



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

Shan Jin,<sup>1</sup> Chenyan Jiang,<sup>2</sup> Tian Xia,<sup>1</sup> Zhen Gu,<sup>1</sup> Huiting Yu <sup>1</sup>, Jing Li,<sup>3,4</sup> Yaxu Zheng,<sup>2</sup> Hao Pan,<sup>2</sup> Jiaying Qiao,<sup>1</sup> Renzhi Cai,<sup>1</sup> Huanyu Wu,<sup>2</sup> Chunfang Wang <sup>1</sup>

**To cite:** Jin S, Jiang C, Xia T, *et al.* Age-dependent and sex-dependent differences in mortality from influenza-associated cardiovascular diseases among older adults in Shanghai, China: a population-based study. *BMJ Open* 2022;**12**:e061068. doi:10.1136/bmjopen-2022-061068

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-061068>).

SJ, CJ and TX contributed equally.

Received 13 January 2022  
Accepted 06 September 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Chunfang Wang;  
jessicascdc@163.com and  
Huanyu Wu;  
wuhuanyc@scdc.sh.cn

## 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.<sup>1</sup> Older adults with ageing immune systems are at high risk for influenza and are susceptible to complications, especially cardiovascular diseases (CVDs).<sup>2,3</sup> Increasing evidence suggests a link between influenza and CVDs, including ischaemic heart disease (IHD) and stroke.<sup>4–6</sup> Studies have found that influenza infection triggers autoimmune inflammation and coagulation changes, leading to myocarditis and acute myocardial infarction, which increases hospitalisation and CVD-related mortality.<sup>2,7</sup> 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,<sup>8–10</sup> reducing the risk of influenza-associated hospitalisations by almost 37%<sup>11</sup> and the risk of deaths by approximately 70%.<sup>12</sup> 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.<sup>13 14</sup> However, the annual vaccination coverage remains low among older adults in Shanghai and is even lower in areas with subsidised vaccine programmes.<sup>15</sup> 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,<sup>16 17</sup> there is limited evidence on the role of sex in the excess mortality related to influenza in older adults.<sup>18</sup>

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  $\geq 60$  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  $\geq 85$  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  $\geq 38^\circ\text{C}$  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.<sup>19</sup> 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>).

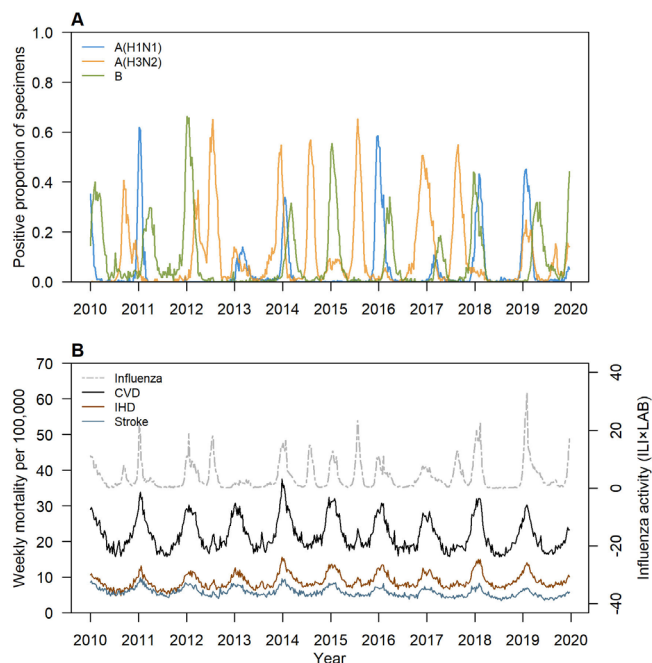
### Statistical analysis

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,<sup>20</sup> 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:

$$\begin{cases} Y_{i,t} \sim \text{quasiPoisson}(u_{i,t}, \varphi_i \mu_{i,t}) \\ \log(u_{i,t}) = \beta_{0i} + \beta_{1i} (ILI \times LAB_{IN})_{i,t-k} \\ \quad + \beta_{2i} (ILI \times LAB_{IB})_{i,t-k} + \beta_{3i} (ILI \times LAB_B)_{i,t-k} \\ \quad + s(t, df=3 \times 10) + s(AHum, df=3). \end{cases}$$

$Y_{i,t}$  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  $\varphi_i$ ). 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 outpatients consultation 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  $s(AHum)$  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



**Figure 1** Time series of weekly cardiovascular mortality in older adults ( $\geq 60$  years) and influenza activity in Shanghai, 2010–2019. Panel A the influenza activity by influenza subtypes; panel B the influenza activity proxy and the weekly mortality rates from cardiovascular disease (CVD), ischaemic heart disease (IHD) and stroke. ILI, influenza-like illness. LAB, the proportion of lab-confirmed positive cases of influenza type/subtypes.

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

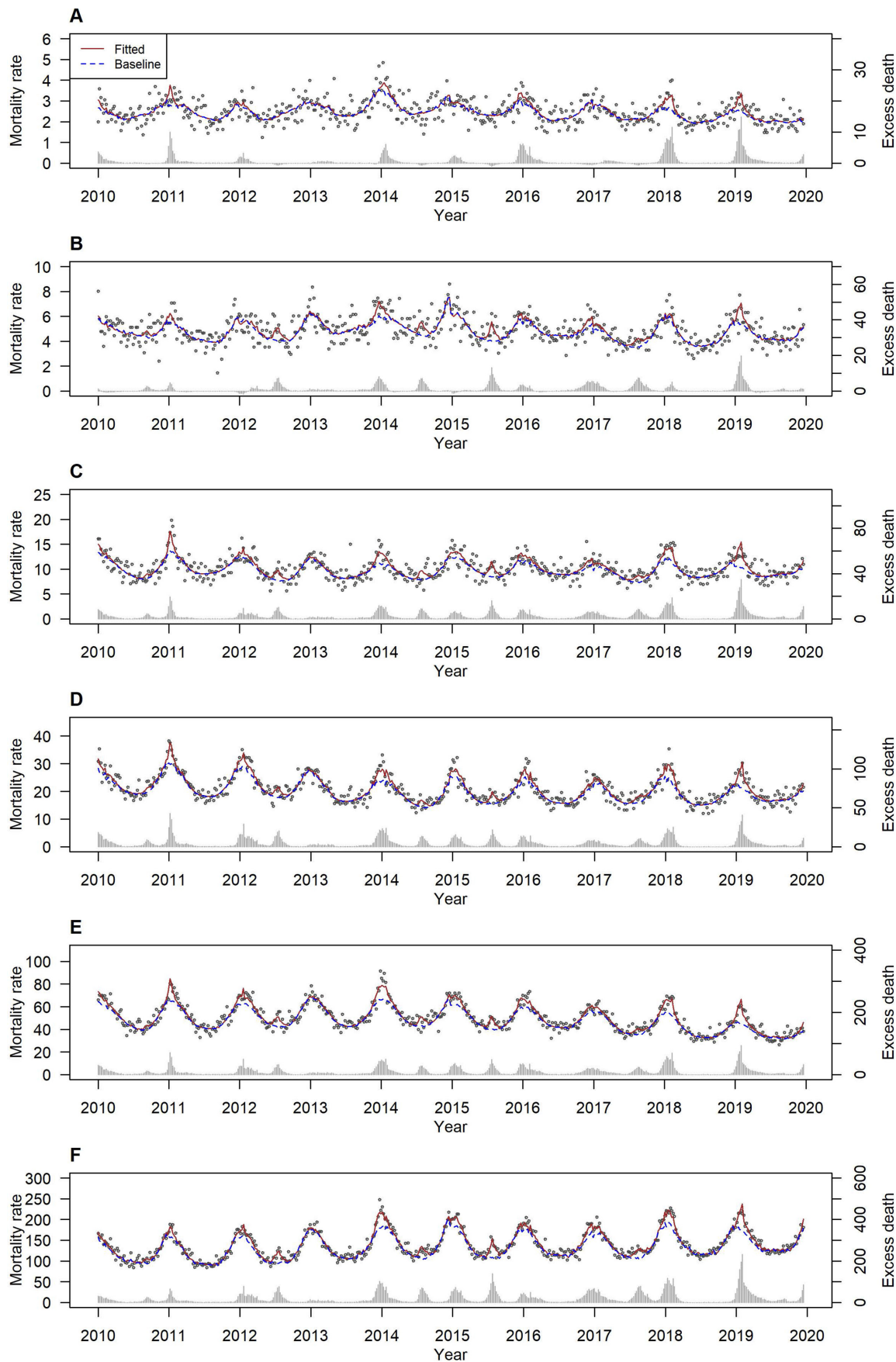
### Descriptive analysis of deaths and influenza surveillance

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  $\geq 60$  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).

**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	13 313	3343 (25.11)	564 (16.87)	864 (25.85)	1915 (57.28)	14
2011	10 582	2214 (20.92)	847 (38.26)	82 (3.70)	1285 (58.04)	13
2012	12 437	4373 (35.16)	6 (0.14)	2414 (55.20)	1953 (44.66)	16
2013	15 765	2453 (15.56)	530 (21.61)	1842 (75.09)	81 (3.30)	17
2014	20 033	5449 (27.20)	1001 (18.37)	2846 (52.23)	1602 (29.40)	18
2015	21 143	6174 (29.20)	968 (15.68)	2913 (47.18)	2293 (37.14)	19
2016	20 240	4894 (24.18)	1447 (29.57)	2194 (44.83)	1253 (25.60)	17
2017	21 643	5956 (27.52)	526 (8.83)	3963 (66.54)	1467 (24.63)	19
2018	19 835	3652 (18.41)	1821 (49.86)	306 (8.38)	1525 (41.76)	20
2019	20 763	6405 (30.85)	2040 (31.85)	1849 (28.87)	2516 (39.28)	26
Total	175 754	44 913 (25.55)	9750 (21.71)	19 273 (42.91)	15 890 (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

Year	Age group											
	60–64		65–69		70–74		75–79		80–84		85–	
	ER	95% CI	ER	95% CI	ER	95% CI	ER	95% CI	ER	95% CI	ER	95% CI
2010	2.42	0.03 to 4.61	2.56	-2.48 to 7.64	18.75	9.38 to 27.39	40.20	26.30 to 54.27	105.84	78.94 to 132.93	213.11	165.28 to 261.53
2011	3.97	1.71 to 6.12	1.53	-2.25 to 5.70	17.47	9.11 to 24.98	38.41	26.23 to 50.26	97.90	74.24 to 121.89	152.87	114.21 to 193.44
2012	1.00	-2.65 to 4.14	8.05	1.38 to 15.14	27.52	15.81 to 39.10	60.73	39.82 to 81.41	147.33	108.91 to 183.64	403.18	326.83 to 482.11
2013	0.68	-1.08 to 2.25	7.15	4.21 to 10.25	14.81	10.50 to 19.67	22.13	15.37 to 28.17	72.95	56.48 to 89.89	187.80	157.57 to 220.08
2014	2.89	-0.20 to 5.57	10.26	4.64 to 16.01	27.60	19.00 to 35.79	51.52	38.88 to 63.59	153.18	123.47 to 181.50	446.45	382.17 to 512.05
2015	2.45	-0.98 to 5.39	9.02	2.33 to 15.74	32.07	20.60 to 43.29	54.79	38.10 to 71.19	156.5	122.01 to 190.64	461.19	381.17 to 541.69
2016	2.53	0.59 to 4.19	6.53	3.08 to 9.99	21.08	14.79 to 26.86	38.67	29.91 to 47.27	105.53	86.66 to 124	281.37	239.67 to 322.63
2017	0.72	-2.20 to 3.18	9.02	3.99 to 13.82	24.07	15.99 to 32.26	43.36	29.64 to 56.22	107.66	81.20 to 132.14	393.32	329.15 to 456.84
2018	4.49	2.05 to 6.80	2.44	-2.23 to 7.55	20.30	10.66 to 28.68	43.07	29.27 to 56.8	106.66	81.73 to 130.19	273.32	204.80 to 342.12
2019	5.69	2.45 to 8.55	9.45	2.91 to 16.32	37.27	24.84 to 47.80	66.89	51.39 to 82.91	162.53	133.08 to 192.08	508.58	429.75 to 589.21
Average	2.78	0.40 to 4.77	6.81	2.15 to 11.39	24.41	16.06 to 31.97	45.71	34.27 to 56.96	122.12	98.97 to 144.91	341.91	290.85 to 394.62

ER, excess rate.

### Estimates of annual influenza-related mortality by age

Figure 2 shows the estimated weekly excess CVD mortality rates per 100 000 and the number of weekly excess deaths in the six age groups of older adults. In 2019, the excess CVD mortality associated with influenza was estimated from 5.69 (95% CI: 2.45 to 8.55) to 508.58 (95% CI: 429.75 to 589.21) per 100 000 persons (table 2). The same year also saw the highest excess mortality from IHD and stroke (online supplemental tables S2 and S3). The mortality rates for CVD, IHD and stroke increased with age. The ≥85 years and 60–64 years groups had the highest and lowest rates of CVD (341.91 (95% CI: 290.85 to 394.62) and 2.78 (95% CI: 0.40 to 4.77)), IHD (193.06 (95% CI: 165.42 to 222.97) and 1.79 (95% CI: 0.34 to 3.06)) and stroke (110.05 (95% CI: 78.13 to 139.53) and 0.56 (95% CI: -1.24 to 2.38)), respectively (table 3). Influenza A (H3N2) virus was associated with the highest CVD, IHD and stroke-related excess mortality in adults aged ≥65 years (table 3).

### Estimates of sex-specific mortality associated with influenza

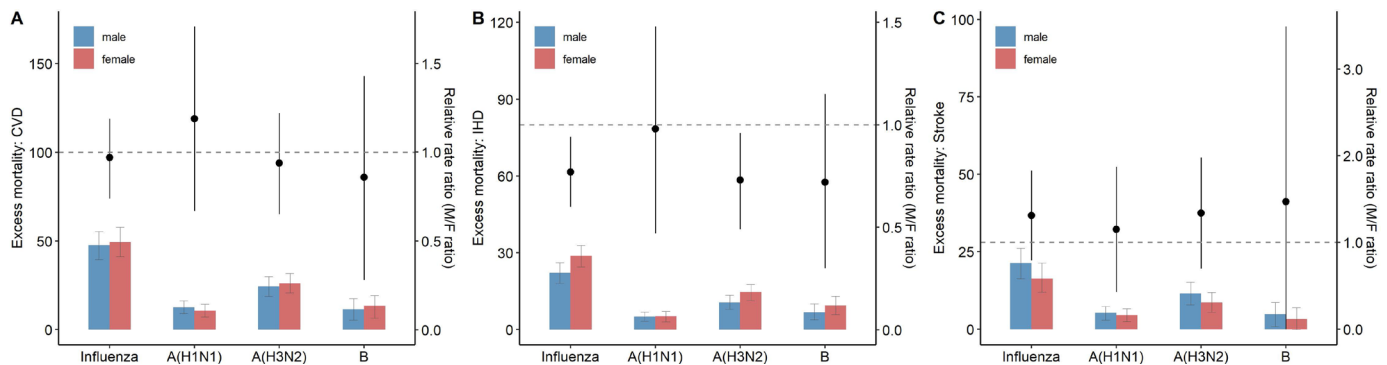
The excess rate of influenza-associated IHD deaths was significantly higher in older women compared with older men (relative rate ratio < 0) (figure 3). The relative rate ratios for the 65–69, 70–74, 75–79 and 80–84 years age groups were all > 1 (table 3), indicating that influenza-related excess mortality 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).

## 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,<sup>21 22</sup> 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. Consistent with reports from the USA<sup>18</sup> and Hefei,<sup>23</sup> a subtropical city in China,

**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 (6.52–17.55)	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)	0.00 (0.00–0.00)	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 (–2.4–12.24)	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.							



**Figure 3** Excess mortality rates for cardiovascular diseases with different influenza types/subtypes and relative rate ratio (M/F ratio) in older adults ( $\geq 60$  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.

the highest excess mortality rate was in the  $\geq 85$  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  $\geq 80$  years old.<sup>5</sup> The ageing population in Shanghai is on the rise, which is an important factor contributing to the persistently high influenza-associated mortality.<sup>24</sup> 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.<sup>19</sup>

Existing evidence indicates that influenza vaccination is associated with a reduced risk of cardiovascular events in older patients.<sup>3 25–28</sup> Although the guidelines for influenza vaccination in China recommend that adults  $> 60$  years be given priority,<sup>13</sup> the coverage in this population is approximately 4%<sup>29</sup> and only 2.28% in Shanghai.<sup>15</sup> 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<sup>30</sup> and Shenzhen,<sup>31</sup> 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.<sup>29</sup> 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.<sup>30</sup> As per China's seventh census in 2020, 23.38% of Shanghai's total population was  $\geq 60$  years, an increase of 8.31% from 2010.<sup>32</sup> 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.<sup>18 22</sup>

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,<sup>25 33</sup> only a few studies have included sex analysis.<sup>18</sup> 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.<sup>34 35</sup> At the same time, changes in oestrogen levels trigger dyslipidaemia, increasing overall cholesterol and decreasing high-density lipoprotein (HDL) cholesterol in women  $> 50$  years.<sup>36</sup> These changes double the risk of developing IHD in women compared with men.<sup>37</sup> Studies in mice have shown that influenza infection results in the loss of the anti-inflammatory properties of HDL cholesterol.<sup>38</sup> Compared with older men, older women have a higher inflammatory response.<sup>39</sup> The inflammatory response to the influenza virus accelerates the occurrence of atherosclerosis and makes the atherosclerotic plaques unstable. In addition, increased metabolic demands over an extended period may lead to cardiac ischaemia, as seen in patients with persistent fever caused by influenza inflammation.<sup>4 39–41</sup> Further evidence is required to confirm the role of age and sex in the burden of influenza-related mortality.

Our study has several limitations. First, the influenza-associated surveillance system in China does not monitor cocirculating viruses, such as respiratory syncytial virus, adenovirus and parainfluenza virus. Infections caused by these cocirculating viruses could lead to biases in estimating excess deaths. Second, around one-third of Shanghai's residents die at home or without medical attention.<sup>42</sup> The COD in these cases is often not determined accurately, leading to an underestimation of

influenza-associated mortality in older adults. Third, despite the influenza vaccination for older adults being cost-effective,<sup>29</sup> due to the lack of vaccination data for people aged  $\geq 60$  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.

### Author affiliations

<sup>1</sup>Institute of Health Information, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China

<sup>2</sup>Institute of Communicable Diseases Control and Prevention, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China

<sup>3</sup>Renal Division, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China

<sup>4</sup>Clinical Research Academy, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China

**Acknowledgements** The authors would like to thank the Department of Vital Statistics of Shanghai Center for Disease Control and Prevention (SCDC) for providing the population data, the Department of Acute Infectious Diseases Prevention and Control of SCDC for providing the influenza surveillance data and the China Meteorological Data Service Center for providing the meteorological data.

**Contributors** SJ, CJ and TX conceived and designed the study. HY, YZ and HP collected and managed the data. ZG, JL, JQ and RC analysed the data. SJ drafted the manuscript. HW and CW commented on and revised the manuscript. All authors read and approved the final manuscript. HW and CW are the guarantors of the manuscript.

**Funding** This research was supported by the Bloomberg Philanthropies Data for Health Initiative (<https://www.bloomberg.org/program/public-health/data-health/>, grant number is not applicable) and Academic Leaders of Three-year Action Program of Shanghai Municipality for Strengthening the Construction of Public Health System (grant number GWV-10.2-XD20 to TX). The funding bodies had no role in the study design, data collection, data analysis, manuscript preparation or the decision to publish.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data may be obtained from a third party and are not publicly available.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

### ORCID iDs

Huiting Yu <http://orcid.org/0000-0002-8979-5238>

Chunfang Wang <http://orcid.org/0000-0003-0513-1109>

## REFERENCES

- 1 Thompson WW, Shay DK, Weintraub E, *et al*. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179–86.
- 2 Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009;9:601–10.
- 3 Cheng Y, Cao X, Cao Z, *et al*. Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-cause mortality. *Ageing Res Rev* 2020;62:101124.
- 4 Foster ED, Cavanaugh JE, Haynes WG, *et al*. Acute myocardial infarctions, strokes and influenza: seasonal and pandemic effects. *Epidemiol Infect* 2013;141:735–44.
- 5 Ang LW, Yap J, Lee V, *et al*. Influenza-associated hospitalizations for cardiovascular diseases in the tropics. *Am J Epidemiol* 2017;186:202–9.
- 6 Pearce DC, McCaw JM, McVernon J, *et al*. Influenza as a trigger for cardiovascular disease: an investigation of serotype, subtype and geographic location. *Environ Res* 2017;156:688–96.
- 7 Nguyen JL, Yang W, Ito K, *et al*. Seasonal influenza infections and cardiovascular disease mortality. *JAMA Cardiol* 2016;1:274–81.
- 8 Grau AJ, Fischer B, Barth C, *et al*. Influenza vaccination is associated with a reduced risk of stroke. *Stroke* 2005;36:1501–6.
- 9 Beyer WEP, McElhaney J, Smith DJ, *et al*. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. *Vaccine* 2013;31:6030–3.
- 10 Restivo V, Costantino C, Bono S, *et al*. Influenza vaccine effectiveness among high-risk groups: a systematic literature review and meta-analysis of case-control and cohort studies. *Hum Vaccin Immunother* 2018;14:724–35.
- 11 Rondy M, El Omeiri N, Thompson MG, *et al*. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. *J Infect* 2017;75:381–94.
- 12 Fabiani M, Volpe E, Faraone M, *et al*. Effectiveness of influenza vaccine in reducing influenza-associated hospitalizations and deaths among the elderly population; Lazio region, Italy, season 2016–2017. *Expert Rev Vaccines* 2020;19:479–89.
- 13 Chinese Center for Disease Control and Prevention. Technical guidance for influenza vaccination 2020–2021. Available: [https://www.chinacdc.cn/jkzt/crb/bl/lxxgm/jszl\\_2251/202009/W020200911453959167308.pdf](https://www.chinacdc.cn/jkzt/crb/bl/lxxgm/jszl_2251/202009/W020200911453959167308.pdf) [Accessed 12 Jan 2021].
- 14 World Health Organization. Fact sheet on seasonal influenza. Available: [https://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)) [Accessed 12 Jan 2021].
- 15 Chen J, Li Y-ting, Gu B-ke, *et al*. Estimation of the direct cost of treating people aged more than 60 years infected by influenza virus in Shanghai. *Asia Pac J Public Health* 2015;27:NP936–46.
- 16 Eshima N, Tokumaru O, Hara S, *et al*. Sex- and age-related differences in morbidity rates of 2009 pandemic influenza A H1N1 virus of swine origin in Japan. *PLoS One* 2011;6:e19409.
- 17 Tadount F, Doyon-Plourde P, Rafferty E, *et al*. Is there a difference in the immune response, efficacy, effectiveness and safety of seasonal influenza vaccine in males and females? - A systematic review. *Vaccine* 2020;38:444–59.
- 18 Quandelacy TM, Viboud C, Charu V, *et al*. Age- and sex-related risk factors for influenza-associated mortality in the United States between 1997–2007. *Am J Epidemiol* 2014;179:156–67.
- 19 Jin S, Li J, Cai R, *et al*. Age- and sex-specific excess mortality associated with influenza in Shanghai, China, 2010–2015. *Int J Infect Dis* 2020;98:382–9.
- 20 Deyle ER, Maher MC, Hernandez RD, *et al*. Global environmental drivers of influenza. *Proc Natl Acad Sci U S A* 2016;113:13081–6.
- 21 Nunes B, Viboud C, Machado A, *et al*. Excess mortality associated with influenza epidemics in Portugal, 1980 to 2004. *PLoS One* 2011;6:e20661.



- 22 Liu R, Liu X, Yang P, *et al.* Influenza-associated cardiovascular mortality in older adults in Beijing, China: a population-based time-series study. *BMJ Open* 2020;10:e042487.
- 23 Hao Y, Huang L, Liu X, *et al.* Influenza-attributable years of life lost in older adults in a subtropical City in China, 2012-2017: a modeling study based on a competing risks approach. *Int J Infect Dis* 2020;97:354-9.
- 24 Li J, Wang C, Ruan L, *et al.* Development of influenza-associated disease burden pyramid in Shanghai, China, 2010-2017: a Bayesian modelling study. *BMJ Open* 2021;11:e047526.
- 25 Liu I-F, Huang C-C, Chan W-L, *et al.* Effects of annual influenza vaccination on mortality and hospitalization in elderly patients with ischemic heart disease: a nationwide population-based study. *Prev Med* 2012;54:431-3.
- 26 Chiang M-H, Wu H-H, Shih C-J, *et al.* Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients. *Am Heart J* 2017;193:1-7.
- 27 Caldeira D, Ferreira JJ, Costa J. Influenza vaccination and prevention of cardiovascular disease mortality. *Lancet* 2018;391:426-7.
- 28 Pang Y, Wang Q, Lv M, *et al.* Influenza vaccination and hospitalization outcomes among older patients with cardiovascular or respiratory diseases. *J Infect Dis* 2021;223:1196-204.
- 29 Yang J, Atkins KE, Feng L, *et al.* Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China: a modelling analysis. *BMC Med* 2020;18:90.
- 30 Lv M, Fang R, Wu J, *et al.* The free vaccination policy of influenza in Beijing, China: the vaccine coverage and its associated factors. *Vaccine* 2016;34:2135-40.
- 31 Jiang X, Shang X, Lin J, *et al.* Impacts of free vaccination policy and associated factors on influenza vaccination behavior of the elderly in China: a quasi-experimental study. *Vaccine* 2021;39:846-52.
- 32 Huang B, Liu Y, Feng Z, *et al.* Residential exposure to natural outdoor environments and general health among older adults in Shanghai, China. *Int J Equity Health* 2019;18:178.
- 33 Lichenstein R, Magder LS, King RE, *et al.* The relationship between influenza outbreaks and acute ischemic heart disease in Maryland residents over a 7-year period. *J Infect Dis* 2012;206:821-7.
- 34 Vasan RS, Larson MG, Leip EP, *et al.* Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med Overseas Ed* 2001;345:1291-7.
- 35 Manrique-Acevedo C, Chinnakotla B, Padilla J, *et al.* Obesity and cardiovascular disease in women. *Int J Obes* 2020;44:1210-26.
- 36 Sanghavi M, Gulati M. Sex differences in the pathophysiology, treatment, and outcomes in IHD. *Curr Atheroscler Rep* 2015;17:511.
- 37 Shaw LJ, Bairey Merz CN, Pepine CJ, *et al.* Insights from the NHLBI-Sponsored women's ischemia syndrome evaluation (wise) study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006;47:S4-20.
- 38 Van Lenten BJ, Wagner AC, Nayak DP, *et al.* High-density lipoprotein loses its anti-inflammatory properties during acute influenza A infection. *Circulation* 2001;103:2283-8.
- 39 Majidi M, Eslami V, Ghorbani P, *et al.* Are women more susceptible to ischemic heart disease compared to men? A literature overview. *J Geriatr Cardiol* 2021;18:289-96.
- 40 Naghavi M, Wyde P, Litovsky S, *et al.* Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-Deficient mice. *Circulation* 2003;107:762-8.
- 41 Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis* 2010;10:83-92.
- 42 Chen L, Xia T, Rampatige R, *et al.* Assessing the diagnostic accuracy of physicians for home death certification in Shanghai: application of SmartVA. *Front Public Health* 2022;10:842880.