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RESEARCH ARTICLE

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The effectiveness of influenza vaccine among elderly Chinese: A regression discontinuity design based on Yinzhou regional health information platform

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ABSTRACT

In China, a free influenza vaccination policy is being implemented among individuals aged 70 years and over in Zhejiang province during the COVID-19 pandemic. The objective was to assess the effectiveness of influenza vaccine in reducing hospitalization and mortality in the elderly. We used data from the Regional Health Information Platform in Yinzhou located in Zhejiang province and applied a regression discontinuity design to estimate the intention-to-treat effect on admission and mortality rates by month of age in the population who was near the age of 70 years threshold. At age 70 years, the influenza vaccination rate increased by 29.1% (95% CI, 28.2% to 29.9%) compared to those under 70 in the study population. When turning age 70 years, the potential effectiveness of receiving influenza vaccine was 8.2% (95% CI, −36.8% to 51.3%) for total hospitalization and the evaluation of vaccine effectiveness was 13.1% (95% CI, −34.2 to 61.8) for the all-cause mortality. An increase in the influenza vaccination rate was associated with a weak decline in most outcomes, but no significance was found for all outcomes. Influenza vaccination had a limited effect on hospital admission and mortality for the free influenza vaccination program that can be related to the low vaccination rate among the Chinese elderly. Supplementation strategies and future studies may be needed to expand immunization coverage and validate this finding, and further provide a reference for other cities to promote the free influenza vaccination policy in China, especially under circumstances of the COVID-19 pandemic.

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Introduction

World Health Organization (WHO) estimates that seasonal influenza causes about 3–5 million serve cases and 290–650 thousand respiratory-related deaths worldwide each year,[1] resulting in social costs of billions of dollars.[2] A study based on national influenza surveillance and cause-of-death surveillance data in China revealed that an annual mean of 88,100 excess deaths, of which elderly adults accounted for 80%, were caused by influenza-associated respiratory diseases during the 2010–11 to 2014–15 seasons.[3] Previous studies of general people have demonstrated that influenza vaccination is associated with lower risk respiratory disease [i.e. influenza, influenza-like illness (ILI) and chronic obstructive pulmonary disease (COPD)] and cardiovascular (i.e. acute myocardial infarction and ischemic cerebrovascular).[4,5] In addition, several studies have suggested that influenza vaccination could reduce the all-cause mortality[4] and the mortality risk in patients with cardiovascular disease[6] and COPD.[7,8] Therefore, many countries implemented annual seasonal influenza vaccination to reduce the burden of influenza-related morbidity and mortality, especially in older adults who are usually at a higher risk of influenza, severe complication and death than others.[9] However, the association between influenza vaccination and hospitalization and mortality is inconsistent among the older adults. Recently, an updated meta-review including 8 RCTs or quasi-RCTs between 1965 and 2000 indicated that the evidence for a lower risk of influenza and ILI with vaccination in the elderly is limited by biases in the design or conduct of the studies and the providing data for mortality and pneumonia hospitalization were underpowered to detect difference.[10] Hence, good evidence of the effect of influenza vaccine on hospitalization and mortality still needs to be provided in the elderly. Due to the limitation of the ethics, new RCTs are not permitted, in turn, observational studies are more feasible, but they are inherently inclined to selection and confounding biases.[11]

Observational studies, such as cohort and case-control studies, have found 20%–50% reductions in hospitalization and deaths in vaccinated elderly people,[12,13] yet the results may be impacted by selection bias and confounding in the real-world setting. Recently, the regression discontinuity design (RDD), a relatively new quasi-RCT study design, has been applied to estimate the overall vaccination effectiveness (VE) for the vaccination program in the elderly people—in United Kingdom[14] and Netherlands,[15] which can maximize controlling above bias. This is a powerful design that is analogous to a random assignment receiving the intervention for an individual,[16] which can protect against selection bias and are not available in the other observational research designs used to study this issue.

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Currently, availability and improvement of high-quality electronic healthcare databases in China, such as Regional Health Information Platform (RHIP), has produced the prospect of providing real-world evidence in the condition when RCT is unfeasible.[17] Yinzhou is one of the earliest areas to build the RIHP, which has become the best regional community-based database and has been confirmed by multiple studies after more than 15 years of integration and development.[18] In addition, the free influenza vaccination program in Zhejiang Province was initiated in 2020 COVID-19 pandemic and targeted on the elderly permanent household residents aged 70 years or older,[19] which makes it possible to evaluate the overall VE of influenza vaccine using RDD.

Therefore, this study aimed to estimate the intention-to-treat effect of influenza vaccine on the hospital admission and mortality for people aged 70 and older, based on Yinzhou RHIP database.

Materials and methods

Data source and study population

This study was based on the data warehouse of Yinzhou RHIP (YRHIP), which located in a developed area of Ningbo City, Zhejiang province, the eastern coastal region of China, and had a total of more than 1.6 million permanent residents in 2020. This platform was originally designed in 2006 by the Yinzhou District Center for Disease Control and Prevention (CDC) to facilitate routine primary care services for local general practitioners, and gradually integrated with information on public health surveillance, population screen, disease management, health information system in hospital and other healthcare services. Since 2009, the YRHIP has covered nearly all health-related activities of residents throughout life, from birth to death, including children, adolescents, pregnant women, adults and elderly people in this district. Until 2017, 98% of permanent residents in Yinzhou have registered in the health information system. YRHIP contains all electronic medical records (EMR) data of outpatient, emergency and inpatient visits, primary and secondary diagnosis, laboratory services and medications usage from a network of all five hospitals (public and private hospital) and 289 primary care institutions across Yinzhou.[20] In 2020, the database was approved and awarded a Five Grade Class B, which was the second-leading level of the Standardization and Maturity Measurement of Regional Health Information Interconnection by the National Health Commission of China. Furthermore, the high-quality, practical data in this platform has already been applied for studies of chronic noncommunicable disease[20–22] and safety and effectiveness of vaccine[23,24] and drugs,[18,25] proving the reliability and accurateness of the data source for performing future researches.

In this study, free influenza vaccination policy was initiated in September 2020 and targeted no the permanent household residents aged 70 years and older or born prior 31 December 1950. All other individuals had to pay for the full cost of influenza vaccine. Since the actual free influenza vaccination has initiated in September, the study period is defined as the influenza season from 1 September 2020 to 31 March 2021. The study population consisted of adults born between 1 January 1930 to 31 December 1970 who had at least 180 days of continuous enrollment in this database and had a local household registration. Simultaneously, these populations who are alive on 1 September 2020 were included in the study.

Procedures and outcomes

We used the integrated data from four data sources. The vaccination data set (a total of 36068 individuals aged 55 to 85 years) was derived from the specified free influenza vaccination data sheet and the immunization administration registry, which provided influenza vaccine uptake data, including NID, gender, birth date, vaccine name, and vaccination date vaccination. The admission data set (a total of 91113 discharges diagnostic records, 19083 patients aged 55 to 85 years and hospitalized during influenza season) comprised the healthcare data of all hospitals and community health centers in Ningbo region. Key variables of each record include NID, gender, birth date, discharge date, and discharge diagnosis name along with the International Classification of Diseases 10th Revision (ICD10). Mortality data set (a total of 2545 individuals aged 55 to 85 years and died during influenza season) was derived from the death surveillance information system which included identity information, sex, birth date, medical certificates of the death and the ICD10 code of leading cause. The electronic health archive data set (a total of 287770 individuals aged 55 to 85 years; age is computed as age on 31 December 2020) was used to define the denominator of all study populations who meet the inclusion criteria. We linked the various data sets using the unique NID number to select the permanent household residents.

Vaccination rate was calculated by age using the integrated data from vaccination data set and electronic health archive data set. For each hospital admission record, if an outcome was extracted in discharge records, we identified the cause of admission by the ICD10 code: any cause, including all hospital admission records; pneumonia and influenza, including ICD-10 codes of J09 to J18; respiratory disease, including J00 to J99; circulatory disease, including I00 to I99; respiratory or circulatory disease, including J00 to J99 and I00 to I99. For each mortality record, we identified the above categories of mortality outcomes by the ICD10 code of leading cause of death. We calculated the admission and mortality rates at the month level for each month-of-birth cohort, using the panel data of electronic health archive data set integrated with the admission data set or mortality data set, respectively. The denominator of each birth cohort was the mean number of persons who were alive in a particular month-of-birth.

Study design

Regression discontinuity design (RDD), a kind of quasi-experimental design, has consistently been demonstrated to closely approximate the findings of RCTs,[26,27] and can provide valuable information on the overall effects (or impacts) of vaccination programs in real-world settings, vaccine safety, the effectiveness of interventions to increase vaccine uptake.[16,28–31] The rationale of RDD is that an assignment variable is used to determine whether or not an individual is assigned to receive treatment or exposure (exposure variable) based on a threshold rule. Individuals just above the threshold are expected to be similar in their distribution of measured and unmeasured baseline covariates to individuals just below the threshold, emulating in the effect of random grouping. Two criteria should be met when using this method: 1) the exposure variable has an apparent jump at the threshold; 2) the relation between the outcomes and assignment variable at the threshold is smooth, before the start of an actual study. RDD divides into sharp RDD and fuzzy RDD according to whether the assignment variable completely determines the exposure probability, and the latter is analogous to the noncompliance setting of RCT within a small local range of the assignment variable.

In this study, we used the two-stage fuzzy RDD since age was not the only determinate of vaccination status. First, we plotted age profile with vaccination rate using the local polynomial regression model. Second, we tested for discontinuous changes in hospital admission and mortality at 70 years to identify the impact of elevation in vaccination rate at 70 years on these outcomes. Finally, we converted these coefficients into a percentage term relative to baseline admission or mortality rates at age of 69 to calculate the effectiveness of the vaccine and their 95% confidence intervals (CI). Additional details on this computation refer to the description of methods by Michael and colleagues.[14]

Statistical analysis

For the free-vaccination-policy effect, we plotted the relation of vaccination rate following the age profile using the local polynomial regression and estimated change of vaccination rate by controlling an indicator variable for age 70 years and older, a quadratic in age, an interaction between that quadratic and the indicator for age 70 years and older. We restricted the sample to a bandwidth of 10 years of age around the age-70 threshold (that is, individuals aged 60 to 80 years) and then checked the robustness of using various alternative bandwidths. The regression was weighted by the number of individuals of that age.

The regression discontinuity analysis was used to test whether the increase in vaccination rate was associated with a corresponding decrease in admission and mortality rates. The regression fitted the admission and mortality rate of month-of-event level (dependent variables) with a month-of-birth indicator, an indicator of age 70 years and above, a quadratic indicator and an interaction between that quadratic and the age indicator. We restricted the sample to a bandwidth of 5 years of age around the age-70 threshold (that is, individuals aged 65 to 75 years) and then checked the robustness of using alternative bandwidths. The regression is weighted by the number of individuals of that month-of-age. This method was analogous to taking the age-70 discontinuity as an instrument variable to identify the causal effect of vaccination. Besides, we conducted sensitivity analyses to examine the validity of RDD using the linear regression model (exclude quadratic of age). The effectiveness of vaccination was calculated as the change in admission or mortality rate at the age-70 threshold divided by the change in vaccination rate when turning age 70 years. Because some individuals aged below 70 years received the influenza vaccine, the raw admission or mortality rate underestimated the true admission rate or mortality rate for unvaccinated persons in this age range when computing confidence interval boundaries. Therefore, the actual admission or mortality rate below 70 years was defined that the raw rate subtracted the vaccination rate below age 70 multiplied by the raw effect estimate, with the assumption that the vaccination effect is similar for vaccinated persons near the age of 70 years.[14] We found that the optimal bandwidth of age was 3.8 years for hospital admission, and 4.3 years for mortality. Whether the 95% CI of the estimate of vaccination effect includes the null value was used to determine whether it is statistically significant. Data management and data link were performed using the Hive SQL. All data analyses were conducted using Stata SE, Version 15.0 (Stata Corp).

Results

Change of influenza vaccination rate at age of 70 years

At age of 70 years, the seasonal influenza vaccination rate increased by 29.1% (95% CI 28.2%–29.9%) in the study population (Table 1). Changes in vaccination rate were higher in women (31.6%, 95% CI 30.7%–32.5%) than in men (26.5%, 95% CI 24.9%–27.9%). The increase in vaccination rate at age of 70 years was jumped discontinuously in the selected individuals aged 60–80 years, and the regression function showed sufficiently flexible to fit the age profiles (Figure 1). The estimate of the variation in the percentage of vaccination at age 70 was robust against the bandwidth of age with years (Suplementary Figure S1).

Change of hospital admission at age of 70 years

There was a higher hospital admission rate in men than women and the rate increased with age; meanwhile, the age profiles of admission for any cause and for respiratory appeared smooth across the age threshold of 70 years in both sexes (Figure 2). Hospital admission rates did not change significantly at the age of 70 years (Table 2). At age of 70 years, the admission rate for any cause changed by −8.8 (95% CI, −20.2 to 4.7) per 10000 persons compared with the baseline rate of 368.4. The overall effectiveness of the decrease in hospital admission was estimated to be 8.2% (95%CI, −36.8 to 51.3). Further, the admission rate for pneumonia or influenza, respiratory, circulatory, and respiratory or circulatory changed by −2.0 (95% CI, −8.2 to 4.1) per 10000 persons, −3.4 (95% CI, −18.2 to 11.5) per 10000 persons, −17.3 (95% CI, −50.7 to 16.0) per 10000 persons, and −18.1 (95% CI, −47.6 to 13.5) per 10000 persons compared with the baseline rate of 6.8, 33.7, 145.3, 158.3, respectively. When we changed the bandwidth with years

Table 1. The change of influenza vaccination rate at age 70 years.

	All	Male	Female
Change in rate at age 70 years	29.1 (28.2–29.9)	26.4 (24.9–27.9)	31.6 (30.7–32.5)
Rate under 70 years	4.8	4.6	4.9
Underlying Observations	195109	95707	99402

The numbers are influenza vaccination rates per 100 people. Estimates of change rate are followed by 95% confidence intervals. A person's age is defined as the vaccination date subtract from the birth date. Rates are estimated based on the number of people alive during the study period. The regressions are estimated based on rates for one-year age cells for the population aged 60 to 80 inclusive. The regressions include a second-order polynomial in age fully interacted with an indicator for being 70 or over. The regressions are weighted by the number in each age group.

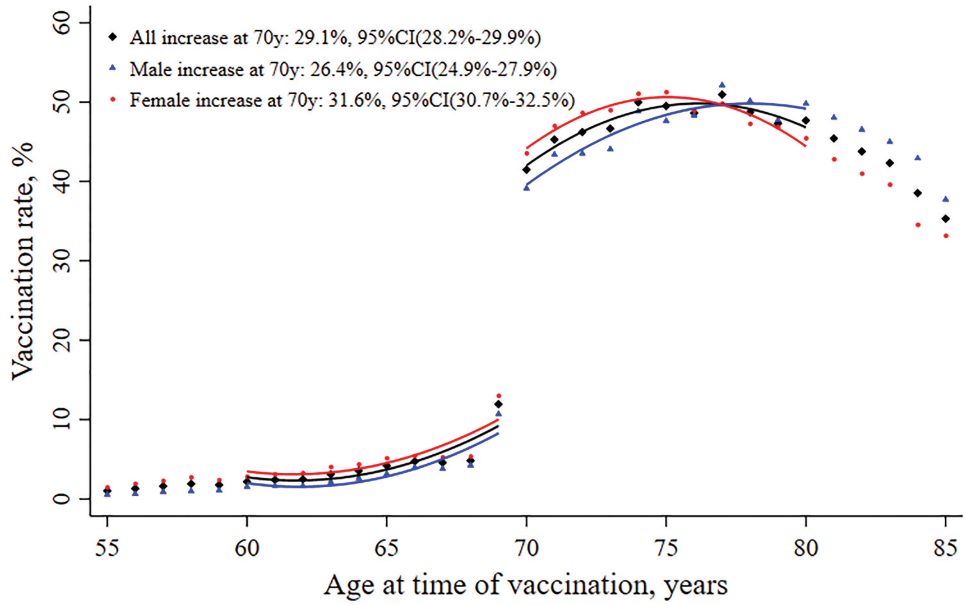

Figure 1. Influenza vaccination rate following age profile.

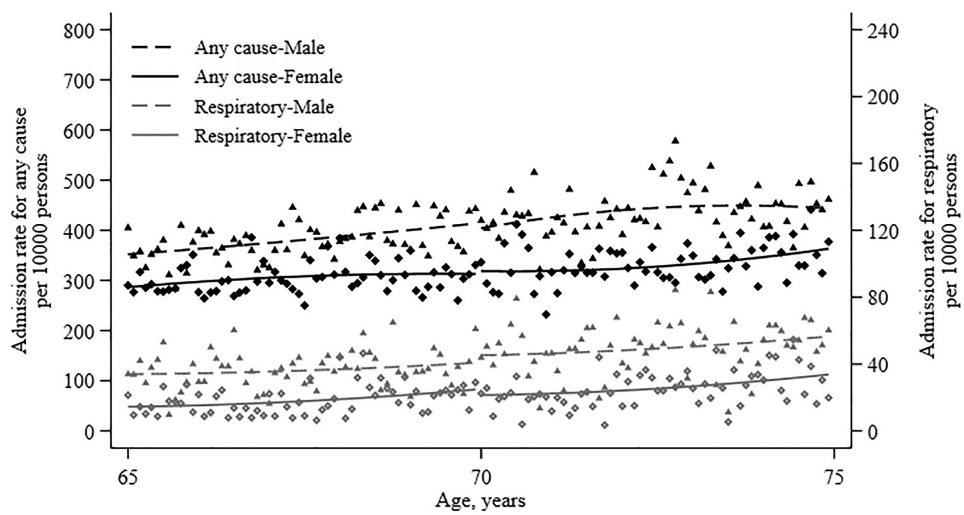

Figure 2. Change in hospital admission rate following age profile.

around the age-70 threshold, the changes of admission rate were consistent with the primary analyses (Supplementary Figure S2). Taking the vaccination rate into account, the potential effectiveness of receiving seasonal influenza vaccine was 8.2% (95% CI, −36.8% to 51.3%) for total admission, 8.3% (95% CI, −40.4% to 69.2%) for pneumonia and influenza admissions, 23.8% (95% CI, −16.9% to 67.5%) for respiratory admission, 30.2% (95% CI, −27.8% to 83.4%) for circulatory admission, and 31.5% (95% CI, −25.7% to 78.3%) for respiratory or circulatory. Results were similar in both men and women for any category of admission. We did not find a strong difference when using a linear function to fit age (Suplementary Table S1).

Change of mortality rate at age of 70 years

The age profiles of mortality for any cause and for respiratory or circulatory generally appeared smooth across the age threshold of 70 years in both sexes (Figure 3). Mortality rate did not change significantly at age of 70 years (Table 3). At age of 70 years, the mortality rate for any cause and for respiratory or circulatory changed by −2.7 (95% CI, −16.4 to 9.9) per 10000 persons and −1.6 (95% CI, −10.9 to 7.8) per 10000 persons compared with the baseline rate of 14.5 and 3.0, respectively. The results were robust against various bandwidths with years around the age-70 threshold (Supplementary Figure S3). The evaluation of vaccine effectiveness was 13.1% (95% CI, −34.2 to 61.8) for the all-cause mortality, 20.1% (95% CI, −43.7% to 87.3%) for respiratory or circulatory death after retrimming the impact of influenza vaccination rate. There were opposite effects of receiving influenza vaccine on mortality between men and women, although the change also exhibited insignificant impact on the mortality in both genders (Table 3). Further, we conducted the sensitivity analyses using the linear fitting model for age, and no strong difference was found (Suplementary Table S2).

Table 2. Effectiveness of influenza vaccination on hospital admission.

Outcomes	Any cause	Pneumonia or influenza	Respiratory	Circulatory	Respiratory or circulatory
All					
Change in admission rate at age 70 y	−8.8 (−20.2, 4.7)	−2.0 (−8.2, 4.1)	−3.4 (−18.2, 11.5)	−17.3 (−50.7, 16.0)	−18.1 (−47.6, 13.5)
Admission rate below age 70 y	368.4	6.8	33.7	145.3	158.3
Effectiveness (95% CI), %	8.2 (−36.8, 51.3)	8.3 (−40.4, 69.2)	23.8 (−16.9, 67.5)	30.2(−27.8, 83.4)	31.5 (−25.7, 78.3)
Men					
Change in admission rate at age 70 y	−34.2 (−77.6, 12.9)	1.9 (−10.3, 18.2)	−11.5 (−38.1, 15.0)	−22.4 (−76.9, 30.2)	−24.9 (−69.3, 29.4)
Admission rate below age 70 y	417.7	8.4	41.0	162.0	180.5
Effectiveness (95% CI), %	29.4 (−34.9, 75.7)	−23.5 (−75.4, 45.5)	40.1 (−18.6, 88.8)	41.1 (−24.6, 89.3)	43.2 (−23.1, 88.3)
Women					
Change in admission rate at age 70 y	16.7 (−22.6, 56.0)	−5.2 (−24.3, 34.1)	3.9 (−7.8, 25.6)	−9.7 (−45.8, 26.5)	−8.1(−40.8, 22.7)
Admission rate below age 70 y	305.2	6.1	25.1	122.5	130.1
Effectiveness (95% CI), %	−27.7 (−61.9, 33.1)	38.0 (−22.1, 82.7)	−19.4 (−65.9, 33.0)	21.6 (−39.3, 79.7)	19.6 (−35.2, 76.8)

The numbers are admission rate per 10000 and vaccine effectiveness. All regressions include month-of-birth dummies. The regressions also include a quadratic polynomial in age fully interacted with an indicator variable for age ≥70 y. The regressions are weighted by the average number of people in age-month. Hospital admissions are included in a category if there is any mention of the condition on the discharge diagnosis. The ICD 10 codes included in each category are as follows: influenza and pneumonia, J09–J18; respiratory diseases, J00–J99; and circulatory diseases, I00 –I99. The hospital admissions are included between September 2020 and March 2021. CI: confidence interval.

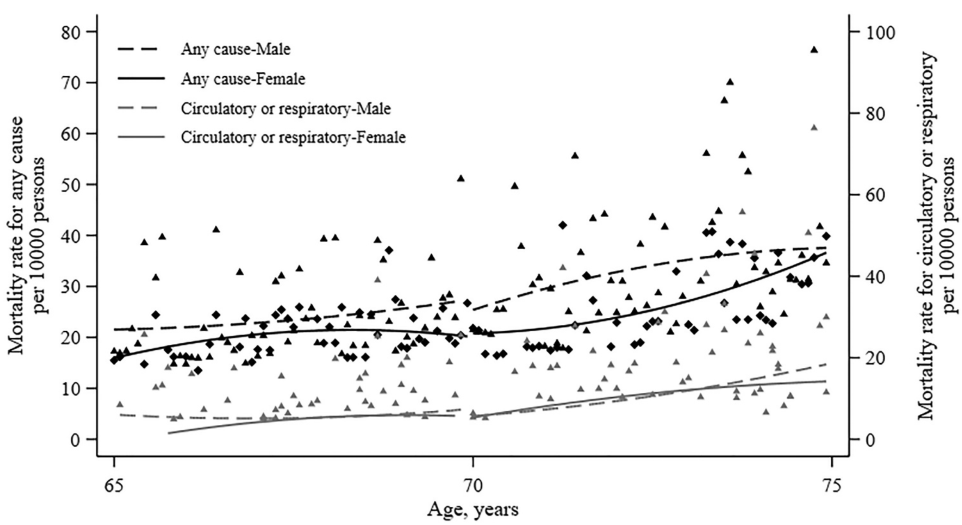

Figure 3. Change in mortality rate following age profile.

Discussion

Our results found that the free vaccination program contributed to a 29.1% sharp increase in influenza vaccination rates at age of 70 years, which corresponded to a merely slight decrease in hospital admission and mortality. The influenza vaccination also presented certain protective effects on the overall admission rate and admission rate from specific diseases, as well as total mortality and mortality due to respiratory or circulatory disease. But there was no statistical significance in any of the above findings.

Many previous observational studies, including cohort and case-control studies as well as test-negative design studies, have reported that influenza vaccine can prevent seasonal influenza (VE, 12%–58%)[32–34] and reduce influenza-related hospitalization (VE, 24%–73%) and mortality (VE, 18%–56%) for the elderly.[35–39] Moreover, influenza vaccine also showed a protective effect against respiratory and cardiovascular disease. Some studies reported that influenza vaccination can reduce acute infections and hospitalizations for COPD, chronic bronchitis and asthma attacks,[40,41] as well as lower the mortality risk in patients with COPD.[4,6] For the elderly people, influenza vaccination was associated with a decrease of the acute cardiovascular events and cardiopathy-related mortality in patients with coronary heart disease, and reduce 18% all-cause death and 18% death from cardiovascular disease in patients with heart failure.[42] Nevertheless, our results showed that influenza vaccination appeared a weak VE for overall hospital admission and mortality, and no significance was found even there were a relatively high VE for the hospitalization and mortality of respiratory or circulatory disease Several reasons may be considered as follows. One explanation for these differences was that RDD based on observational data had a more conservative conclusion, due to the fact that selection and confounding bias can be controlled at the lowest level in the real-world settings.[16] Another factor that may help explain our results was immune-response attenuated with age.[43] The selected population at near age-70 years was older than the average age for most previous studies (usually threshold at age of 65 years). Moreover, due to the

Table 3. Effectiveness of influenza vaccination on mortality.

Outcomes	Any cause	Respiratory or circulatory
All		
Change in admission rate at age 70 y	−2.7 (−16.4, 9.9)	−1.6 (−10.9, 7.8)
Mortality rate below age 70 y	14.5	3.0
Effectiveness (95% CI), %	13.1 (−34.2, 61.8)	20.1 (−43.7, 87.3)
Men		
Change in admission rate at age 70 y	−3.1 (−10.7, 4.6)	−5.3 (−28.1, 16.9)
Mortality rate below age 70 y	28.8	9.3
Effectiveness (95% CI), %	28.6 (−23.6, 79.5)	35.7 (−20.1, 89.5)
Women		
Change in admission rate at age 70 y	9.9 (−22.1, 40.8)	16.9 (−30.2, 62.4)
Mortality rate below age 70 y	10.1	2.1
Effectiveness (95% CI), %	−25.5 (−76.4, 30.7)	−21.7 (−87.3, 44.5)

The numbers are mortality rate per 10000 and vaccine effectiveness. All regressions include month-of-birth dummies. The regressions also included a quadratic polynomial in age fully interacted with an indicator variable for age ≥70 y. The regressions are weighted by the average number of people in age-month. Deaths are included in the category of primary cause from medical certificates of the dead. The ICD10 codes included in each category are as follows: respiratory diseases, J00–J99; and circulatory diseases, I00 –I99. The dead is included between September 2020 and March 2021. CI: confidence interval.

impact of the COVID-19 pandemic, the health behavior changes, e.g. wearing masks, keeping social distancing and restricting the number of people in the public areas, reduced the occurrence of influenza-like-illness, which may offset the effect of influenza vaccine. A recent study using the RDD method and General Practitioners Research Database (GPRD) revealed that the free influenza vaccination program did not bring the moderate effectiveness for severe outcomes in elderly people.[14] Although all results did not reach statistical significance in our study which was similar to the GPRD study, there were higher point estimates of VE for the hospitalization and mortality. Possible reasons, such as lower vaccination rates in the entire population (Suplementary Table S3) and ineffective herd immunity effect, might explain higher effect when a sharp increase of the vaccination rate at age 70 years in our study. Additionally, a relatively small sample size of analytical data set for the near age-70 years (admission data set or mortality data set converted to ecological panel data set) led to wider CIs compared with the GPRD study,[14] which simultaneously provided an explanation for the absence of an effect on mortality caused by influenza/pneumonia and respiratory.

Influenza vaccination for the elderly adults is recommended in most developed countries,[44–46] but only several developed areas or regions in China provided free influenza vaccination. A national cross-sectional survey showed that the overall influenza vaccination rate was 4.5% for Chinese urban population aged 60 years or older.[47] Even Yinzhou, a developed urban area in China, had a higher proportion (15.3% for population aged 60 or older after the implementation of the policy) of influenza vaccination than other most regions, the vaccination rate for the targeted elderly population was far lower than the WHO recommended 75%[48] and the vaccination rate for the developed countries[49–52] like South Korea (75.6%), Australia (70.9%), United States (71.5%) and United Kingdom (70.8%). Therefore, low vaccination coverage showed a worse herd immunity. Furthermore, because the cross-epidemic of COVID-19 and influenza will bring a burden of cascading effect, it will complicate the differential diagnosis of COVID-19 cases in healthcare facilities and, in turn, increase the risk of COVID-19 transmission. Hence, taking free vaccination policy into account in the administrative plan is particularly important under the circumstance of the COVID-19 pandemic.

Although the first free influenza vaccination program was urgently implemented before 2020 2021 influenza season, the overall vaccine uptake rate is still not very high in the elderly. The following supplementary strategies, including improvement of vaccination services, promoting vaccination facilitation, strengthening the policy promotion and boosting the influenza vaccine deployment, could increase the vaccination coverage. Primary healthcare institutions should increase the number of primary influenza vaccination sites, appropriately early initiate vaccination process, extend of vaccination time, increase daily service duration to provide the convenient services for the old people. Some specific measures, such as centralized vaccination in the nursing home, making an appointment with Party and government organs and enterprises and public institutions for collective vaccination, should be considered to improve vaccination efficiency. The communities should step up the promotion of free influenza vaccination policy and enhance the public's scientific understanding of influenza prevention. In addition, for CDC, it is necessary to assess the influenza vaccine demand, closely track of the status of vaccine procurement, supply, distribution and vaccination, and timely strengthen the dynamic deployment of influenza vaccine to ensure balanced vaccine supply at vaccination sites. On the basis of increasing vaccination rate, expanding the free policy to the children and others who are most likely to spread influenza, may also be necessary to address the high burden of influenza-related complications among older adults.[53]

In this study, the results showed a different or contrary effectiveness of influenza vaccination on hospital admission and mortality between men and women. Potential reasons may be the immune-response heterogeneity, the discrepancy of health awareness, the willingness of medical consultations and the disease spectrum between the genders. In addition, a small sample size for panel data near the age threshold in both men and women is possible to lead to a large variation of point estimates and a wide range of CI from the point view of statistics. The study with a large sample size of panel data is necessary to validate and complete our findings.

The major strength of this study included the use of population-based electronic healthcare database and the utilization of RDD that allows mitigating selection and confounding bias, as well as unmeasured or unknown bias.[54] To the best of our knowledge, this is the first study that evaluates the effect of influenza vaccine using an electronic healthcare database in China. Some limitations should be considered. First, the inherent locality of RDD means that it can only explain the causal effect of those observations near the age of 70 years threshold, and it was difficult to generalize to the whole older population. Second, the medical certificates of death contained only the ICD10 codes for the primary cause of death. As a result, some causes of death cannot be captured, thus the effect of vaccination on a particular cause of death could not be fully assessed.

Third, due to the data use policy that there was a data six-month cache period to ensure data security, we cannot access the latest data when conducting data clean and analysis in March 2022. Additionally, the age threshold of the free vaccination was set at 65 years and older in the next free programs (2021–2022, 2022–2023 influenza seasons), hence, the evaluation of the effectiveness of influenza vaccination had to included just one influenza season data (2020–2021 influenza season) in this study. A single season data resulted in a small sample size of ecologic panel data near the threshold and then led to a large confidence interval range. However, sensitivity analysis with similar results using linear regression could enhance the reliability of this study. Further studies that included the data of more than one influenza season are needed to validate and assess the more comprehensive and accurate effect of influenza vaccine for the elderly.

Conclusions

In summary, these findings revealed a limited effect on hospital admission and mortality for the free influenza vaccination program, which could be related to the low vaccination rate among the elderly. The supplementation strategies of expending immunization coverage and the future studies that included more influenza seasons data and multiple data source are needed to validate the effect of vaccination in the real-world setting, especially under the circumstances of the COVID-19 pandemic, and further provide a more scientific reference for the promotion of free influenza vaccination project to other cities in China.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data can be shared upon request to the corresponding authors in a collaborative research approach.

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