study period. The period effects declined after 2013. The cohort effects of mortality in males were higher than that in females.

**Conclusions:** The decrease of ASIR and ASMR indicated that measures to prevent IHD have been effective in China. However, the cardiovascular health of the elderly and males should be considered in future policy decisions.

**Key Words:** Age-period-cohort analysis; China; Incidence; Ischemic heart disease; Mortality

Ischemic heart disease (IHD) is a major public health issue and the main burden of cardiovascular diseases. IHD has become the first leading global years-of-life lost (YLL) cause in 2019, whereas in 1990, it ranked only third. The trends of IHD incidence and mortality vary from region to region. Regions such as North Africa and the Middle East, Central Asia, and Eastern Europe have higher prevalence rates of IHD. For the high Sociodemographic Index (SDI) and high-middle SDI countries, the age-standardized incidence rate of IHD decreased by 27.4% from 1990 to 2017. Regarding mortality, in Central Asia, the age-standardized death rate (ASDR) increased by 16.7% from 1990 to 2017. However, in Korea, the ASDR decreased by 30% in males and by 37% in females from 2002 to 2012. Also, the ASDR reduced from 65.3 to 51.3 per 100,000 and from 48.8 to 26.3 per 100,000 among Japanese males and females during 1995–2000, respectively.

Typical statistical analysis cannot decompose the risks when estimating incidence or mortality; therefore, an age-period-cohort (APC) model was developed and has been used for evaluating the long-term trend of IHD incidence and mortality. Specifically, the APC model is a generalized linear model that separates age effects, period effects, and cohort effects, and quantifies the influence of age, time, and birth cohort factors on disease rate. Estimable APC functions provide a useful parametric framework that complements standard non-parametric descriptive methods. Although prior studies in China have applied the APC model to IHD analysis, the data used in these studies was from 1987 to 2013, and the cohorts analyzed were born between 1904 and 1993. The cohort effects in younger generations have not yet been investigated.

This study analyzed and quantified the age, period, and cohort effects on the secular trends of IHD incidence and mortality in China by using the data over an extended period obtained from the Global Burden of Disease Study (GBD) 2019. We aimed to determine the effects of IHD prevention in China, and to identify the high-risk population group, which should be taken into account in policy decision-making. The results may help to improve the long-term national IHD prevention policies and measures.

**Methods**

**Data Sources**

This study obtained the IHD incidence and mortality rates...
ASR per 100,000 = \sum_{i=1}^{A} a_i w_i \times 100,000
\sum_{i=1}^{A} w_i

APC Model
We performed an APC analysis using the R-based web tool from the US National Cancer Institute (http://analysistools.nci.nih.gov/apc/).\(^9\) It was also used in our previous study on APC analysis of stroke.\(^10\) The web tool applies the APC model to the data to estimate parameters (trends and deviations). The parameters are combined to produce functions that describe relationships between the observed rate of disease and attained age, calendar period, and birth cohort. The web tool also calculates a number of statistical hypothesis tests (Wald Tests), which address whether the rate of disease is significantly different by age, period, and cohort factors. Net drifts represent the estimated annual percentage change (EAPC) rates over time. Local drifts represent the EAPC of the expected age-specific rates over time. Age effects (longitudinal age curves) are defined as the risks of the outcomes associated with different age brackets. Longitudinal age curves are expected age-specific rates in reference cohort, \(c_0\), adjusted for period effects. The period effects (period rate ratios \(RRs\)) are defined as the variations in the outcomes over time that influenced all age groups simultaneously. Period \(RRs\) are the ratios of age-specific rates in each period relative to reference period, \(p_0\). The cohort effects (cohort \(RRs\)) are defined as the changes in outcomes across groups of individuals with the same birth years. Cohort \(RRs\) are the ratios of age-specific rates in each cohort relative to reference cohort, \(c_0\).\(^7\)

Statistics
The age-standardized rates were calculated by using the GBD 2019 data for a global age-standard population. Net drifts, local drifts, age effects, period effects, and cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sex</th>
<th>1990</th>
<th>%</th>
<th>2019</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td>441,055,582</td>
<td>51.38</td>
<td>599,961,799</td>
<td>50.57</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>417,364,026</td>
<td>48.62</td>
<td>586,415,623</td>
<td>49.43</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td></td>
<td>126,882,208</td>
<td>14.78</td>
<td>75,136,217</td>
<td>6.33</td>
</tr>
<tr>
<td>20–24</td>
<td></td>
<td>132,399,760</td>
<td>15.42</td>
<td>81,867,264</td>
<td>6.90</td>
</tr>
<tr>
<td>25–29</td>
<td></td>
<td>110,196,445</td>
<td>12.84</td>
<td>110,718,581</td>
<td>9.33</td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td>88,511,800</td>
<td>10.31</td>
<td>129,094,492</td>
<td>10.88</td>
</tr>
<tr>
<td>35–39</td>
<td></td>
<td>91,508,665</td>
<td>10.66</td>
<td>100,894,600</td>
<td>8.50</td>
</tr>
<tr>
<td>40–44</td>
<td></td>
<td>67,242,515</td>
<td>7.83</td>
<td>101,645,720</td>
<td>8.57</td>
</tr>
<tr>
<td>45–49</td>
<td></td>
<td>51,719,841</td>
<td>6.03</td>
<td>121,366,280</td>
<td>10.23</td>
</tr>
<tr>
<td>50–54</td>
<td></td>
<td>47,801,977</td>
<td>5.57</td>
<td>125,103,335</td>
<td>10.54</td>
</tr>
<tr>
<td>55–59</td>
<td></td>
<td>43,462,552</td>
<td>5.06</td>
<td>94,839,582</td>
<td>7.99</td>
</tr>
<tr>
<td>60–64</td>
<td></td>
<td>35,420,587</td>
<td>4.13</td>
<td>78,555,834</td>
<td>6.62</td>
</tr>
<tr>
<td>65–69</td>
<td></td>
<td>27,367,474</td>
<td>3.19</td>
<td>70,383,716</td>
<td>5.93</td>
</tr>
<tr>
<td>70–74</td>
<td></td>
<td>18,856,418</td>
<td>2.20</td>
<td>47,855,920</td>
<td>4.03</td>
</tr>
<tr>
<td>75–79</td>
<td></td>
<td>11,410,485</td>
<td>1.33</td>
<td>29,846,507</td>
<td>2.52</td>
</tr>
<tr>
<td>80–84</td>
<td></td>
<td>5,638,881</td>
<td>0.65</td>
<td>19,067,374</td>
<td>1.63</td>
</tr>
</tbody>
</table>
effects were estimated by applying the APC model. In the APC model, participants with IHD were divided into consecutive 5-year age groups, sequential 5-year periods from 1990 to 2019, and relevant successive 5-year birth cohorts. The central age group, period, and birth cohort were defined as the reference group in all APC analyses. Wald chi-squared tests were adopted test the significance of the estimable functions. A 2-sided P value <0.05 was considered significant.
Increased consistently among males aged 20–45 years and the elderly aged 70–84 years.

**APC Analysis**

Age-specific annual percent changes (local drifts) and the overall annual percent changes (net drifts) of IHD incidence/mortality for different genders are shown in Figure 3 and Table 2. The results showed that the net drift values of IHD incidence were 0.037% (95% CI: −0.046, 0.200) per year for males and 0.212% (95% CI: 0.130, 0.293) per year for females. The net drift values for IHD mortality were 0.371% (95% CI: 0.220, 0.523) per year for males and −1.648% (95% CI: −1.976, −1.319) per year for females.

The local drift values for IHD incidence reached its maximum at age 80–84 years (male: 1.075% [0.925, 1.225]; female: 0.958% [0.835, 1.080]). These values were above 0 for males aged ≥55 years. For females, the local drift values were above 0 in all age groups (Figure 3A). The local drift values for IHD mortality also peaked at age 80–84 years (male: 1.804% [1.602, 2.008]; female: 1.641% [1.366, 1.916]). These values were above 0 in males aged >20 years and in females aged >65 years (Figure 3B).

**Results**

**Characteristics of Study Participants**

Table 1 shows the characteristics of study participants in 1990 and 2019. The cumulative percentage of the participants aged ≥65 years in 2019 (14.11%) was higher than that in 1990 (7.37%).

**Incidence and Mortality of IHD**

Trends of the CIR/CMR and ASIR/ASMR of IHD by gender from 1990 to 2019 are shown in Figure 1. The CIR and CMR of IHD increased over time. After age-standardization, the ASIR increased slightly from 2000 to 2011 and reached peaks of 249.5 per 100,000 in males and 168.1 per 100,000 in females before a declined trend was observed. The ASMR of IHD increased until 2005; after that, there was a relatively steep increase for males and a gradual increase for females. The ASMR peaked at 172.3 per 100,000 in 2013 among males and at 105.7 per 100,000 in 2011 among females. Then the ASMR decreased over time for both genders. In 2019, the ASMR was 151.6 (95% CI: 127.2, 176.8) and 93.0 (95% CI: 75.4, 110.4) per 100,000 in males and females, respectively.

Figure 2 shows the trends of age-specific incidence and mortality of IHD by birth cohorts. Incidence rates of IHD showed that upward trends increased over generations in older age groups (70–84 years). Mortality rates of IHD increased consistently among males aged 20–45 years and the elderly aged 70–84 years.
Figure 4. Longitudinal age curves of ischemic heart disease (IHD) incidence/mortality rates in China. Fitted longitudinal age-specific rates of IHD incidence/mortality rates (per 100,000 person-years) and the corresponding 95% confidence intervals. (A) IHD incidence rate. (B) IHD mortality rate.

Figure 5. Period rate ratios (RRs) and the corresponding 95% confidence intervals (95% CI) of ischemic heart disease (IHD) incidence/mortality rates in China. The RRs of each period compared with the reference period (2002–2003) adjusted for age and non-linear cohort effects. (A) Period RRs and 95% CI of IHD incidence. (B) Period RRs and 95% CI of IHD mortality.

Figure 6. Cohort rate ratios (RRs) and the corresponding 95% confidence intervals (95% CI) of IHD incidence/mortality rates in China. The relative risk of each cohort compared with the reference cohort (1950s) adjusted for age and non-linear period effects. (A) Cohort RRs and 95% CI of IHD incidence. (B) Cohort RRs and 95% CI of IHD mortality.
Aged ≥65 years increased at the fastest pace compared to those participants who were younger (Figure 4A). The IHD mortality rates also increased for both genders, especially for those aged ≥65 years (Figure 4B).

The estimated period RRs by gender are shown in Figure 5. The period effects of both IHD incidence and mortality declined after 2013. Specifically, the period effects on IHD incidence increased slightly in females, but decreased in males (Figure 5A). Regarding the mortality, period RRs decreased dramatically in females, but only decreased mildly in males (Figure 5B).

The estimated cohort RRs by gender are presented in Figure 6. The influence of cohort on incidence followed an upward pattern for females, whereas for males, the cohort RRs increased until 1970; after that a downward pattern was found (Figure 6A). The cohort effect of IHD mortality on females was higher than that on males before 1955. Then, it was lower in females than in males (Figure 6B).

The Wald test results for the APC analyses are presented in Table 2. For IHD incidence and mortality in both genders, significant differences in local drifts, cohort and period deviations indicated potential cohort and period effects on the observed temporal trends.

Discussion

We found that the ASIR and ASMR of IHD decreased after 2013. Age effects of IHD incidence and mortality showed elevated trends. Period effects for IHD incidence decreased after 2013. Period effects for IHD mortality decreased among females during 1990–2019, but decreased among males only during 2013–2019. The cohort effect of IHD incidence increased till 1970 and then remained relatively stable. The cohort effect of IHD mortality declined rapidly among females but not in males. The results of this study indicated that the prevention and management for cardiovascular diseases in China have improved. More targeted measures should be taken for males and the elderly.

Age Effects

The longitudinal age curves of the incidence and mortality rate of IHD increased by age, especially in participants aged ≥65 years. China is rapidly aging as a result of a birth boom during the 1950s–1970s.11 Aging is accompanied by reduction in physiological reserve function and is positively associated with heart disease mortality.12 In our study, we found that ASIR and ASMR decreased since 2013. Consistently, such a decreasing trend of IHD mortality has also been reported in high-income countries.13,14 The ASMR of IHD in China in 2019 was similar to those of people in Korea in 1983, but was much higher than that in Japan during 1969–1978.5,15 Since the 1970s, Japan had begun to control the risk factors of cardiovascular diseases and achieved favorable results,16 whereas in China, prevention and control of cardiovascular diseases started late in the 1990s.17 It’s worth learning from the Japanese success story in terms of health promotion. In the past decade, the Chinese government has made considerable efforts to build healthy environments.18 More targeted programs for public health are required to cope with the current situation, especially for the elderly and young and middle-aged males.

Period Effects

Our results showed that period effects on IHD incidence strengthened over time, but decreased after 2013. The reasons for the strengthening include improved medical care, prolonged life expectancy, as well as increased lifestyle and metabolic risk factors among younger populations.18,19 Since 1990, China has experienced rapid economic development; factors such as western dietary habits, smoking, drinking, and a sedentary lifestyle become more and more common.20 There was a declining trend in period effects on IHD mortality for females from 1990 to 2019; this might be due to the improvement in medical care,21 however, a rising trend in period effects on IHD mortality for males was observed, which was consistent with the study by Wang et al.22 Males are more likely to smoke and drink,23 but were less likely to seek health care than females in China,24 and this may lead to a more severe disease and worse prognosis.

Cohort Effects

Cohort effects on IHD incidence showed an increasing trend before 1970. The temporary increase in the cohort effect might be partly due to the effects of World War II (1939–1945) and the Great Chinese Famine (1959–1961). Early sensitization to environmental stressors may be associated with a higher prevalence of current posttraumatic stress disorder, and excess cardiovascular disease risk factors in subjects exposed to extraordinary war-time trauma may lead to extreme exhaustion.24,25 The rapid economic expansion started in 1978 when China implemented the open-door policy. Since then, the standard of living has greatly improved.26 However, more and more people also suffer from psychological stress. In our results, the cohort effects on IHD incidence in females were slightly higher than those in males since 1970. Possible reasons could be that females tend to suffer from more mental stress than males,27 and factors such as family conflicts and obligations, depression, and anxiety are all associated with an increased risk of heart disease.28

The cohort effect on IHD mortality in females was higher than that in males before 1955. Then the situation was reversed. In times of war, females feel more pressure of survive than males. In times of peace, such pressure was largely reduced in females. Males are subjected to greater pressures of social expectations and are more sensitive to socio-economic inequalities than females.29 Poor coping with stress, such as smoking, drinking, and eating a poor diet, is associated with a higher risk of death.

There are several limitations in the present study. First, the causal mechanisms through which age, period, and cohort influence mortality cannot be drawn from our study. To avoid succumbing to the ecological fallacy, it should be noted that our findings based on population-level data were not appropriate for individuals. Further analyses using individual-level data are required to identify these causal mechanisms. Second, during the study period, the shift from ICD-9 to ICD-10 may influence statistical accuracy of IHD incidence and mortality. Yet, studies on cardio-cerebrovascular disease in the United States and China had shown that the transition of ICD only had a minimal effect on cardiovascular disease estimates.30,31 Third, although differences between males and females in terms of IHD mortality (ASMR increased dramatically in males until 2013, but not in females) was found in our study, the data are not sufficient to analyze the causes of these differences; therefore, more studies are needed to explore the possible reasons for such differences.

Our findings indicate that the rapid aging and economic
development in China might play a role in the rising trend in IHD incidence and mortality; however, there is room for Chinese policymakers to improve the prevention of IHD and to reduce the disease burden.

Acknowledgments
The authors would like to acknowledge the funding for the research about strategies for cardiovascular disease intervention by the National Natural Science Foundation of China (Nos. 71704131).

Sources of Funding
This study was funded by the National Natural Science Foundation of China (Nos. 71704131).

Disclosures
The authors declare that they have no conflicts of interest.

IRB Information
The present study was granted an exemption from requiring ethics approval by Tianjin Medical University because it used a public database to obtain the study data.

References