Age-dependent and sex-dependent differences in mortality from influenza-associated cardiovascular diseases among older adults in Shanghai, China: a population-based study

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ABSTRACT

Objectives Influenza epidemics lead to substantial morbidity and mortality among older adults. This study aimed to analyse and assess the age-specific and sex-specific differences in mortality rates for cardiovascular disease (CVD) associated with influenza in older adults.

Design We obtained weekly data on mortality from CVD in adults ≥60 years, categorised into five age groups. We used a quasi-Poisson model and adjusted for long-term and seasonal trends and absolute humidity as confounding factors. The male-to-female ratio (M/F ratio) was an indicator for assessing sex differences.

Setting Shanghai, China.

Participant We analysed 440 107 CVD deaths in adults aged ≥60 years, including 44 913 cases positive for influenza and 1 927 487 outpatient visits for influenza-like illness from 2010 to 2019.

Main outcome measures Age-specific and sex-specific excess CVD mortality rates in older adults for various combinations of CVDs and influenza viruses.

Results Variations were observed in the excess mortality from CVD, ischaemic heart disease (IHD) and stroke depending on the influenza types/subtypes in different age and sex categories. The ≥85 years group had the highest excess mortality rates per 100 000 persons for CVD, IHD and stroke, while influenza A (H3N2) virus accounted for the highest mortality from CVD, IHD and stroke in people aged ≥65 years. Older men had a significantly lower influenza-associated IHD mortality rate than women, with an M/F ratio of 0.77 (p<0.05).

Conclusions Excess mortality rates for CVDs associated with influenza increased with age in older adults. The risk for influenza-associated IHD mortality was significantly higher in older women than men. Our findings will help implement targeted health strategies, including the promotion of influenza vaccination and early therapeutic intervention for the older population with CVD, to curb the influenza burden effectively.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This population-based study is the first to estimate the mortality rates for cardiovascular diseases (CVDs) associated with influenza types/subtypes based on age and sex in an ageing Chinese population.
⇒ Outpatient data from 30 sentinel hospitals and laboratory test data were used to quantify influenza activity.
⇒ The model adjusted long-term and seasonal trends and absolute humidity as confounding factors.
⇒ The male-to-female ratio was applied to assess sex differences in mortality rates from CVDs associated with influenza in older adults.
⇒ Viruses cocirculating with influenza, such as respiratory syncytial virus, were not included in the surveillance system, which may potentially have resulted in biased estimates.

INTRODUCTION

Influenza epidemics result in considerable morbidity and mortality in older adults. Annually, approximately 90% of influenza-attributable deaths occur in adults aged ≥65 years.1 Older adults with ageing immune systems are at high risk for influenza and are susceptible to complications, especially cardiovascular diseases (CVDs).2 3 Increasing evidence suggests a link between influenza and CVDs, including ischaemic heart disease (IHD) and stroke.5 6 Studies have found that influenza infection triggers autoimmunity inflammation and coagulation changes, leading to myocarditis and acute myocardial infarction, which increases hospitalisation and CVD-related mortality.7 8 Estimates of mortality from influenza-associated CVD in older adults are extremely important for developing targeted influenza prevention...
and control strategies and optimising the allocation of medical resources.

Vaccination is the most effective protection against infection and related complications in older adults,\(^6\)\(^{-10}\) reducing the risk of influenza-associated hospitalisations by almost 37%\(^{11}\) and the risk of deaths by approximately 70%.\(^{12}\) Both the WHO and the Chinese Center for Disease Control and Prevention have recommended older adults be given priority for influenza vaccination in the annual influenza prevention strategies.\(^{13}\)\(^{14}\) However, the annual vaccination coverage remains low among older adults in Shanghai and is even lower in areas with subsidised vaccine programmes.\(^{15}\) Although older adults are at high risk for influenza infection, most studies did not categorise them into more detailed groups, making it challenging to identify the more accurate characteristics of such high-risk groups. At the same time, although sex factors (such as hormones) appear to influence an individual’s susceptibility to infectious diseases,\(^{16}\)\(^{17}\) there is limited evidence on the role of sex in the excess mortality related to influenza in older adults.\(^{18}\)

Accurate estimates of excess mortality from influenza-related CVD in older adults could help identify the high-risk groups of patients, implement targeted measures such as government-subsidised vaccination programmes and reduce the disease burden. Our study aimed to assess the age-specific and sex-specific mortality burden from influenza-related CVD in older adults in Shanghai from 2010 to 2019.

**METHODS**

**Mortality and population data**

We collected data on the annual population of individuals aged ≥60 years and the weekly mortality rates in this group from 2010 to 2019 from the Shanghai Center for Disease Control and Prevention (SCDC). The death reports are subject to monthly quality control by the SCDC staff to ensure they are complete and report the exact causes of death (CODs). In the population-based death registration and surveillance system, the CODs are coded by international standards (the 10th revision of the International Classification of Diseases (ICD-10)). We extracted mortality data on CVD (ICD-10: I00-I99) in older adults, including IHD (ICD-10: I20-I25) and stroke (ICD-10: I60-I69). The data were stratified based on age into six groups (60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years and ≥85 years). The older population in this study was restricted to residents with registered permanent residence in Shanghai.

**Influenza surveillance and virological data**

There are 30 sentinel hospitals in Shanghai’s influenza surveillance system and all participate in national surveillance networking. These hospitals report cases of influenza-like illness (ILI, body temperature ≥38°C with cough or sore throat) weekly. Nineteen of these hospitals are also responsible for delivering samples from patients with ILI to network laboratories to identify the type/subtype of influenza virus. The influenza surveillance process in Shanghai was introduced in a previous study.\(^9\) We obtained unpublished influenza surveillance and virological data from the Department of Acute Infectious Disease Prevention and Control of SCDC, including the weekly rates of outpatient visits for ILI in sentinel hospitals, the weekly numbers of total laboratory specimens and those positive for influenza A (H1N1), A (H3N2) and B. Moreover, the daily average temperature and relative humidity were downloaded from the China Meteorological Data Service Center (http://data.cma.cn/en).

**Statistical analysis**

We analysed the weekly numbers of three underlying CODs (CVD, IHD and stroke) for each age group using a quasi-Poisson regression model, which can handle overdispersion mortality data. The products of weekly ILI outpatient consultation rates and weekly positivity rates for influenza A (H1N1), influenza A (H3N2) and influenza B were included as explanatory variables in our model. The long-term and seasonal trends and the absolute humidity were adjusted as confounding factors. Based on a previous study that demonstrated the effect of absolute humidity on influenza transmission,\(^20\) we selected absolute humidity as a confounding factor. The absolute humidity in Shanghai was highly correlated with temperature (r=0.9584, p<0.0001). Details are as follows:

\[
Y_{i,t} \sim \text{quasiPoisson} (\mu_{i,t}, \phi_i)
\]

\[
\log (\mu_{i,t}) = \beta_0 + \beta_1 (ILI \times LABH)_{i,t-k} + \beta_2 (ILI \times LABB)_{i,t-k} + \beta_3 (ILI)_{i,t-k} + \beta_4 (LABH)_{i,t-k} + \beta_5 (LABB)_{i,t-k} + \beta_6 (\text{AGE} \times LABH)_{i,t-k} + \beta_7 (\text{AGE} \times LABB)_{i,t-k} + \epsilon_i (t, df = 5 \times 10) + \epsilon (\text{Hum}, df = 5).
\]

\(Y_{i,t}\) is the number of deaths for the specific disease category in age group \(i\) for week \(t\) and it follows the Poisson distribution (mean \(\mu_{i,t}\) and overdispersion parameter \(\phi_i\) ). The operator \(k\) represents the lag between infection and death, typically ranging from 1 to 3 weeks. \(ILI \times LAB\) represents proxy variables for the activity of influenza viruses, where \(ILI\) refers to the number of influenza-like illness cases per 1000 outpatient consultations and LAB refers to the proportion of lab-confirmed positive cases of influenza A (H1N1), influenza A (H3N2) and influenza B virus. Natural cubic spline functions \(s(t)\) and \(s(\text{AHum})\) denote the long-term and seasonal trends and the absolute humidity, two potential confounding factors of the model, and \(df\) denotes the degree of freedom of the function. The lag week for each model was selected based on the minimised Generalised Cross-Validation Score (online supplemental table S1). Autocorrelation and partial autocorrelation graphs were drawn for the residual of the optimal model to test its autocorrelation. No multicollinearity was detected among the variables (the absolute value of Spearman correlation coefficients<0.55).

The difference between the number of deaths fitted by the model and the baseline (influenza proxy variable in
the model set to 0) was defined as excess deaths associated with influenza. To assess the role of sex, we calculated the ratio of excess mortality rates between the male and female populations for a given subgroup, defined as the relative rate ratio (M/F ratio). The negative estimate of excess mortality was adjusted to 0, and the relative rate ratio for the negative estimate was not calculated. The 95% CI for excess deaths and M/F ratio was calculated using the bootstrap and delta methods, respectively. We set the corresponding population size as the denominator to calculate excess mortality and applied R V.3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) for data analysis.

**Patient and public involvement**

Patients and the public were not involved in this study’s design, conduct, reporting or dissemination plans.

**RESULTS**

**Descriptive analysis of deaths and influenza surveillance**

In older adults, deaths from CVD, IHD and stroke occurred mainly in winter, consistent with peak influenza activity (figure 1). Table 1 shows the influenza surveillance data. During the study period (2010–2019), there were 440,107 deaths from CVD among adults ≥60 years, including 180,551 and 220,877 deaths from IHD and stroke, respectively. Between 2010 and 2019, 175,754 specimens from patients with ILI were sent to the network laboratories for testing and an average of 25.5% (15.56% to 35.16%) of them tested positive for influenza. Influenza A (H1N1), A (H3N2) and B viruses accounted for 21.71%, 42.91% and 35.38% positivity, respectively (table 1). During the study period, the annual ILI consultation rates ranged from 13 to 26 per 1000 outpatient visits in the sentinel hospitals (table 1). Influenza A (H3N2) was the predominant infectious agent in Shanghai from 2012 to 2017 (figure 1), while influenza B was the predominant virus in 2010, 2011 and 2019, generally peaking in winter (figure 1).

![Figure 1](http://bmjopen.bmj.com/)

**Table 1** Annual specimens tested, number of specimens positive for influenza and ILI rate in Shanghai, China, 2010–2019

| Year | Specimens tested | Number (%) of specimens positive for influenza | Number (%) by type/subtypes | ILI rate (per 1000 outpatient* visits) |
|------|------------------|-----------------------------------------------|----------------------------|---------------------------------------|
|      |                  |                                               | A (H1N1) | A (H3N2) | B                               |                                |
| 2010 | 13313            | 3343 (25.11)                                  | 564 (16.87) | 864 (25.85) | 1915 (57.28) | 14                         |
| 2011 | 10582            | 2214 (20.92)                                  | 847 (38.26) | 82 (3.70)   | 1285 (58.04) | 13                         |
| 2012 | 12437            | 4373 (35.16)                                  | 6 (0.14)   | 2414 (55.20) | 1953 (44.66) | 16                         |
| 2013 | 15765            | 2453 (15.56)                                  | 530 (21.61) | 1842 (75.09) | 81 (3.30)    | 17                         |
| 2014 | 20033            | 5449 (27.20)                                  | 1001 (18.37) | 2846 (52.23) | 1602 (29.40) | 18                         |
| 2015 | 21143            | 6174 (29.20)                                  | 968 (15.68) | 2913 (47.18) | 2293 (37.14) | 19                         |
| 2016 | 20240            | 4894 (24.18)                                  | 1447 (29.57) | 2194 (44.83) | 1253 (25.60) | 17                         |
| 2017 | 21643            | 5956 (27.52)                                  | 526 (8.83)   | 3963 (66.54) | 1467 (24.63) | 19                         |
| 2018 | 19835            | 3652 (18.41)                                  | 1821 (49.86) | 306 (8.38)   | 1525 (41.76) | 20                         |
| 2019 | 20763            | 6405 (30.85)                                  | 2040 (31.85) | 1849 (28.87) | 2516 (39.28) | 26                         |
| Total| 175754           | 44913 (25.55)                                 | 9750 (21.71) | 19273 (42.91) | 15890 (35.38) | 18                         |

*Outpatients in sentinel hospitals.
ILI, influenza-like illness.
Figure 2  Model fitting (solid and dashed lines) of the weekly mortality rate (per 100,000 persons) for cardiovascular diseases and estimates of the weekly excess deaths in different age groups, Shanghai, 2010–2019. (A) 60–64 years of age. (B) 65–69 years of age. (C) 70–74 years of age. (D) 75–79 years of age. (E) 80–85 years of age. (F) 80 years of age and older.
Table 2: Annual age-specific influenza-associated excess mortality rates (per 100 000 persons) for cardiovascular disease in older adults in Shanghai, China, 2010–2019

| Age group | ER (95% CI) |
|-----------|-------------|
| 60–64     | 2.42 (0.03 to 4.61) |
| 65–69     | 1.00 (-2.65 to 4.14) |
| 70–74     | 0.68 (-1.08 to 2.25) |
| 75–79     | 2.89 (2.05 to 6.80) |
| 80–84     | 2.45 (2.45 to 8.55) |
| 85+       | 2.53 (0.59 to 4.15) |

DISCUSSION

To the best of our knowledge, this study is the first to explore the excess mortality from CVD associated with influenza type/subtypes based on age and sex in old adults. During the study period, 4.28% (18 829) of all deaths from CVD were associated with influenza and 53.76% of them occurred in people older than 85 years. Our estimate of influenza-associated CVD and IHD mortality rates in older adults was higher than the previous findings from Portugal and Beijing, which might be due to differences in the modelling approaches and study periods. Based on our model, in older adults, influenza-associated excess mortality rates for CVD, IHD and stroke increased with age. The excess rate of influenza-associated IHD deaths was significantly higher in older women compared with older men (relative rate ratio < 1) (figure 3). The relative rate ratios for the 65–69, 70–74, 75–79 and 80–84 years age groups were all > 1 (table 3), indicating that influenza-related excess mortality was higher in older men than older women (online supplemental tables S4 and S5). In the 65–69 years group for influenza A (H3N2), the relative rate ratios related to CVD, IHD and stroke were 1.19, 0.44 and 6.21, respectively (table 3). Influenza A (H1N1) showed a similar sex pattern in the 75–79 years group, while influenza B virus showed the opposite pattern in the 60–64 years group. Among adults ≥ 85 years, men had higher mortality from stroke associated with influenza A (H1N1) and CVD associated with influenza B. The difference in influenza-associated excess mortality between the sexes in almost all combinations was not significant (the 95% CI contains 1), except for excess CVD mortality in the 80–84 years group with an M/F ratio of 1.7 (95% CI: −1.1 to 2.3) (table 3).
# Table 3  Excess mortality rates (per 100,000 persons) and relative rate ratio (M/F ratio) for cardiovascular diseases associated with influenza type/subtypes by age in older adults in Shanghai, China, 2010–2019

| Influenza type/subtypes | Underlying cause | 60–64 years | 65–69 years | 70–74 years | 75–79 years | 80–84 years | 85 years |
|-------------------------|-----------------|-------------|-------------|-------------|-------------|-------------|----------|
| **Influenza-associated excess mortality** |
| Influenza | CVD | 2.78 (0.40–4.77) | 6.81 (2.15–11.39) | 24.41 (16.06–31.97) | 45.71 (34.27–56.96) | 122.12 (98.97–144.91) | 341.91 (290.85–394.62) |
| | IHD | 1.79 (0.34–3.06) | 3.59 (1.33–5.63) | 8.69 (4.15–13.1) | 17.42 (10.74–24.8) | 65.90 (52.94–78.60) | 193.06 (165.42–222.97) |
| | Stroke | 0.56 (–1.24–2.38) | 2.24 (–1.53–5.46) | 12.09 (6.12–17.86) | 24.59 (16.01–32.68) | 47.78 (32.64–63.30) | 110.05 (78.13–139.53) |
| A (H1N1) | CVD | 2.13 (1.08–3.07) | 1.84 (–0.10–3.73) | 7.41 (3.87–11.17) | 13.07 (8.30–17.84) | 36.68 (26.76–46.94) | 63.48 (40.68–87.84) |
| | IHD | 0.66 (0.10–1.21) | 0.49 (–0.59–1.42) | 2.11 (0.05–3.89) | 6.90 (4.07–9.85) | 18.11 (12.51–23.85) | 32.93 (18.70–46.78) |
| | Stroke | 1.04 (0.31–1.76) | 1.69 (0.36–2.90) | 3.44 (0.66–5.53) | 6.50 (3.23–9.88) | 11.73 (4.98–18.01) | 21.55 (7.94–34.62) |
| A (H3N2) | CVD | 0.00 (0.00–0.00) | 6.31 (3.52–9.08) | 12.09 (6.52–17.75) | 19.37 (11.86–27.02) | 49.55 (32.73–64.84) | 193.53 (156.58–228.68) |
| | IHD | 0.16 (–0.82–1.13) | 1.75 (0.17–3.17) | 4.09 (1.07–6.74) | 5.48 (0.69–10.08) | 29.50 (20.63–37.88) | 99.70 (79.66–122.12) |
| | Stroke | 0.00 (0.00–0.00) | 3.00 (0.73–5.12) | 6.87 (3.00–10.40) | 9.61 (3.93–15.44) | 21.76 (11.54–32.30) | 72.56 (50.41–93.51) |
| B | CVD | 1.03 (–0.72–2.78) | 0.00 (0.00–0.00) | 5.35 (–0.95–11.52) | 13.96 (5.53–22.73) | 38.04 (19.68–55.56) | 90.06 (49.18–129.87) |
| | IHD | 1.00 (0.05–1.97) | 1.39 (–0.22–2.98) | 2.65 (–0.95–5.64) | 5.35 (–0.12–10.51) | 19.87 (9.45–29.11) | 63.96 (41.93–83.82) |
| | Stroke | 0.42 (–0.86–1.65) | 1.95 (2.83–6.32) | 8.82 (2.26–15.12) | 14.85 (2.83–26.23) | 17.06 (–7.56–39.92) |  |
| **M/F ratio** |
| Influenza | CVD | 0.40 (–0.82–1.63) | 1.99 (–0.63–4.61) | 2.84 (0.67–5.01) | 1.50 (0.77–2.22) | 1.70 (1.10–2.30) | 1.07 (0.79–1.36) |
| | IHD | 1.01 (–0.44–2.47) | 4.69 (–6.31–15.69) | 1.76 (–0.02–3.55) | 1.22 (0.26–2.17) | 1.36 (0.85–1.87) | 0.89 (0.64–1.15) |
| | Stroke | 0.07 (–1.64–1.78) | – | 3.53 (–0.87–7.92) | 1.61 (0.49–2.74) | 1.93 (0.71–3.15) | 1.27 (0.66–1.88) |
| A (H1N1) | CVD | 1.58 (0.36–2.80) | 2.91 (–3.94–9.75) | 1.97 (0.25–3.69) | 1.77 (0.54–3.01) | 2.11 (0.99–3.22) | 1.05 (0.30–1.81) |
| | IHD | 2.50 (–6.46–11.46) | – | 2.61 (–3.29–8.51) | 0.80 (0.08–1.52) | 2.11 (0.79–3.42) | 1.13 (0.21–2.05) |
| | Stroke | 1.48 (–0.03–2.98) | 2.00 (–1.79–5.79) | 1.28 (–0.32–2.88) | 3.19 (–1.27–7.66) | 2.44 (–0.02–4.89) | 0.44 (–0.26–1.15) |
| A (H3N2) | CVD | – | 1.19 (0.05–2.33) | 4.92 (–2.42–12.24) | 1.40 (0.35–2.44) | 1.42 (0.67–2.17) | 1.14 (0.77–1.51) |
| | IHD | 0.20 (–2.28–2.69) | 0.44 (–0.70–1.58) | 1.88 (–0.68–4.44) | 1.40 (–0.29–3.09) | 1.07 (0.46–1.67) | 0.98 (0.62–1.34) |
| | Stroke | – | 6.21 (–14.69–27.1) | 9.06 (–21.89–40.02) | 1.18 (–0.17–2.52) | 2.17 (0.02–4.32) | 1.67 (0.65–2.69) |
| B | CVD | 0.81 (2.09–3.72) | – | 1.84 (–2.01–5.69) | 1.42 (–0.31–3.16) | 1.87 (–0.08–3.82) | 0.96 (0.21–1.70) |
| | IHD | 1.30 (–0.97–3.57) | – | 1.25 (–1.70–4.19) | 1.98 (–4.41–8.37) | 1.35 (0.07–2.63) | 0.68 (0.21–1.16) |
| | Stroke | 0.56 (–1.43–2.54) | – | 3.63 (–12.67–19.93) | 1.46 (–0.62–3.54) | 1.36 (–0.64–3.36) | 1.41 (–0.74–3.57) |

CVD, cardiovascular disease; IHD, ischaemic heart disease; M/F ratio, male-to-female ratio.
the highest excess mortality rate was in the ≥85 years group. A study from Singapore found that the burden of influenza on CVD increased with age and was significantly associated with excess hospitalisations for CVD, mainly in people ≥80 years old. The ageing population in Shanghai is on the rise, which is an important factor contributing to the persistently high influenza-associated mortality. In 2019, about 4.7 million adults ≥60 years were registered in Shanghai, an increase of 48.51% compared with 2010, accounting for 32.05% of the total population. CVD had been the leading COD in older adults during this period. In the older adults in Shanghai, the burden of influenza on CVD has exceeded its burden on respiratory diseases. 

Existing evidence indicates that influenza vaccination is associated with a reduced risk of cardiovascular events in older patients. Although the guidelines for influenza vaccination in China recommend that adults ≥60 years be given priority, the coverage in this population is approximately 4% and only 2.28% in Shanghai. This low coverage rate is probably because the individuals have to bear the cost of influenza vaccination. Except for a few developed regions such as Beijing and Shenzhen, most of China does not have a government-funded influenza vaccination programme for older adults. However, a recent study suggested that a government fully funded vaccination programme for older adults in China could be cost-effective. Adopting a free vaccination policy for older adults using government revenue could help promote the influenza vaccination rate in Shanghai. Since Beijing introduced free vaccines for older adults in 2007, the vaccination rate in this group has increased to 38.7% in 2012. As per China’s seventh census in 2020, 23.38% of Shanghai’s total population was ≥60 years, an increase of 8.31% from 2010. Therefore, our findings have important implications for encouraging targeted interventions in older adults, such as promoting influenza vaccinations, providing free vaccines for older adults with CVD and providing timely treatment once influenza-like symptoms are detected. The treatment should comply with the guidelines for using antiviral drugs to mitigate the mortality burden of influenza in Shanghai. 

We observed differences between sexes in the influenza-associated excess mortality for the different CVDs and influenza virus combinations. Overall, in several age groups, the influenza-associated excess mortality rates for CVD were higher in men than women. Interestingly, for the older population, we found the risk of influenza-associated IHD death was significantly higher (0.77 times) in men than women. Influenza A (H3N2) contributed the most to the difference in mortality rates between the sexes. Although the association between IHD and influenza has been validated, only a few studies have included sex analysis. Sex differences in IHD incidence might result from a hormone imbalance in older women. Increased postmenopausal obesity and hypertension in women are additional risk factors for IHD. At the same time, changes in oestrogen levels trigger dyslipidaemia, increasing overall cholesterol and decreasing high-density lipoprotein (HDL) cholesterol in women≥50 years. These changes double the risk of developing IHD in women compared with men.

Figure 3 Excess mortality rates for cardiovascular diseases with different influenza types/subtypes and relative rate ratio (M/F ratio) in older adults (≥60 years), Shanghai, 2010–2019. The dotted line indicates a reference line with an M/F ratio of 1, and a ratio >1 indicates more males than females. CVD, cardiovascular disease; IHD, ischaemic heart disease; M/F ratio, male-to-female ratio.
influenza-associated mortality in older adults. Third, despite the influenza vaccination for older adults being cost-effective,20 due to the lack of vaccination data for people aged ≥60 years, the impact of vaccination on differences in excess mortality between the sexes could not be measured.

CONCLUSIONS
Influenza-associated excess mortality rates for CVDs increased with age in older adults. The mortality risk from influenza-related IHD was significantly higher in older women than older men. Patterns of age-dependent and sex-dependent differences in excess CVD mortality associated with influenza type/subtypes requires further investigation. Our findings highlight the need to promote influenza vaccination in older adults and explain the age and sex differences in mortality from CVD associated with influenza.

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