BMJ Open

Influenza-associated cardiovascular mortality in older adults in Beijing, China: a population-based time-series study

Rong Liu [ID],[1] Xiaoshuang Liu,[2] Peng Yang,[3] Xin Du,[1,4,5] Liu He,[4] Tiange Chen,[2] Xiang Li,[2] Guotong Xie,[2,6,7] Shuangsheng Wu,[3] Jianting Su,[3] Shijun Xia,[4] Chao Jiang [ID],[4] Mark D. Huffman,[5,8] Chandini Raina MacIntyre,[9] Zaihua Wei,[3] Quanyi Wang,[3] Jianzeng Dong,[4,10] Craig Anderson[5,11]

For numbered affiliations see end of article.

Correspondence to
Dr Quanyi Wang;
bjcdcxm@126.com

ABSTRACT

Objective This study comprehensively estimated the excess cardiovascular disease (CVD) mortality attributable to influenza in an older (age ≥65 years) population.

Design Ecological study.

Setting Aggregated data from administrative systems on CVD mortality, influenza surveillance and meteorological data in Beijing, China.

Main outcome measure Excess overall CVD, and separately for ischaemic heart disease (IHD), ischaemic stroke, haemorrhagic stroke mortality attributable to influenza, adjusting for influenza activity, time trend, seasonality and ambient temperature.

Results CVD (risk ratio (RR) 1.02, 95% CI 1.01, 1.02), IHD (RR 1.01, 95% CI 1.01, 1.02), ischaemic stroke (RR=1.03, 95% CI 1.02, 1.04), but not haemorrhagic stroke (RR=1.00, 95% CI 0.99, 1.01) mortality, were significantly associated with every 10% increase in influenza activity. An increase in circulating A(H1N1)09pdm, A(H3N2) and B type virus were all significantly associated with CVD and ischaemic stroke mortality, but only A(H3N2) and B type virus with IHD mortality. The strongest increase in disease mortality was in the same week as the increase in influenza activity. Annual excess CVD mortality rate attributable to influenza ranged from 54 to 96 per 100 000 population. The 3%–6% CVD mortality attributable to influenza activity was related to an annual excess of 916–1640 CVD deaths in Beijing, China.

Conclusions Influenza activity has moderate to strong associations with CVD, IHD and ischaemic stroke mortality in older adults in China. Promoting influenza vaccination could have major health benefit in this population.

Background Influenza may trigger serious CVD events. An estimation of excess CVD mortality attributable to influenza has particular relevance in China where vaccination is low and CVD burden is high.

Methods This study analysed data at the population level (age ≥65 years) using linked aggregated data from administrative systems on CVD mortality, influenza surveillance and meteorological data during 2011 to 2018. Quasi-Poisson regression models were used to estimate the excess overall CVD, and separately for IHD, ischaemic stroke, haemorrhagic stroke mortality attributable to

Strengths and limitations of this study

► This population-based data linkage study estimated influenza-associated cardiovascular mortality in a setting where vaccination rates are low and cardiovascular disease (CVD) burden is high.

► Seasonality, time trends and ambient temperature were adjusted as potential cofounders.

► Time lags were applied to assess any delayed time interval between influenza activity and CVD deaths.

► Individual-level analysis can be considered if data are available.

► Season-varying factors such as lifestyle and physiological changes could still have contributed to residual confounding.

influenza, adjusting for influenza activity, time trend, seasonality and ambient temperature. Analyses were also undertaken for influenza subtypes (A(H1N1)09pdm, A(H3N2) and B viruses), and mortality risk with time lags of 1–5 weeks following influenza activity in the current week.

INTRODUCTION

Evidence is accumulating that influenza can trigger major cardiovascular disease (CVD) events, exacerbate underlying CVD and cause myocarditis and pericarditis. However, there remains uncertainty over the strength of associations, overall and for specific CVD conditions,[1–3] which is important for informing public health decisions over resource allocation for prevention and treatment. The CVD consequences of influenza[4–6] have received limited attention, and opportunities for vaccination and other prevention strategies have been poorly implemented. In particular, influenza vaccination covers only 2% of the Chinese population, compared with approximately 60% of those in many high-income countries.[7 8] Despite the WHO recommending

influenza vaccination in all high-risk people, such as the elderly and those with chronic conditions, rates appear to be declining worldwide.[9]

In China, the burden of CVD has a unique profile, with more people dying from stroke than ischaemic heart disease (IHD) and considerable higher rates of haemorrhagic stroke than in many other countries.[10] Yet, there are no data on the excess CVD mortality related to influenza.[11] In the past decade, the Beijing Center for Disease Control and Prevention (BJCDC) has established robust mortality and influenza surveillance systems for its residents, but rates of influenza vaccination remain low (see online supplemental file 1).[12 13] Herein, we present analysis of the relation of influenza and primary causes of CVD deaths using city-wide vital statistics and weekly influenza surveillance during 2011–2018.

METHODS
Study design and data sources
We undertook a population-level observational study, using aggregated mortality, population, influenza surveillance and meteorological data extracted from routinely-collected administrative data systems (figure 1). Cause-specific deaths were filtered by International Classification of Diseases (ICD-10) codes: all CVD (I00-I99), IHD (I20-I25), ischaemic stroke (I63), haemorrhagic stroke (I61, I62) between 3 January 2011 and 1 July 2018 through the Beijing Mortality Register and Surveillance System, a real-time internet-based system maintained by Beijing CDC that captures all deaths, both in and out of hospital. Underlying cause of death data were manually coded and verified by trained staff at every hospital or community health centre in Beijing.[13] Annual registered resident data by age group and sex between 2011 and 2018 were extracted from Beijing Statistics Yearbook (http://tjj.beijing.gov.cn/tjsj_31433/). Age-stratified and sex-stratified population from the sixth census in China in 2010 were used as the standard reference population. Weekly mortality data were retrieved from the mortality surveillance system for each week (from Monday to Sunday), and standardised by age and sex using data from Beijing Statistical Yearbook.

The Beijing influenza surveillance system was established in 2007 to allow influenza-like illness (ILI) and laboratory-confirmed influenza (ILI+) to be prospectively tracked across 153 general hospitals in Beijing.[12] Throat-swab specimens were tested using reverse-transcriptase polymerase chain reaction (RT-PCR) techniques at 23 sentinel hospitals in Beijing.[14–16] The results of testing are entered into the platform of Beijing CDC, ILI+/ILI, the proportion of positive specimens in throat-swab specimen tested ILI patients, were calculated for each week as an indicator for influenza activity.

Weekly highest mean temperature and lowest mean temperature data between Monday, 3 January 2011 and Sunday, 1 July 2018 were obtained from an online repository (http://www.tianqihoubao.com/lishi/). All the retrieved data were linked by the calendar time.
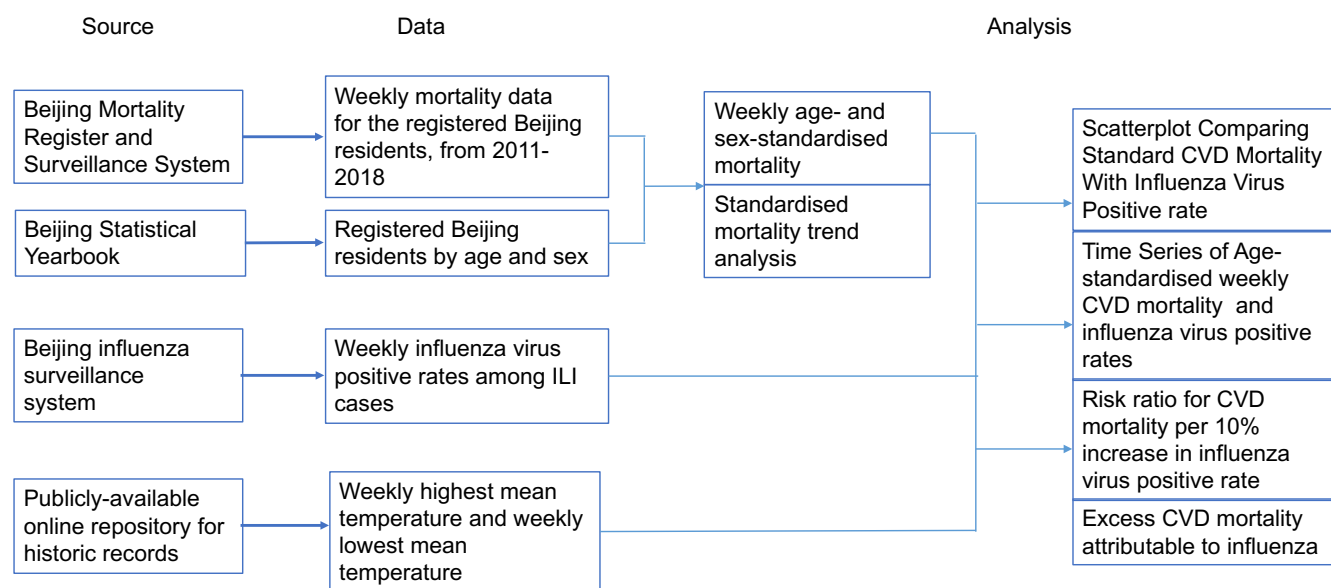

Figure 1 Data sources and analysis. CVD, cardiovascular disease; ILI, influenza-like illness.

Data analysis

Age-standardised and sex-standardised death rates were calculated from the 2010 census data of registered population (aged ≥65 years) in Beijing according to six age-groups (65–69, 70–74, 75–79, 80–84, 85–89 and 90+) using the following formula:

$$Death\ Number_{standardised} = \sum_{k=1}^{n} \left(\frac{D_{fk} \times P_{fk}}{p_{fk}} + \frac{D_{mk} \times P_{mk}}{p_{mk}} \right)$$

$$Death\ Rate_{standardised} = \frac{Death\ Number_{standardised}}{\sum_{k=1}^{n} (P_{fk} + P_{mk})} \times 100,000$$

where n is the number of age-groups. D_{fk} represents the actual number of deaths for women in the age-group k. D_{mk} represents the actual number of deaths for men in the age-group k. p_{fk} represents the woman population in the age-group k. p_{mk} represents the male population in the age-group k. P_{fk} represents the standard population of women in the age-group k. P_{mk} represents the standard population of men in the age-group k.

Mann-Kendall trend analysis was used to test the annual age-standardised and sex-standardised disease mortality rates during 2011–2018. Weekly age-standardised and sex-standardised CVD mortality rates were compared with weekly ILI+/ILI using Spearman correlation coefficient to determine the magnitude of any association. Quasi-Poisson regression modelling, which accounts for overdispersed variables when the variance in weekly deaths is greater than the mean,[17] was applied to associate weekly influenza activity with CVD mortality. The models included terms for influenza activity (ILI+/ILI), seasonality, time trends, and confounding variable ambient temperature. The models were fitted separately for weekly numbers of deaths from different causes between 2011 and 2018, as outlined below:

$$Y_t = \alpha/100,000 * exp(\beta_1[t]) + (\beta_2[t^2]) + (\beta_3[t^3] +$$
$$(\beta_4[sin((2t\pi/(365.25/7))] + \beta_5[2t\pi/(365.25/7)] +$$
$$\beta_6[(virus\ positive\ rate)_t] + \beta_7[identified\ confounder] + e_t$$

Where Y_t represents the age-standardised and sex-standardised weekly CVD death number; α is the offset term equal to the standard population size (≥65 years); β_1 accounts for any linear time trend, β_2 and β_3 account for nonlinear time trends; β_4 and β_5 account for seasonal changes in CVD mortality; β_6 is the coefficient associated with the weekly proportion of specimens tested positive for a sum of influenza A(H1N1)pdm09, A(H3N2) and B subtypes and β_7 is the coefficient of a confounder that is identified from potential factors (eg, highest or lowest mean temperature in a week) and e_t represents the error term.

We also applied 1- to 5-week lags on weekly influenza virus-positive rates in the regression model to account for any delayed time interval between influenza activity and CVD deaths. Negative binomial regression models were used as sensitivity analysis, separately for each disease outcome.

Excess mortality rates were estimated according to the difference between observed mortality and predicted mortality rates with the coefficient of influenza infection variable set as 0 in the fitted model.[18 19] The annual influenza season in northern hemisphere is defined as from the 27th week of the previous year to the 26th week of the current.[20] The quasi-Poisson regression model was also used to estimate the excess CVD mortality. Estimation of the annual number of excess CVD death was obtained as the sum of all positive weekly differences for each influenza season (ie, negative weekly differences were recoded to 0). Influenza-associated excess deaths were estimated separately for influenza A(H1N1)pdm09, A(H3N2) and B viruses.

Bootstrap resampling with 1000 resamples was to calculate 95% CIs for each estimated excess death number. All statistical analyses were performed using R, V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/).

Role of the funding source

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 shows that age-standardised and sex-standardised annual CVD (from 1545 to 1783 per 100 000 population, p=0.002) and IHD (from 742 to 938 per 100 000 population, p=0.002) mortality rates increased significantly during 2011–2018, while there were non-significant declines in ischaemic stroke (from 209 to 166 per 100 000 population, p=0.27) and haemorrhagic stroke (from 148 to 108 per 100 000 population, p=0.27) mortality rates. The median of influenza virus-positive rates ranged from 1.5% to 12.3%, with subtype A(H3N2) being the most frequent, followed by subtype B and subtype A(H1N1), respectively. ILI+ and ILI numbers by year are presented in the online supplemental file 1. The two lowest influenza years of 2011–2012 and 2013–2014, correlated with the two lowest age-standardised and sex-standardised CVD mortality rates over the study period. Age-standardised and sex-standardised mortality rates were generally higher than the crude rates, likely reflecting population ageing.

Overall crude CVD (r=0.69, p<0.001), IHD (r=0.67, p<0.001), ischaemic stroke (r=0.43, p<0.001) and haemorrhagic stroke (r=0.27, p<0.001) mortality rates were all significantly correlated with influenza activity (see online supplemental file 1). Influenza virus activity showed marked seasonality matching CVD mortality patterns. Figure 2 shows the overall trend for influenza activity to have regular annual peaks at the end and beginning of each year; disease mortality and influenza activity peaks overlapped and without any time-lag. After adjusting

Table 1 Cardiovascular diseases mortality rate (per 100 000 population age ≥65 years) and influenza virus-positive rate (%) in Beijing, China during 2011–2018

	Year						
	2011–2012	2012–2013	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018
Crude mortality							
CVD	1596.8	1620.4	1528.8	1540.8	1551.1	1559.4	1595.3
IHD	767.6	786.2	752.3	762.7	775.9	798.0	822.1
Ischaemic stroke	217.5	213.2	185.3	169.6	165.8	153.5	146.7
Haemorrhagic stroke	153.0	143.4	122.5	118.6	106.0	94.9	96.2
Age-standardised and sex-standardised mortality*							
CVD	1544.7	1634.0	1607.9	1690.4	1775.6	1783.0	1825.7
IHD	741.6	791.7	790.8	836.6	888.3	910.8	938.4
Ischaemic stroke	209.3	214.2	192.9	184.5	188.3	174.2	165.9
Haemorrhagic stroke	147.6	143.6	127.3	129.1	119.6	106.8	107.6
Influenza virus-positive rate, median (IQR)							
A(H1N1)pdm09	0.0 (0.0–0.0)	0.5 (0.0–7.3)	0.0 (0.0–2.2)	0.0 (0.0–0.0)	0.0 (0.0–3.5)	0.4 (0.0–5.0)	0.7 (0.0–9.1)
A(H3N2)	0.0 (0.0–1.5)	6.5 (1.1–14.5)	1. (0.4–5.9)	4.7 (1.2–12.0)	4.2 (1.7–9.7)	2.1 (0.3–12.1)	6.4 (1.1–8.7)
B	0.5 (0.0–9.5)	0.0 (0.0–0.0)	1.0 (0.0–7.0)	0.4 (0.0–11.2)	1.2 (0.0–17.3)	0.0 (0.0–0.3)	0.9 (0.3–9.8)
All Influenza	1.5 (0.0–18.3)	8.5 (3.3–17.1)	2.7 (0.5–23.4)	11.2 (4.9–29.8)	8.2 (3.6–28.0)	5.7 (1.0–25.1)	12.3 (3.3–29.5)

*Standard population from the sixth China Census in 2010.
CVD, cardiovascular disease; IHD, ischaemic heart disease.

for weekly temperature and study time, CVD, IHD and ischaemic mortality rates were all significantly associated with influenza virus activity (risk ratio (RR) and 95% CI: 1.02 (1.01, 1.02), 1.01 (1.00, 1.02) and 1.03 (1.02, 1.04), respectively, with every 10% increase in influenza virus-positive rate). This translated into an estimated RR of CVD, IHD and ischaemic stroke mortality of 1.08 (1.05, 1.11), 1.07 (1.03, 1.11), 1.17 (1.10, 1.24), respectively,
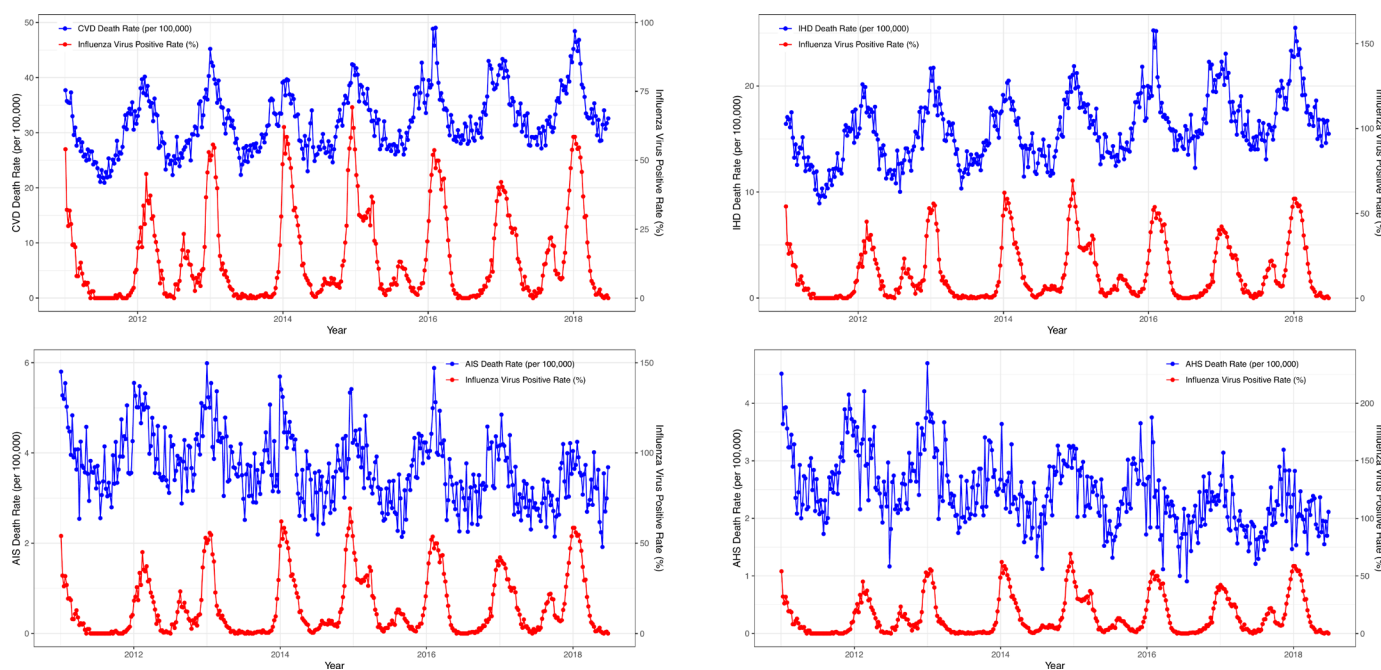

Figure 2 Time series of age-standardised and sex-standardised weekly cardiovascular mortality and weekly positive influenza virus rate in the population (≥65 years) in Beijing, China during 2011–2018. AHS, acute haemorrhagic stroke; AIS, acute ischaemic stroke; CVD, cardiovascular disease; IHD, ischaemic heart disease.
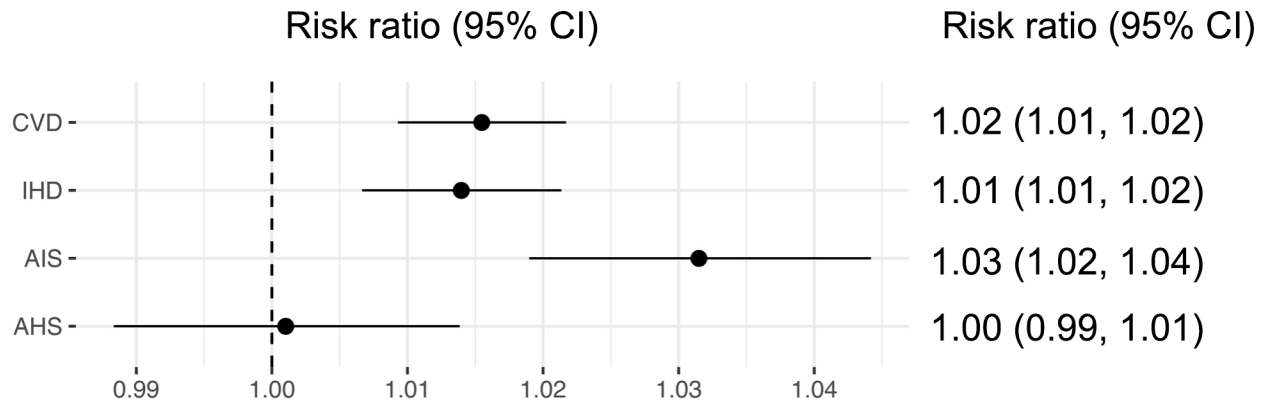
Risk ratio (95% CI)

	Risk ratio (95% CI)
CVD	1.02 (1.01, 1.02)
IHD	1.01 (1.01, 1.02)
AIS	1.03 (1.02, 1.04)
AHS	1.00 (0.99, 1.01)

Figure 3 Incidence risk ratio for cardiovascular mortality per 10% increase in influenza virus-positive rate in the population (≥65 years) in Beijing, China during 2011–2018. AHS, acute haemorrhagic stroke; AIS, acute ischaemic stroke; CVD, cardiovascular disease; IHD, ischaemic heart disease.

when influenza virus-positive rate increased to 50%. However, haemorrhagic stroke mortality was not associated with influenza virus activity (RR 1.0 (0.99, 1.01) with every 10% increase in influenza virus-positive rate) (figure 3). Sensitivity analysis using negative binomial models showed robust results (see online supplemental file 1).

Figure 4 shows that all subtypes of influenza virus were associated with increased CVD mortality: influenza A(H1N1)pdm09, RR 1.01 (95% CI 1.00, 1.02); influenza
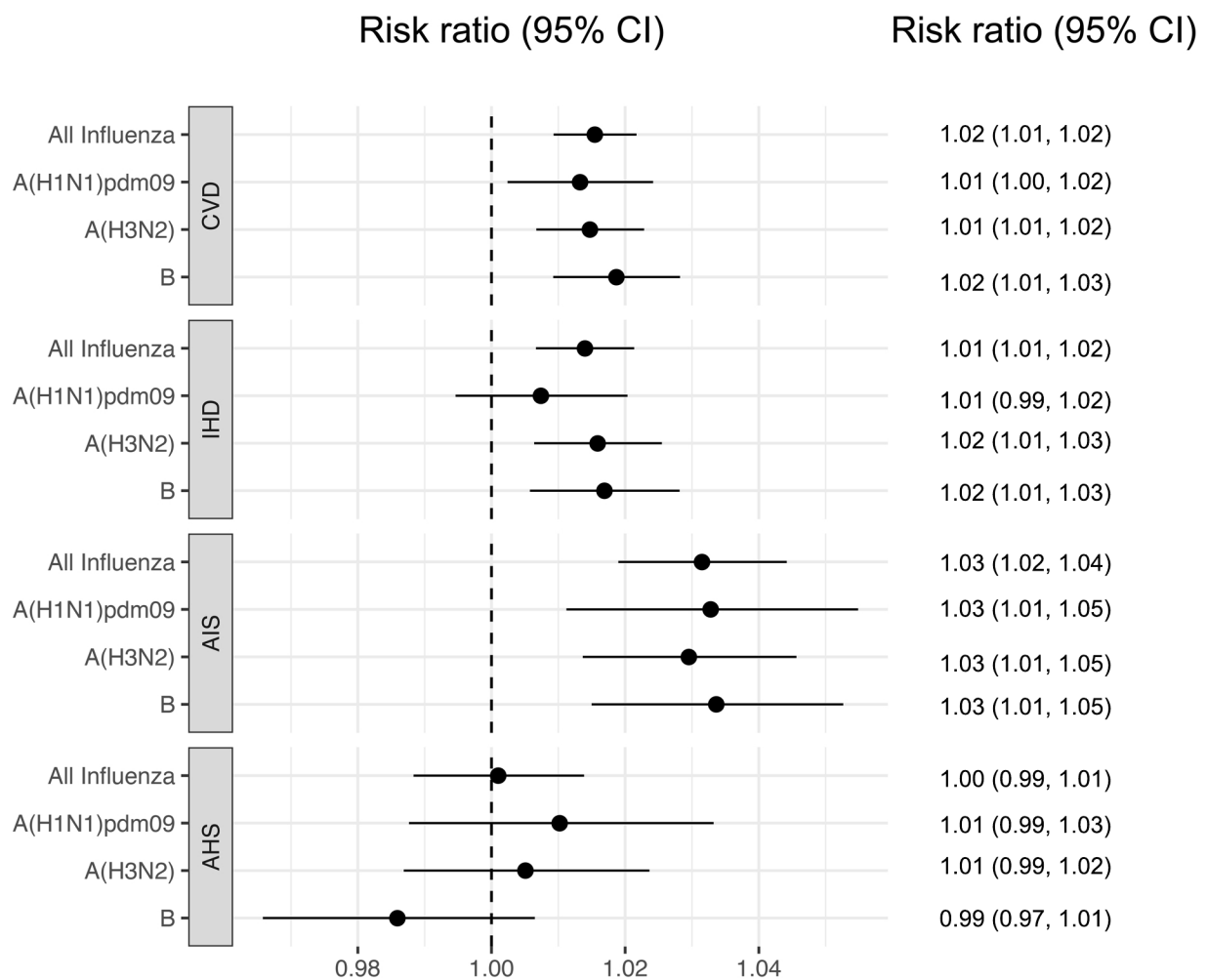

Figure 4 Incidence risk ratio for cardiovascular mortality per 10% increase in influenza virus-positive rate by influenza virus subtypes in the population (≥65 years) in Beijing, China during 2011–2018. AHS, acute haemorrhagic stroke; AIS, acute ischaemic stroke; CVD, cardiovascular disease; IHD, ischaemic heart disease.
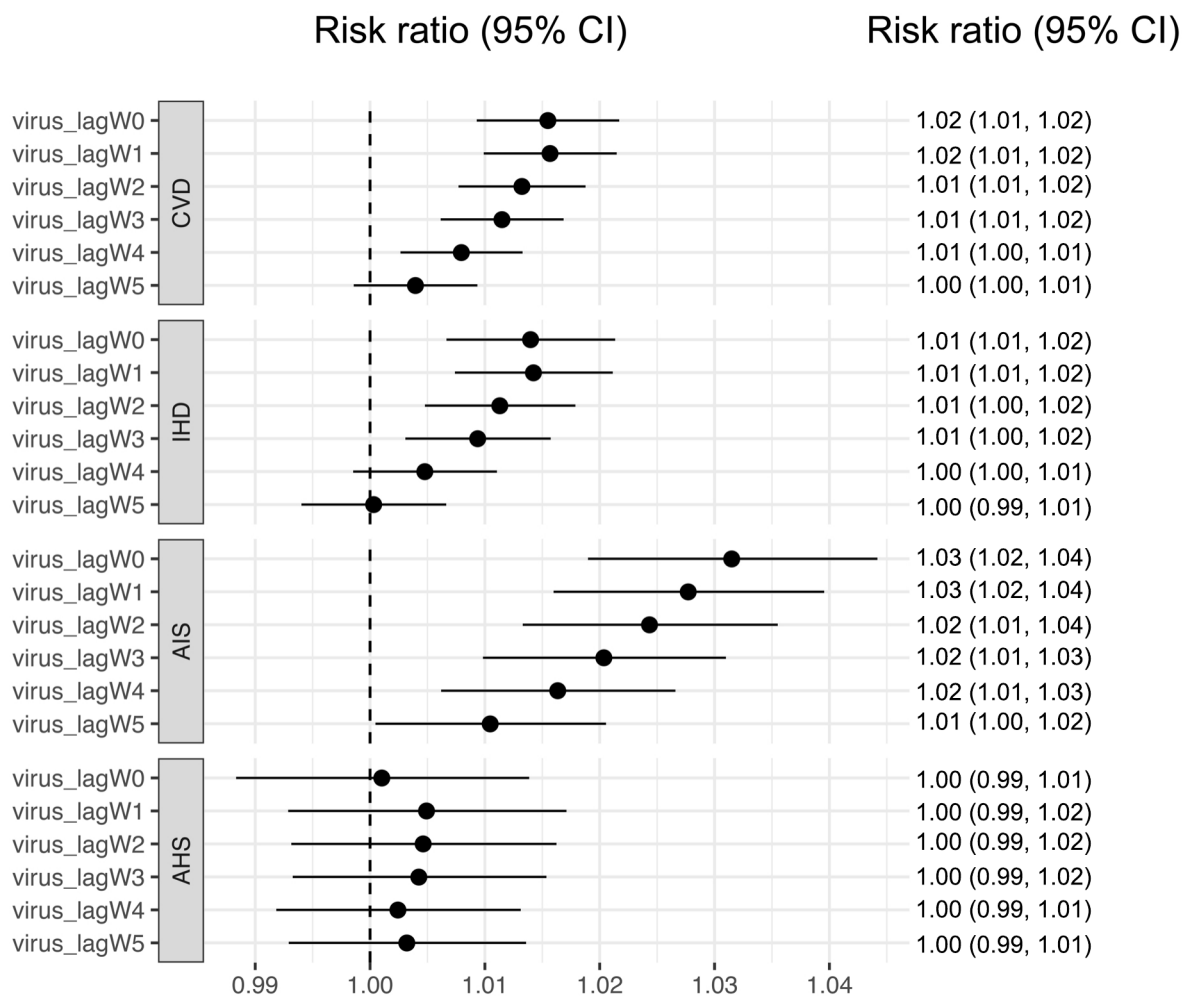
Figure 5 Incidence risk ratio for cardiovascular mortality per 10% increase in influenza virus-positive rate with time lags in the population (≥65 years) in Beijing, China during 2011–2018. AHS, acute haemorrhagic stroke; AIS, acute ischaemic stroke; CVD, cardiovascular disease; IHD, ischaemic heart disease.

A(H3N2), RR 1.01 (95% CI 1.01, 1.02) and influenza B, RR 1.02 (95% CI 1.01, 1.03). Similar associations were evident for ischaemic stroke mortality: 1.03 (1.01, 1.05), 1.03 (1.01, 1.05) and 1.03 (1.01, 1.05) for influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B, respectively. Only influenza A(H3N2) and influenza B were associated with increased IHD mortality (RR 1.02 (1.01, 1.03) and 1.02 (1.01, 1.03)). No subtype of influenza virus was associated with haemorrhagic stroke.

There was no apparent time lag for influenza virus activity and increased CVD, IHD and ischaemic stroke mortality; the strongest association during or within a week of activity. The association declined but remained statistically significant up to 4, 3 and 5 weeks after influenza activity with CVD, IHD and ischaemic stroke mortality (figure 5).

Annual excess CVD mortality attributable to influenza ranged from 54 to 96 per 100 000 population, which accounted for 3%–6% of the background CVD mortality without any influenza activity. This excess mortality was estimated to contribute between 916 and 1640 excess CVD deaths annually in those aged ≥65 years in Beijing. For CVD subcategories, IHD was associated with the highest excess mortality (27–49 per 100 000 per year), but ischaemic stroke showed the larger proportion of excess mortality over background mortality (8%–11%) (table 2).

DISCUSSION

Our population-based data linkage study has shown consistent association of increased respiratory specimens testing positive for influenza virus (ILI+) in ILI cases with increased CVD, IHD and ischaemic stroke mortality in Beijing in the last decade. When influenza virus activity increased such that ILI+/ILI equalled to 50%, we estimated the excess CVD, IHD and ischaemic stroke mortality increased by 8%, 7% and 17%, respectively, in those aged ≥65 years. The association had minimal temporal lag and there was no significant excess haemorrhagic stroke mortality with influenza virus activity. These findings were consistent across different subtypes (A(H1N1)pdm09, A(H3N2) and B) of influenza infection, except A(H1N1)pdm09 was not associated with IHD mortality.

Our study provides important findings that differ from previous reports. First, the association of increased CVD mortality risks and influenza lagged for several weeks.

Table 2 Influenza-associated excess cardiovascular mortality in the population (≥65 years) Beijing, China during 2011–2018

	Year						
	2011–2012	**2012–2013**	**2013–2014**	**2014–2015**	**2015–2016**	**2016–2017**	**2017–2018**
CVD							
Rate*	78.1 (45.3, 113.3)	96.0 (61.8, 136.8)	53.6 (31.0, 82.5)	72.8 (41.9, 109.4)	81.5 (43.2, 130.1)	75.2 (46.4, 106.1)	71.3 (41.6, 111.4)
%	5.1 (2.9, 7.3)	5.9 (3.8, 8.4)	3.3 (1.9, 5.1)	4.3 (2.5, 6.5)	4.6 (2.4, 7.3)	4.2 (2.6, 6.0)	3.9 (2.3, 6.1)
n	1333.8 (774.3, 1936.6)	1640.0 (1056.2, 2337.2)	915.8 (529.9, 1409.0)	1243.4 (716.7, 1869.3)	1392.9 (738.2, 2223.9)	1284.4 (793.1, 1812.2)	1217.9 (710.0, 1903.7)
IHD							
Rate	41.7 (24.5, 60.9)	49.3 (31.9, 71.8)	26.5 (14.8, 42.1)	40.6 (22.6, 62.4)	40.5 (21.3, 65.7)	46.2 (29.9, 63.9)	39.6 (22.7, 59.4)
%	5.6 (3.3, 8.2)	6.2 (4.0, 9.1)	3.4 (1.9, 5.3)	4.9 (2.7, 7.5)	4.6 (2.4, 7.4)	5.1 (3.3, 7.0)	4.2 (2.4, 6.3)
n	712.4 (418.3, 1040.2)	842.0 (545.8, 1227.1)	452.5 (252.4, 719.3)	694.1 (386.0, 1066.2)	692.8 (363.8, 1122.7)	790.0 (510.1, 1091.8)	676.9 (387.7, 1015.7)
Ischaemic stroke							
Rate	16.2 (9.6, 23.4)	22.4 (14.8, 30.6)	18.0 (11.2, 26.5)	14.2 (8.0, 21.4)	20.0 (11.9, 29.3)	15.7 (9.7, 21.7)	13.6 (8.5, 19.8)
%	7.7 (4.6, 11.2)	10.5 (6.9, 14.3)	9.3 (5.8, 13.8)	7.7 (4.4, 11.6)	10.6 (6.3, 15.6)	9.0 (5.5, 12.5)	8.2 (5.1, 12.0)
n	276.5 (163.7, 399.2)	383.0 (253.1, 522.4)	308.1 (191.1, 453.5)	243.2 (137.2, 366.0)	340.9 (202.5, 501.4)	267.4 (164.9, 371.3)	231.6 (144.6, 338.7)

*Per 100 000 (≥65 years).
CVD, cardiovascular disease; IHD, ischaemic heart disease.

Second, the fatal consequence of influenza happens within a short time window, which is contrary to some but not all studies.[21 22] This could reflect our focus on older adults, those at highest risk of CVD, rather than broader population. As the strength of association for ischaemic stroke mortality and influenza was the strongest of all the CVD categories, it is possible that predisposing factors in the vascular tree or susceptibility to respiratory infection were higher in our study population compared with others.

Few studies have assessed the association of infection and haemorrhagic stroke. One large prospective study showed no such association of influenza and haemorrhagic stroke,[23] and trials assessing the efficacy of influenza vaccination have failed to show significant benefits for haemorrhagic stroke.[24 25] The large sample size of our study allowed us to optimise statistical power to examine associations of influenza activity and individual CVD subtypes including haemorrhagic stroke, with adjustment for various factors, such as daily temperature, seasonality and time. The stronger association of influenza with ischaemic CVD rather than haemorrhagic stroke deaths supports studies indicating that inflammation destabilises vulnerable atherosclerotic plaques and enhances circulating clotting factors.[26 27]

Our finding of no significant association of A(H1N1) pdm09 and IHD mortality is consistent with other data suggesting this strain is less likely to infect the elderly with existing immunity.[28] Thus, the adverse consequence of A(H1N1)pdm09 infection could be mitigated, with few

deaths reported from this virus in China.[29] Conversely, A(H1N1)pdm09 was significantly associated with CVD and ischaemic stroke mortality, although the explanations are less clear. Host responses may differ across various circulating strains of the virus subtypes, with influenza-associated death rates highest when influenza B virus being dominant in China, while the highest death rates are associated with A(H3N2) activity in the USA.[20 30] Both A(H3N2) and influenza B had comparable strengths of association for CVD, IHD and ischaemic stroke mortality, raising complexities over the allocation of resources based on circulating strains of influenza activity.

There are many studies suggesting that influenza vaccines protect against CVD, both primary and secondary prevention. However, most of them have employed different observational designs, which are prone to many biases.[31–34] The question of whether influenza vaccination can prevent CVD mortality can only be answered in randomised trials, although as challenging as they are in accumulating adequate outcome events related to plausibly modest treatment effects.[35 36] Yet, such studies are warranted given the need for evidence-based clinical and health policy recommendations over the coverage of influenza vaccination.

We recognise our study has several limitations. Most importantly, we lacked vaccination and other data at the individual level, and thus were unable to estimate the contribution of vaccination to the excess mortality. Furthermore, although temperature, seasonality and study time were accounted for in our analyses, other

season-varying factors such as lifestyle and physiological changes, as well as other possible time-varying variables, could still have contributed to residual confounding. Although the large population of Beijing lies in the north of China, our results may not be generalisable to other areas, particularly those in the south of the country where the climate tends to be subtropical. Finally, despite BJCDC having established a robust mortality and influenza surveillance system, there is still the potential for misclassification and under-reporting of deaths leading to an underestimation of influenza-associated excess mortality.

In summary, our data linkage study extends earlier findings in showing a clinically important association of influenza and CVD mortality, overall and across specific subtypes and provides support for the broad population-wide benefits of vaccination as a simple and safe approach to improving outcomes for those at high risk of CVD events in the community.

Author affiliations
[1]Heart Health Research Center, Beijing, China
[2]Ping An Healthcare Technology, Beijing, China
[3]Beijing Center for Disease Prevention and Control, Beijing Research Center for Preventive Medicine, Beijing, China
[4]Beijing Anzhen Hospital, Capital Medical University, National Clinical Research Centre for Cardiovascular Diseases, Beijing, China
[5]The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[6]Ping An Health Cloud Company Limited, Beijing, China
[7]Ping An International Smart City Technology Co., Ltd, Beijing, China
[8]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[9]Biosecurity Research Program, Kirby Institute, The University of New South Wales, Sudney, New South Wales, Australia
[10]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[11]The George Institute China at Peking University Health Science Center, Beijing, China

ORCID iDs
Rong Liu http://orcid.org/0000-0002-8609-5463
Chao Jiang http://orcid.org/0000-0003-1138-7960

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