Age-Period-Cohort Analysis of Type-Specific Stroke Morbidity and Mortality in China

Yuan Wang, PhD; Qin Peng; Jian Guo; Lihui Zhou; Wenli Lu, PhD

Background: Stroke has become the leading cause of death in China. This study aimed to assess the age-period-cohort (APC) effects on the long-term trends of type-specific stroke morbidity and mortality in China between 1993 and 2017.

Methods and Results: The data were obtained from the Global Burden of Disease 2017 (GBD 2017) and were analyzed with the age-period-cohort framework. The net drifts of mortality were below 0 (hemorrhagic stroke [HS]: males: –1.620%, females: –3.531%; ischemic stroke [IS]: males: –1.041%, females: –3.002%), and the local drift values were below 0 in all age groups and for both genders. The net drifts of HS incidence were below 0 (males: –1.412%, females: –2.688%), while those of IS were above 0 (males: 1.425%, females: 1.117%). Period effect of mortality showed similar monotonic downward patterns for both genders, with a faster decrease for females than for males. Period effect of incidence showed a declined trend of incidence for HS, but an elevated trend for IS in both genders. After controlling for age and period effects, cohort effects on incidence found a monotonic decline trend for HS, while for IS, an elevated trend was found at first to peak during the 1950–1970 s, then declined steadily afterwards. Cohort effects on mortality showed a monotonic declined trend.

Conclusions: By using Age-Period-Cohort (APC) analysis, a disparity between HS and IS was identified. Different prevention and control strategies should be used depending on the subtypes of stroke.

Key Words: Age-period-cohort analysis; Hemorrhagic stroke; Incidence; Ischemic stroke; Mortality

S troke has become the leading cause of mortality globally and in China. During the past 3 decades, the risk of stroke in China has increased rapidly due to health transitions and sociodemographic changes. From 1990 to 2016, stroke occurrences had more than doubled to ~5,510,276, and the stroke mortality had increased by 29.06%.[1] Stroke incidence and mortality rate increases with aging. The age-standardized incidence of ischemic stroke (IS) increased dramatically, but that of hemorrhagic stroke (HS) decreased slightly,[2] and the age-standardized mortality caused by stroke decreased dramatically.[3]

To better understand the long-term trend of stroke burden, an age-period-cohort (APC) model has been used to investigate the possible reasons underlying the temporal trend. The APC model is a comprehensive method that considers the effect of age, period and birth cohort. The majority of APC studies of stroke mainly focused on mortality.[4-8] Yet, other important factors such as age, period, birth cohort effect on type-specific stroke incidence and mortality has not been fully investigated.

We aimed to investigate the long-term trends of type-specific stroke incidence and mortality in China between 1990 and 2017, examining age-, period-, and cohort-specific effects by gender using the APC framework. We used the data from the Global Burden of Disease Study 2017 (GBD 2017). In doing so, we anticipate that findings from our study could provide etiologic implications for the Chinese population, and provide evidence-based information to inform prevention strategies.

Methods

Data Sources
This study used the data from the GBD 2017. The GBD study used DisMod-MR 2.1, a Bayesian meta-regression tool, as the main method of estimation, ensuring consistency between rates of incidence, prevalence, remission, and cause of death for each condition. The GBD study provides internally consistent estimates of age- and gender-specific all-cause and cause-specific mortality for 282 causes of death and incidence for 354 diseases and injuries globally, regionally, and nationally from 1990 to 2017. Stroke was identified based on the 9th and 10th revision of the International Classification of Disease. In the GBD data set, stroke incidence and mortality were diagnosed and were defined based on the World Health Organization clinical
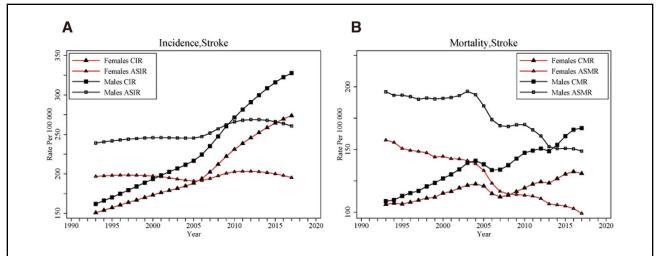
Figure 1. Trends of the crude incidence/mortality rates and the age-standardized incidence/mortality rates per 100,000 population for stroke by gender in China during 1993 to 2017. (**A**) Trends of the crude incidence rates (CIR) and the age-standardized incidence rate (ASIR). (**B**) Trends of the crude mortality rates (CMR) and the age-standardized mortality rate (ASMR).

criteria and the International Statistical Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) revisions and Related Health Problems.[9] Stroke mortality was defined using ICD-9 codes (430–435.9, 437.0–437.2, 437.5–437.8) and ICD-10 codes (G45–G46.8, I60–I63.9, I65–I66.9, I67.0–I67.3, I67.5–I67.6, I68.1–I68.2, I69.0–I69.3). IS mortality was defined using ICD-9 codes (433–435.9, 437.0–437.1, 437.5–437.8) and ICD-10 codes (G45–G46.8, I63–I63.9, I65–I66.9, I67.2–I67.3, I67.5–I67.6, I69.3). HS mortality was defined using ICD-9 codes (431–432.9, 437.2) and ICD-10 codes (I61–I62, I62.1–I62.9, I68.1–I68.2, I69.1–I69.2).

To characterize the temporal trends in China, stroke incidence and mortality rates for males and females were age-standardized by using the GBD 2017 data for a global age-standard population.[10]

APC Model

The standard APC model assumed that the observed number of diseases followed a Poisson distribution and that the incidence or mortality was a multiplicative function of age, cohort and period, such that the logarithm of the rates is an additive function of the parameters.[11–14] With the aim of detailed analyses, we performed an APC analysis using the R-based web tool from the US National Cancer Institute (http://analysistools.nci.nih.gov/apc/).[15] The benefit of this online web tool was that the output was easy to understand and it can solve the problem of identifying model parameters such as the exact linear dependence of the regression variables (Age=Period−Cohort) causing the identifiable problem.

The age effects represented differing risks of the outcomes associated with different age brackets; the period effects represented variations in the outcomes over time that influenced all age groups simultaneously; the cohort effects were associated with the changes of outcomes across groups of individuals with the same birth years. Holford has proposed that if age, period, and cohort trends were orthogonally decomposed into their linear and non-linear parts, many useful functions can be estimated.[16]

In this study, we mainly focused on the following estimable functions:[15] net drift, which was an analog of the

annual percent change in the incidence and mortality over the study period, and it estimated the average annual percentage change in the logarithm of the incidence and mortality with the adjustments of a non-linear period and cohort effects; local drift indicated the average annual percentage changes in incidences over time across different age groups; longitudinal age curve indicated the fitted longitudinal age-specific rates in the reference cohort adjusted for period deviations; the period (or cohort) rate ratios (RR) would be the relative risk adjusted for age and non-linear effects in a period (or cohort) vs. the reference. To conduct APC analysis, the mortality and population data were arranged into consecutive 5-year periods from 1993 to 2017 and successive 5-year age intervals from 15~ years to 85~ years. The central age group, period, and birth cohort were defined as the reference in all APC analyses; in case of an even number of categories, the reference value was set as the lower of the 2 central values. Wald chi-squared tests were adopted for the significance of the estimable functions. To compare the significance of the slope of the period/cohort RRs, we used a general linear model to check the interaction effect between gender and calendar year/birth cohort. All statistical tests were 2-sided.

Results

Incidence and Mortality Trend of Stroke

Trends of the crude incidence/mortality rates (CIR/CMR) and the age-standardized incidence rates (ASIR)/mortality rates (ASMR) for stroke by gender for the period of 1993 to 2017 are shown in **Figure 1**. The CIR for stroke showed overall increasing trends, from 161.9 to 327.8 per 100,000 for males and 150.9 to 274.0 per 100,000 for females. The CMR in both genders also showed increasing trends, from 108.8 to 167.1 per 100,000 for males and 106.2 to 130.9 per 100,000 for females. After age-standardization, the ASIR showed a slightly increasing trend; the ASMR showed a decreasing trend for both males and females.

APC Analysis

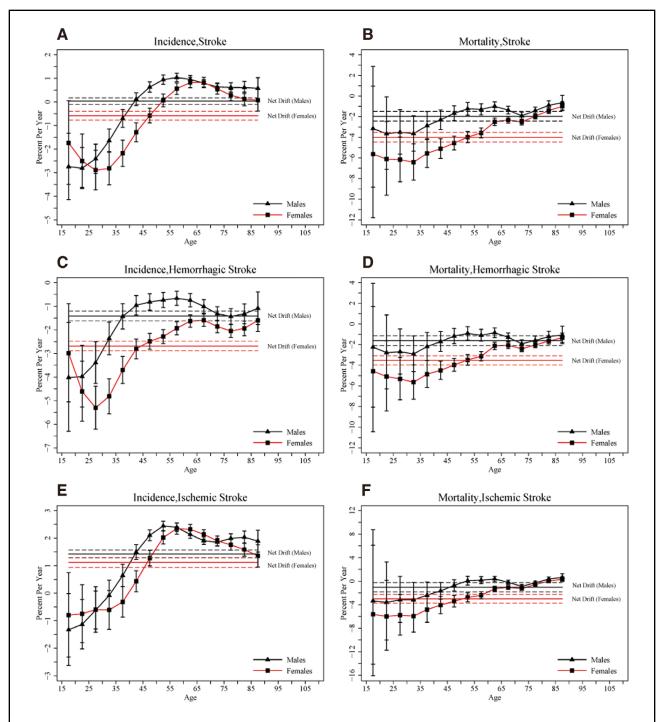Age group-specific annual percent changes (local drifts) with

Figure 2. Age group-specific annual percent change (local drift) with the overall annual percent change (net drift) for type-specific stroke incidence/mortality rates with 95% confidence intervals. (**A**) Local drift with net drift for Stroke incidence rate. (**B**) Local drift with net drift for Stroke mortality rate. (**C**) Local drift with net drift for HS incidence rate. (**D**) Local drift with net drift for HS mortality rate. (**E**) Local drift with net drift for IS incidence rate. (**F**) Local drift with net drift for IS mortality rate.

the overall annual percent change (net drift) in stroke incidence/mortality for different genders are shown in **Figure 2**. We found that the majority net drift values were below 0 (**Figure 2**, **Table**), the exceptions being the net drift values for males in stroke incidence (0.037% [95% CI=−0.100, 0.175] per year), for males in IS incidence (1.425% [95% CI=1.284, 1.566] per year) and for females

in IS mortality (1.117% [95% CI=0.936, 1.298] per year).

The local drift values for stroke incidence reached its maximum at age ~60 years in males (**Figure 2A**). All of the HS-related local drift values were below 0 in all age groups in both genders (**Figure 2C**). For IS, the local drift values were almost above 0 after age 35 years for males and after age 40 years for females (**Figure 2E**). However, regarding

Table. Statistical Parameters for Overall and Age-Specific Annual Percent Changes in Age-Period-Cohort Models

Disease / Sex	Type	Net drift (% per year; 95% CI)	P value		
			All local drifts=net drift	All cohort deviations=0	All period deviations=0
Stroke					
Male	Incidence	0.037 (−0.100, 0.175)	<0.001	<0.001	<0.001
	Mortality	−1.965 (−2.428, −1.500)	0.001	<0.001	0.514
Female	Incidence	−0.584 (−0.774, −0.394)	<0.001	<0.001	<0.001
	Mortality	−3.995 (−4.461, −3.526)	<0.001	<0.001	0.009
IS					
Male	Incidence	1.425 (1.284, 1.566)	<0.001	<0.001	<0.001
	Mortality	−1.041 (−1.824, −0.252)	<0.001	<0.001	0.411
Female	Incidence	1.117 (0.936, 1.298)	<0.001	<0.001	<0.001
	Mortality	−3.002 (−3.747, −2.251)	<0.001	<0.001	0.042
HS					
Male	Incidence	−1.412 (−1.619, −1.205)	<0.001	<0.001	<0.001
	Mortality	−1.620 (−2.093, −1.144)	0.015	0.031	<0.001
Female	Incidence	−2.688 (−2.892, −2.484)	<0.001	<0.001	<0.001
	Mortality	−3.531 (−3.973, −3.087)	<0.001	<0.001	<0.001

CI, confidence interval; IS, ischemic stroke; HS, hemorrhagic stroke.

mortality, the local drift values were almost below 0 in all age groups for both genders (**Figure 2B,D,F**).

Figure 3 shows the longitudinal age curves of type-specific stroke incidence and mortality by gender. The incidence of stroke continued on an upward trend for all age groups. It was noted that the fastest-growing age group was 65–85 years (**Figure 3A,C,E**). Stroke and its subtype mortality rates were also increasing for both genders, especially for those aged over 70 years (**Figure 3B,D,F**). Males had a higher stroke incidence and mortality than women across all age groups.

The estimated period RRs by gender are shown in **Figure 4**. Period RRs were found in similar declined declined patterns for type-specific stroke mortalities for both genders (**Figure 4B,D,F**), a more rapid decrease for females than males for the whole study period. Regarding incidence, period RRs showed a downward trend before 2005 and the RRs of females decreased faster than that of males before the RRs began to show an upward trend and RRs for males rose faster than females for stroke and IS (**Figure 4A,E**). Period RRs declined for both genders for HS incidence (**Figure 4C**) and it decreased quicker for females than males during the whole study period.

The estimated cohort RRs by gender are shown in **Figure 5**. Cohort effects for stroke incidence showed elevated trends peaking in the 1950s and 1970s for females and males respectively, before declining steadily for stroke (**Figure 5A**). For HS, cohort effect for incidence showed a monotonic decline trend (**Figure 5C**). For IS, trend of cohort effect for incidence is similar with stroke (**Figure 5E**). Cohort effects for mortality showed a monotonic declined trend. Cohort effects of HS decreased more than that for IS. The declined trends of the cohort RRs for mortality were more noticeable for females than that for males (**Figure 5B,D,F**).

The Wald test results for the APC analyses are presented in **Table**. For type-specific stroke incidence in both genders, significant differences in local drifts, cohort and period deviations indicated potential cohort and period effects on the observed temporal trends. For type-specific stroke mortality in both genders, significant differences in local drifts and cohort deviations indicated potential cohort effects on the observed temporal trends, though period effects could not be ruled out in the analysis of female data.

Discussion

In this study, we found that compared with the elevated trend of crude incidence and mortality rate, the ASIR showed a slightly increasing trend and the ASMR showed a decreasing trend. These trends can be explained from an age, period, and cohort prospective.

Age Effects
The rapid increase of the older population forms the foundation for stroke incidence and mortality. China had the largest population globally and has experienced a combined situation of accelerated aging and decreasing birth rate. Report of population prediction showed that between 2017 and 2050, the share of population who are aged ≥60 years will increase from 16% to 35% in China.[17,18]

Period Effects
Period effects showed an opposite effect on the incidence for different types of stroke; a declined trend for HS, but an elevated trend for IS. These findings indicated different distribution of risks for the 2 specific types of stroke. During the past 3 decades, in China, the prevalence of risk factors for stroke has changed. Smoking had decreased from 37.6% to 28.15%, hypertension increased from 13.6% to 23.2%, obesity increased from 2.9% to 8.7%, dyslipidemia increased from 18.6% to 39.91%, and diabetes has increased from 2.51% to 10.9%. Apart from the common risk factors such as smoking, IS was associated more closely with atherosclerosis risks such as diabetes, obesity and dyslipidemia than HS. The prevalence of atherosclerosis risks has been increasing since the 1990s, which would result in an increase of IS. Meanwhile, serum cholesterol level was negatively associated with HS. The increase of dyslipidemia was accompanied by a decrease of HS inci-
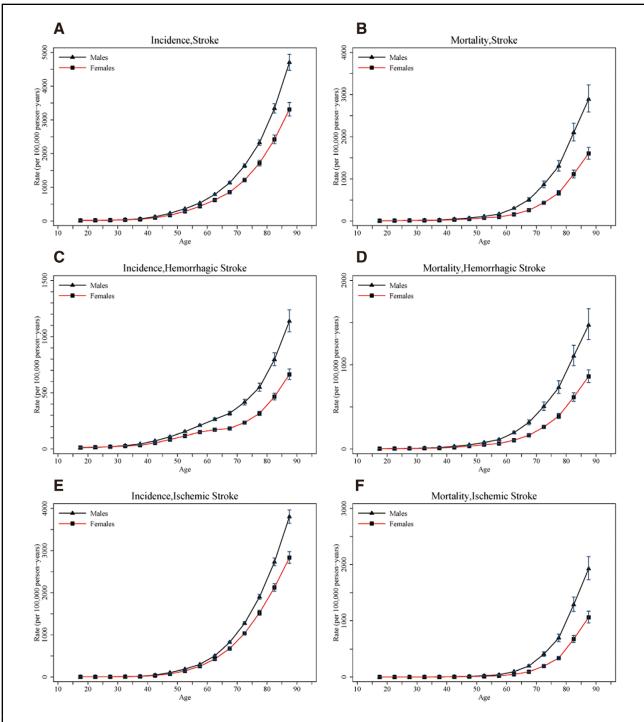
Figure 3. Longitudinal age curves of type-specific stroke incidence/mortality rates in China. Fitted longitudinal age-specific rates of type-specific stroke incidence/mortality rates (per 100,000 person-years) and the corresponding 95% confidence intervals. (**A**) Stroke incidence rate. (**B**) Stroke mortality rate. (**C**) Hemorrhagic Stroke incidence rate. (**D**) Hemorrhagic Stroke mortality rate. (**E**) Ischemic Stroke incidence rate. (**F**) Ischemic Stroke mortality rate.

dence but there was an increase of IS incidence in the eastern Asian population.[19]

Improvement of medical care is the main reason of the monotonic declined association between period and stroke mortality. In China, the rapid socio-economic development improves stroke diagnosis and treatment,[20,21] which decreases the fatality rate. As HS is the main sub-type of

stroke mortality, HS is more beneficial than IS from the improved medical care. Meanwhile, the progress of urbanization and basic medical coverage promotes the availability, accessibility, and affordability of medical care in China. During 1990 to 2010, the proportion of the urban population increased from 26% to 50%, and the coverage of basic medical services had achieved 90% in urban and
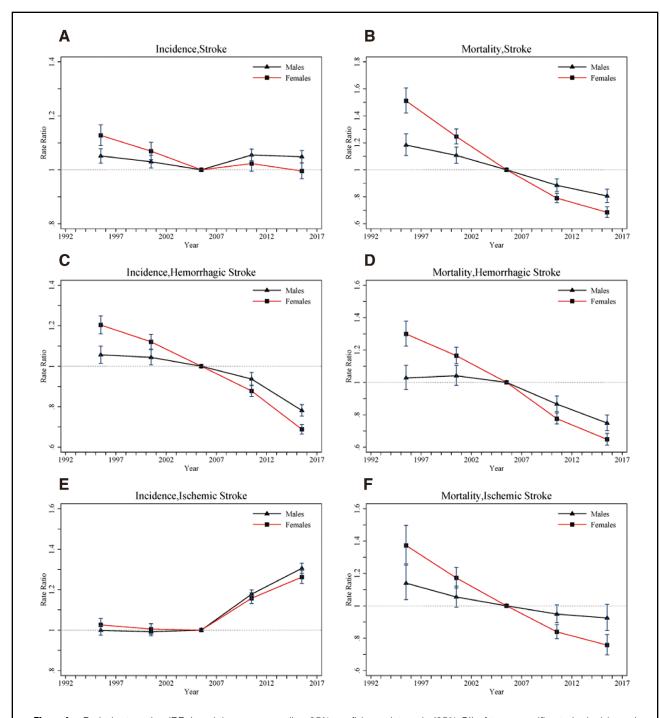
Figure 4. Period rate ratios (RRs) and the corresponding 95% confidence intervals (95% CI) of type-specific stroke incidence/mortality rates in China. The RRs of each period compared with the reference period (2003–2007) adjusted for age and non-linear cohort effects. (**A**) Period RRs and 95% CI of stroke incidence. (**B**) Period RRs and 95% CI stroke mortality. (**C**) Period RRs and 95% CI of hemorrhagic stroke incidence. (**D**) Period RRs and 95% CI of hemorrhagic stroke mortality. (**E**) Period RRs and 95% CI of ischemic stroke incidence. (**F**) Period RRs and 95% CI of ischemic stroke mortality.

95% in rural in 2013.[22,23]

Cohort effects on stroke incidence showed an opposite trend for IS and HS, which could be explained by different type-specific risks. IS was associated with atherosclerosis more closely than HS. During the 1910s–1960s, China had experienced total wartime (Warlord dogfight [1917–1928], Anti-Japanese War and War of Liberation [1937–1949] and

Great Chinese Famine [1959–1961]). Long-term turbulence would bring high stress and induce negative emotions.[24] It can activate the sympathetic nervous system through the hypothalamic-pituitary-adrenal axis,[25,26] which affects blood pressure, blood glucose and lipid metabolism. This association between chronic stress and cardio-cerebrovascular disease had been observed in refugees of the Croatian
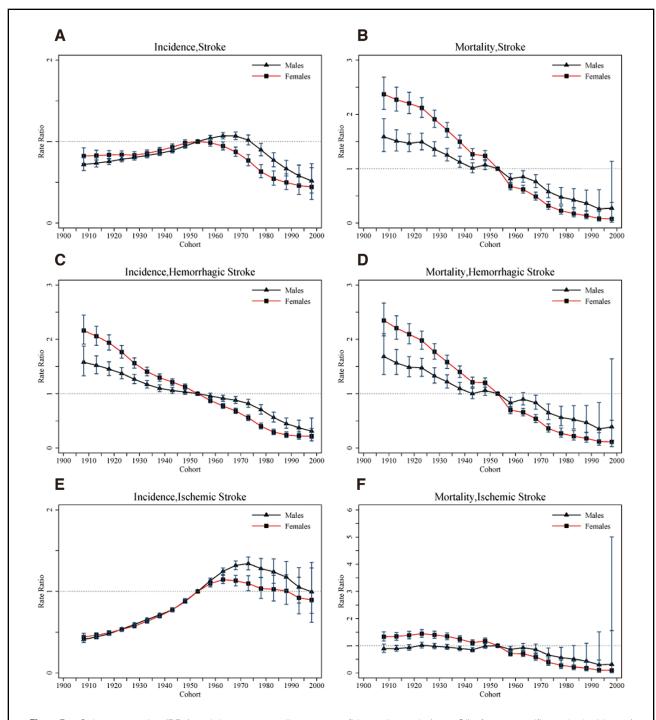
Figure 5. Cohort rate ratios (RRs) and the corresponding 95% confidence intervals (95% CI) of type-specific stroke incidence/mortality rates in China. The relative risk of each cohort compared with the reference cohort (1953 s) adjusted for age and non-linear period effects. (**A**) Cohort RRs and 95% CI of stroke incidence. (**B**) Cohort RRs and 95% CI stroke mortality. (**C**) Cohort RRs and 95% CI of hemorrhagic stroke incidence. (**D**) Cohort RRs and 95% CI of hemorrhagic stroke mortality. (**E**) Cohort RRs and 95% CI of ischemic stroke incidence. (**F**) Cohort RRs and 95% CI of ischemic stroke mortality.

War.[26,27] Until the 1960s–1970s, China had entered a period of economic development. The medical environment and technology had been improved. During the 1980s–2010s, rapid economic development resulted in the prevalence of metabolic syndrome. Thus, the accumulation of long-term stress during the turbulent period and the prevalence of atherosclerosis risks during the peaceful period may increase the risk of IS. When entered elder age, the cohort before 1910 may have a higher risk of IS than the cohort born after the 1970s. Meanwhile, the decline trend of the cohort effect on HS incidence could also be explained by the similar reason, as during the peace period, living and medical conditions had been improved for elderly which were born since 1910s.

Cohort effects on mortality showed a declined trend for stroke, which was consistent with previous studies.[4,8] These studies argued long-term improvement in nutrition in early life might be the main reason. However, as we mentioned before, China had experienced a long-term period of turbulent during the 1910s–1960s,[24] and as a result, nutrition for children during their early years might not have seen improvement. A study in Japan found that the generation born during the war period experienced a lack of proper nutrition.[7] Moreover, an APC study in China found different trends; for example, the cohort effect on stroke mortality remained steadily low during the war period, before increasing rapidly in urban areas, but remaining low in rural areas during peaceful times.[28] A study in England confirmed that stroke mortality increased rapidly after the war because of the improvement in living conditions and the prevalence of an unhealthy lifestyle.[6] In the present study, the declined cohort effects on stroke mortality might be due to the improved medical conditions, which reduced the number of fatality cases caused by stroke among generations born since the 1910s when they entered older age during the peaceful period.[29]

There are several limitations in the present study. First, during the study period, the transition from ICD-9 to ICD-10 may influence statistical accuracy of stroke incidence and mortality. Yet, studies on cardio-cerebrovascular disease in the United States and China had shown that the transition of ICD only had minimal effect on stroke estimates.[30,31] Second, despite many methods in Global Burden of Disease study estimations used to reduce bias, including misclassification corrections, incompleteness and redistribution of garbage codes, it might be difficult to avoid inaccuracy of data thoroughly; therefore, the results of the present study should be interpreted carefully.

Conflicts of Interests

The authors declare that they have no conflicts of interest.

Grants

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