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Review

Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-cause mortality

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ABSTRACT

Keywords: Influenza vaccination Cardiovascular disease Respiratory disease All-cause mortality

Background: Influenza vaccination is a simple strategy recommended for the prevention of influenza infection and its complications. This meta-analysis aimed to provide current supportive evidence for the breadth and validity of the observed protective effects of influenza vaccination on cardiovascular and respiratory adverse outcomes and all-cause mortality in older adults and in general adult population.

Methods: We searched PubMed, Embase, Web of Science, and the Cochrane Library to identify all published studies comparing influenza vaccination with placebo from the database inception to November 11, 2018. These included studies reporting the associations of influenza vaccination with the risk of aforementioned adverse outcomes.

Results: The pooled adjusted relative risks among influenza-vaccinated people relative to unvaccinated people for the outcomes of interest were 0.74 (95% confidence interval [CI] = 0.70 – 0.78) for cardiovascular diseases (63 studies), 0.82 (95% CI = 0.75 – 0.91) for respiratory diseases (29 studies), and 0.57 (95% CI = 0.51 – 0.63) for all-cause mortality (43 studies). We performed subgroup analysis of age, sex, and region/country and found that these protective effects were evident in the general adult population and particularly robust in older adults and in those with pre-existing specific diseases.

Conclusion: Influenza vaccine is associated with a significant risk reduction of cardiovascular and respiratory adverse outcomes as well as all-cause mortality. Such a preventative measure can benefit the general population as well as those in old age and with pre-existing specific diseases.

1. Introduction

Despite significant progress in the advancement of medical and surgical treatment and healthcare delivery, influenza remains to be a cause of significant morbidity and mortality. According to the World Health Organization (WHO), up to 650,000 people die from influenza infection worldwide each year (Organization, 2014). Influenza also causes tremendous loss of productivity and economic burden. For example, in 2015, influenza-related direct medical costs topped $3.2 billion while lost earnings and productivity for adults reached $8 billion in the US (Putri et al., 2018).

Older adults are particularly vulnerable to influenza infection and its complications. In fact, over 90% influenza-related mortality occur in adults aged 65 years and older (Simonsen et al., 2005; Thompson et al., 2009). This is likely because of the multifaceted immune system re-modeling during aging, leading to immune functional decline in older adults, or immunosenescence (Nikolich-Zugich, 2018). The aging immune system also manifests a chronic low-grade inflammatory phenotype (CLIP) or inflamaging that has been implicated in the pathogenesis of almost all age-related chronic conditions including those in the cardiovascular and respiratory systems (Chen et al., 2019; Franceschi et al., 2000). This increased vulnerability to respiratory...
infections is further demonstrated by the ongoing coronavirus disease 2019 (COVID-19) pandemic as older adults suffer disproportionately high rate of severe COVID-19 disease and deaths (Salje and Tran Kiem, 2020; Zhou et al., 2020). While the underlying mechanism for this COVID-19 susceptibility is not known at the present time, CLIP or inflamming is hypothesized to play an important role (Bonafè et al., 2020). Older adults with chronic diseases are particularly at higher risk for influenza infection and its complications and, in turn, influenza infection may worsen their chronic conditions (Sanei and Wilkinson, 2016).

Influenza vaccination has been approved as a simple protective strategy for reducing influenza and its complications (Grohskopf et al., 2016; Wang et al., 2018). It is considered the most effective measure for the prevention of influenza. Especially in the elderly, influenza vaccination has been shown to halve the incidence of serological and clinical influenza (in periods of antigenic drift) (Govaert et al., 1994). Previous studies indicated that influenza vaccination is associated with a significant reduction in respiratory diseases, including influenza and secondary pneumonia (Gross et al., 1995; Nichol et al., 1994; Wang et al., 2002), exacerbation of chronic lung disease (Nichol et al., 1999) including chronic obstructive pulmonary disease (COPD) (Kopsaftis et al., 2018) and acute episodes of asthma (Vasileiou et al., 2017). In recent years, growing attention has turned to cardiovascular diseases, as influenza vaccination has been linked to a significant risk reduction for cardiovascular diseases like stroke (Christiansen et al., 2019; Smeeth et al., 2004), acute coronary syndrome (ACS) (Phrommintonkul et al., 2011; Sung et al., 2014), heart failure (Christiansen et al., 2019; Vardeny et al., 2016), and myocardial infarction (Christiansen et al., 2019; Naghavi et al., 2000; Smeeth et al., 2004). Influenza vaccination is also associated with a significant reduction in mortality in adults aged 65 years and older. In one study after adjusting for age, sex, and risk status, influenza vaccination was found to be associated with a 44% reduction in all-cause mortality (Wang et al., 2007).

However, comprehensive analyses of the data available in the literature that are supportive of protective effects of influenza vaccination beyond influenza prevention in the general population as well as those in old age and with comorbidities are few and far between. Therefore, the objective of this study was to conduct an in-depth synthesis of the available data addressing the breadth and validity of the reported protective effects of influenza vaccination against cardiovascular and respiratory adverse outcomes and all-cause mortality in adults. To this end, we have conducted a meta-analysis of the evidence across existing studies.

2. Methods

2.1. Search strategy

We searched PubMed, Embase, Web of Science, and the Cochrane Library to identify all published studies comparing influenza vaccination with placebo from the database inception to November 11, 2018 and limited the search to English-language papers. The search used key terms, including influenza, influenza vaccination, cohort, case control and randomized controlled trial (RCT).

2.2. Inclusion and exclusion criteria

Our study inclusion criteria were (i) reporting the association between influenza vaccination and cardiovascular diseases, respiratory diseases, and all-cause mortality risk in adults; (ii) comparing an influenza-vaccinated group with an unvaccinated control group; (iii) all RCTs, observational studies, cohort studies (including prospective, retrospective and ambispective cohort studies), and case-control studies; (iv) published in English; (v) results reporting adjusted measures of association (e.g., hazard ratio, risk ratio, or odds ratio) and their 95% confidence intervals (CIs).

We excluded studies that included children, adolescents or pregnant women; studies that measured adverse events like narcolepsy or Guillain-Barre Syndrome after taking influenza vaccination; as well as case series (including self-controlled case series), case reports, reviews, and commentaries. Additionally, studies with incomplete data or duplicate publications were excluded.

2.3. Data extraction and quality assessment

Two investigators (YYC and XXC) extracted data independently, and any disagreement was resolved by consensus or consultation with a third author (ZC). For each study, we collected the first author, journal, year of publication, study design, sample size, population demographics (including study region/country, number of males, and mean age or age range), the number of vaccinated subjects, outcomes, and fully adjusted measures of association with the corresponding 95% CIs.

The Newcastle-Ottawa Scale (NOS) was designed for the evaluation of case-control and cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The quality of each study was graded as good, fair, or poor. To be rated as good, studies needed to meet all the criteria. A study was rated as poor when one or more domains were assessed as having a serious flaw. Studies that met some but not all of the criteria were rated as fair quality. Trail quality was determined as high quality by the Cochrane criteria if at least the first 3 criteria were accounted for, or otherwise of uncertain risk of material bias. Any disagreements or discrepancies regarding study selection, data extraction, and quality assessment were resolved by consensus. The Cochrane Collaboration was employed to evaluate the quality of each RCT (Higgins et al., 2011).

2.4. Outcomes measures, data synthesis and analysis

Outcomes measures for this meta-analysis included overall or composite cardiovascular outcomes and respiratory diseases as well as all-cause mortality. According to the disease outcome extracted from the original studies, the cardiovascular outcomes were further evaluated as individual conditions including stroke, myocardial infarction, ACS, heart failure, ischemic heart disease (IHD), major adverse cardiovascular events (MACEs), cardiovascular mortality, and unspecified heart disease. Similarly, respiratory outcomes were further evaluated as individual conditions, such as COPD, asthma, pneumonia, respiratory failure, respiratory infection, respiratory mortality, and unspecified respiratory disease.

We used a random-effects model to estimate the effect of the influenza vaccination. For each outcome measure of interest, we pooled the confounder-adjusted HR/OR/RR and used the Cochran’s Q chi-square test and $I^2$ statistic to assess the heterogeneity. Subgroup analyses and sensitivity analyses were performed to assess the associations found by selected studies with risks for cardiovascular diseases, respiratory diseases, and all-cause mortality, including age, sex, seasonality, pre-existing specific diseases (e.g., cardiovascular diseases, chronic kidney, COPD, etc.), and region/country. Finally, a funnel plot and Egger’s rank were used to evaluate the publication bias. All statistical procedures used a two-sided significance level of 0.05 and were conducted by Stata v.15.0.

3. Results

3.1. Identification of the studies included in this meta-analysis

Fig. 1 showed a flow diagram for the identification of studies included in this meta-analysis. First, our initial search yielded a total of 53,830 articles, 33,560 articles were included after the removal of duplicates. After screening the titles and abstracts, 33,078 records were excluded because the studies did not meet the selection criteria (e.g., no related outcome [n = 14,657], influenza, not vaccination [n =
11,895], vaccination not our aim [n = 4834], comment/reply/letter [n = 284], subjects not human [n = 205], and meta-analysis [n = 1203]. Full-text articles were assessed for eligibility, 408 records were excluded because they included children or pregnant women [n = 53], did not involve influenza vaccination [n = 80], were conference abstracts [n = 30], or presented outcomes not related to our aim [n = 245]. Finally, we were left with 74 articles (including 75 studies) relevant for our meta-analysis. Among them, 47 were observational cohort studies, 22 were case–control studies, and 6 were RCTs.

3.2. Characteristics of included studies and quality assessment

Table 1 showed the details of the included articles. These articles were published between 1999 and 2018. The sample size of the included studies ranges from 60 to 2,244,594 participants. Among the included studies, one study was performed in the Europe, two were multi-national, and others were conducted in individual countries or regions. Among the latter, eleven were in the United States, three in Argentina, two in Canada, one in Germany, three in China-Hong Kong, three in Israel, one in Italy, three in Japan, three in the Netherlands, two in Poland, one in Saudi Arabia, seven in Spain, two in Sweden, twenty in China-Taiwan, two in Thailand, one in Turkey, and five in the United Kingdom. Some of these studies [n = 63] examined mainly outcomes related to cardiovascular diseases, such as stroke, myocardial infarction, ACS, heart failure, IHD, MACEs, cardiovascular mortality, and unspecified heart disease. Others mainly examined all-cause mortality [n = 43] or respiratory diseases [n = 34] including COPD, asthma, pneumonia, respiratory failure, respiratory infection, respiratory mortality, and unspecified respiratory disease.

Of the 47 cohort studies, 23 were good quality, 19 were fair quality and 5 were poor quality; of the 22 case–control studies, 8 were good quality, 11 were fair quality and 3 were poor quality (details in Supplement Table A).

3.3. Cardiovascular diseases

Influenza vaccination was associated with lower risk of adverse cardiovascular outcomes overall, with a relative risk of 0.74 (95% CI = 0.70 – 0.78; Table 2 and Fig. 2). When stratified by specific cardiovascular conditions, the results showed that influenza vaccination was associated with reduced risk of stroke (RR = 0.80, 95% CI = 0.72 – 0.88), myocardial infarction (RR = 0.81, 95% CI = 0.76 – 0.86), ACS (RR = 0.44, 95% CI = 0.32 – 0.60), heart failure (RR = 0.60, 95% CI = 0.44 – 0.83), IHD (RR = 0.83, 95% CI = 0.77 – 0.90), MACEs (RR = 0.71, 95% CI = 0.62 – 0.82), and cardiovascular mortality (RR = 0.78, 95% CI = 0.65 – 0.94).

In the subgroup analyses, most associations between influenza vaccination and cardiovascular risk reduction remained robust, while some were not significant. There were significant differences in the subgroup analyses according to the presence or absence of pre-existing specific diseases. Individuals with pre-existing diseases had a lower risk of 0.62 (95% CI = 0.54 – 0.72), while individuals without them had a risk of 0.83 (95% CI = 0.80 – 0.86; Table 3).

3.4. Respiratory diseases

Influenza vaccination was also associated with lower risk of adverse respiratory outcomes overall, with a relative risk of 0.82 (95% CI = 0.75 – 0.91; Table 2 and Fig. 3). Regarding specific respiratory diseases, there were no statistically significant differences for COPD (RR = 0.82, 95% CI = 0.47 – 1.43), unspecific respiratory diseases (RR = 1.00, 95% CI = 0.90 – 1.11), respiratory failure (RR = 0.62, 95% CI =
Table 1
Details of the studies included in this meta-analysis.

| Study (year)         | Trial design | Study area, country | Sample size (total) | Sample size (man) | Vaccination (Yes) | Age (years) | Follow-up time | Specific disease | Outcome measured |
|----------------------|--------------|---------------------|---------------------|-------------------|-------------------|-------------|----------------|-----------------|-----------------|
| (Chen et al., 2016)  | Cohort       | China-Taiwan        | 4406                | 1835              | 2206              | 70          | 9 years        | Chronic Kidney Disease | ACS |
| (Lavallée et al., 2014) | Cohort       | Multinational       | 10,108              | 6083              | 5054              | 70          | —              | Recent ischemic stroke or TIA | MACEs, Myocardial infarction, Stroke |
| (Johnstone et al., 2012) | Cohort       | Multinational       | 31,546              | 18,278            | 12,241            | ≥ 55        | 6 months-5.5 years | Vasculardisease | MACEs |
| (Hu et al., 2013)    | Cohort       | China-Taiwan        | 29,178              | 14,581            | 7613              | All ages    | 8 years        | COPD           | IHD |
| (Kao et al., 2017)   | Cohort       | China-Taiwan        | 5670                | 3470              | 2547              | 73.39 ± 9.65 | 8 years        | Atrial fibrillation | Stroke |
| (Jia et al., 2012)   | Cohort       | China-Taiwan        | 1964                | 111               | 501               | ≥ 50        | 8 years        | Acute heart failure | All-cause mortality |
| (Hev et al., 2016)   | Cohort       | China-Taiwan        | 202,058             | 101,746           | 93,051            | ≥ 65        | 64 weeks       | Pneumonia, COPD, Asthma, Stroke, BID, Myocardial infarction, Heart failure, All-cause mortality |
| (Jin et al., 2019)   | Cohort       | China-Taiwan        | 202,058             | —                 | 93,051            | ≥ 65        | —              | —              | — |
| (Chen et al., 2013)  | Cohort       | China-Taiwan        | 25,609              | 13,860            | 3345              | ≥ 55        | 12 months      | COPD           | IHD |
| (Arriola et al., 2017) | Cohort       | US                  | 16,284              | 7450              | 8142              | ≥ 75        | 1 year         | Hospitalization of influenza | Heart failure, Cardiovascular mortality |
| (Kaya et al., 2017)  | Cohort       | Turkey              | 656                 | 473               | 265               | 62 ± 13     | 15 ± 6 months  | Heart failure | Heart failure, Cardiovascular mortality |
| (Tay et al., 2016)   | Cohort       | Thailand            | 2,244,594           | 770,913           | 874,221           | 51.5 ± 18.7 | 6 months       | Respiratory infection | Pneumonia |
| (Chang et al., 2018) | Cohort       | China-Taiwan        | 16,284              | 7450              | 8142              | ≥ 75        | 1 year         | All-cause mortality | Pneumonia |
| (Christensen et al., 2019) | Cohort       | Sweden              | 163,931             | 134,045           | 75                  | ≥ 65        | 12 months      | All-cause mortality | Respiratory infection, Pneumonia, COPD, Heart failure |
| (Li et al., 2018)    | Cohort       | China-Taiwan        | 8080                | 4596              | 4434              | ≥ 20        | 9 years        | Chronic hepatitis B virus infection | Heart disease, Respiratory failure, All-cause mortality |
| (Herag et al., 2019) | Cohort       | US                  | 12,566              | 5899              | 8479              | ≥ 65        | 1 year         | —              | All-cause mortality |
| (Landi et al., 2020) | Cohort       | Italy               | 2082                | 837               | 1245              | 78.8 ± 9.5  | 12 months      | —              | All-cause mortality |

(continued on next page)
| Study | Trial design | Study area, country | Sample size (total) | Sample size (man) | Vaccination (Yes) | Age (years) | Follow-up time | Specific disease | Outcome measured |
|-------|--------------|---------------------|--------------------|------------------|------------------|-------------|---------------|----------------|-----------------|
| Armstrong et al., 2004 | Cohort | UK | 24,535 | — | — | ≥75 | 4 years | — | All-cause mortality, Cardiovascular mortality, Respiratory mortality, Stroke, Myocardial infarction | — |
| Voordouw et al., 2004 | Cohort | Netherlands | 26,071 | 15,131 | 11,759 | ≥65 | 6 years | — | All-cause mortality, Cardiovascular mortality, Respiratory mortality | — |
| Vila-Córcoles et al., 2008 | Cohort | Spain | 1298 | 960 | 836 | 75.4±6.9 | 40 months | COPD | All-cause mortality | — |
| de Diego et al., 2009 | Cohort | Spain | 1340 | 635 | 860 | 76.2±7.1 | 3 years and 3 months | CHD | All-cause mortality | — |
| Li et al., 2012 | Cohort | China-Taiwan | 5048 | 2793 | 2750 | Non-vaccinated: 75.7±7.0 Vaccinated: 74.8±6.3 | 4 years | IHD | All-cause mortality, Cardiovascular diseases | — |
| Chan et al., 2013 | Cohort | China-Hong Kong | 1859 | 634 | 1214 | Non-vaccinated: 85.8±7.9 Vaccinated: 85.8±7.5 | 1 year | — | All-cause mortality, Pneumonia mortality | — |
| Mahamat et al., 2013 | Cohort | France | 43,818 | 13,562 | 18,671 | >65 | 1 year | — | All-cause mortality | — |
| Li et al., 2014 | Cohort | China-Taiwan | 5063 | 2370 | 3393 | — | 1 year | — | All-cause mortality, Respiratory diseases | — |
| Castilla et al., 2015 | Cohort | Spain | 208,296 | — | 112,480 | ≥65 | 5 months | — | All-cause mortality | — |
| Chan et al., 2016 | Cohort | China-Taiwan | 10,125 | 1172 | 1750 | >18 | 1 year | — | Systemic Lupus Erythematosus, Pneumonia, Heart disease, All-cause mortality | — |
| Gurfinkel and de la Fuente, 2004 | RCT | Argentina | 301 | 126 | 175 | >21 | 2 years | ACS | Myocardial Infarction/PCI | — |
| Gurfinkel et al., 2002 | RCT | Argentina | 301 | 126 | 175 | >21 | 6 months | — | Myocardial Infarction/PCI | — |
| Gurfinkel et al., 2004 | RCT | Argentina | 292 | 126 | 176 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
| Siscovick et al., 2000 | Case-control | US | 891 | 713 | 255 | 25−74 | 6 years | — | Cardiac arrest | — |
| Graue et al., 2005 | Case-control | Germany | 740 | 510 | 230 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
| Siriwardena et al., 2010 | Case-control | UK | 78,706 | 30,339 | 18,575 | ≥40 | — | — | Myocardial infarction | — |
| Huan et al., 2017 | Case-control | China-Taiwan | 19,788 | 11,574 | 6226 | ≥45 | ≥5 years or until date of death | COPD | Respiratory failure, Stroke, TIA | — |
| Tsai et al., 2007 | Case-control | Taiwan | 1729 | 906 | 867 | 72.9±6.1 | 1 year | — | Respiratory infection, Stroke, TIA | — |
| Heffelfinger et al., 2006 | Case-control | US | 2485 | 819 | 1666 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
| Yokomichi et al., 2014 | Case-control | Japan | 150 | 116 | 52 | ≥18 | — | Myocardial Infarction/PCI | — |
| Bond et al., 2012 | Case-control | US | 20,220 | 9494 | 10,726 | ≥21 | 1 year | — | Myocardial Infarction/PCI | — |
| Chang et al., 2016 | Case-control | China-Taiwan | 56,870 | 31,539 | 16,431 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
| Chan et al., 2017 | Case-control | China-Taiwan | 160,726 | 89,474 | 71,252 | ≥21 | 1 year | — | Myocardial Infarction/PCI, Stroke, Myocardial infarction, Stroke | — |
| Lavallee et al., 2002 | Case-control | France | 270 | 168 | 102 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
| Li et al., 2019 | Case-control | US | 534 | 279 | 325 | >21 | 1 year | — | Myocardial Infarction/PCI | — |
Table 1 (continued)

| Study | Trial design | Study area, country | Sample size (total) | Sample size (man) | Vaccination (Yes) | Age (years) | Follow-up time | Specific-disease | Outcome measured |
|-------|--------------|---------------------|---------------------|-------------------|------------------|-------------|----------------|------------------|------------------|
| (Naghavi et al., 2000) | Case-control | US | 218 | 137 | 123 | cases:62.9 ± 11.9 controls:64.6 ± 13.5 | — | CHD | Myocardial infarction |
| (Piñol-Ripoll et al., 2008) | Case-control | Spain | 794 | 426 | 311 | cases:73.48 ± 11.45 controls:73.18 ± 10.08 | — | Chronic Bronchitis and Acute Infections | Stroke |
| (Siriwardena et al., 2014) | Case-control | UK | 94,022 | 45,168 | 7021 | ≥ 18 | — | — | Stroke, TIA |
| (Ting et al., 2011) | Case-control | UK | 586 | 380 | 293 | 68 | — | COPD | COPD |
| (Razavi et al., 2005) | Case-control | Saudi Arabia | 51,100 | — | 17,565 | — | — | Respiratory diseases |
| (Kondo et al., 2015) | Case-control | Japan | 60 | 33 | 18 | ≥ 65 | — | — | Pneumonia |
| (Washio et al., 2016) | Case-control | Japan | 160 | 98 | 74 | ≥ 65 | — | — | Pneumonia |
| (Jordan et al., 2007) | Case-control | UK | 796 | — | 591 | ≥ 65 | — | Acute respiratory illness | Respiratory diseases |
| (Puig-Barberà et al., 2007) | Case-control | Spain | 1301 | — | 971 | ≥ 65 | — | — | ACS, Stroke, Pneumonia |

RCT: randomized controlled trial; COPD: Chronic Obstructive Pulmonary Disease; HBV: Hepatitis B Virus; ACS: Acute Coronary Syndrome; TIA: Transient Ischemic Attack; MACEs: Major Adverse Cardiovascular Events; IHD: Ischemic Heart Disease; PCI: Percutaneous Coronary Intervention.

“—” represented data not available.
Our results indicated that influenza vaccination had protective effects as well as RCTs evaluating potential impact of influenza vaccination on severe cardiovascular and respiratory outcomes and all-cause mortality. Our results indicated that influenza vaccination had protective effects against morbidity and mortality of cardiovascular diseases (RR = 0.74, 95 % CI = 0.70–0.78) and respiratory diseases (RR = 0.82, 95 % CI = 0.75–0.91) as well as all-cause mortality (RR = 0.57, 95 % CI = 0.51–0.63). Subgroup analyses showed that those effects of influenza vaccination were evident in the general population as well as in older adults and those with pre-existing specific diseases.

The results on composite and specific cardiovascular adverse outcomes are consistent with two meta-analyses of RCTs that demonstrate significant association between influenza vaccination and a lower risk of major adverse cardiovascular events (Clar et al., 2015; Udell et al., 2013), with a more pronounced effect in high-risk patients with recent coronary artery disease (Udell et al., 2013). In patients with heart failure, influenza vaccination in the previous year has been shown to reduce the risk of mortality and hospitalization (Fukuta et al., 2019; Poudel et al., 2019; Rodrigues et al., 2020). Influenza vaccination is also reported to reduce the risk of stroke (Lee et al., 2017; Smeeth et al., 2004; Tsivgoulis et al., 2018).

The underlying mechanisms for the observed protective effects of influenza vaccination against cardiovascular adverse events (and all-cause mortality) are likely complex and yet to be elucidated. However, several hypotheses have been proposed. First, respiratory infections including influenza can acutely increase cardiac and pulmonary workload and burden and, thus, trigger acute cardiovascular events, particularly in individuals with existing clinical or subclinical atherosclerosis or coronary artery disease. As such, by virtue of infection prevention, influenza vaccination provides cardiovascular protection. While this is a plausible mechanism, it cannot account for the effect size of cardiovascular protective effects from influenza vaccination, particularly during mild influenza seasons. Immune modulation on chronic inflammation, i.e., aforementioned age-related CLIP or inflammaging, has also been proposed as an attractive underlying mechanism. This is because age-related CLIP or inflammaging is known to play an important role in the development of atherosclerosis, coronary artery disease, and stroke (Chen et al., 2019; Elkind, 2009; Ferrucci and Fabbri, 2018). Acutely, influenza infection can cause local and systemic inflammatory response (Madjid et al., 2007) that can adversely impact plaque stability, leading to plaque rupture and acute cardiovascular events (Barnett, 2019). Therefore, annual influenza vaccination may prevent or delay the development or progression of atherosclerosis through its immune modulation of age-related CLIP or inflammaging for the long term and prevent adverse cardiovascular events acutely through its regulation on influenza-induced inflammatory response. By extension of the latter, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes acute systemic inflammatory response or “cytokine storm” in severe COVID-19 (Moore and June, 2020). Whether influenza vaccination could regulate such cytokine storm and mitigate

### Table 2

Characteristics and main findings from the studies reporting pertinent outcomes.

| Outcomes                          | No. of studies | Relative risk (95 % CI) | P value | I² (%) | Tau-squared | Egger's test |
|-----------------------------------|----------------|-------------------------|---------|--------|-------------|--------------|
| Cardiovascular diseases           | 63             | 0.74 (0.70 – 0.78)      | 0.000   | 88.2   | 0.025       | 0.013        |
| Stroke                            | 15             | 0.80 (0.72 – 0.88)      | 0.000   | 89.9   | 0.024       |              |
| Myocardial infarction             | 10             | 0.81 (0.76 – 0.86)      | 0.161   | 31.0   | 0.092       |              |
| Acute coronary syndrome           | 4              | 0.44 (0.32 – 0.60)      | 0.002   | 79.2   | 0.066       |              |
| Heart failure                     | 8              | 0.60 (0.44 – 0.83)      | 0.000   | 93.5   | 0.172       |              |
| Ischemic heart disease            | 4              | 0.83 (0.77 – 0.90)      | 0.000   | 0.0    | 0.000       |              |
| MACIs                             | 9              | 0.71 (0.62 – 0.82)      | 0.000   | 83.7   | 0.029       |              |
| Cardiovascular mortality          | 7              | 0.78 (0.65 – 0.94)      | 0.129   | 39.3   | 0.021       |              |
| Unspecific heart disease          | 3              | 0.74 (0.52 – 1.05)      | 0.009   | 78.7   | 0.064       |              |
| Respiratory diseases              | 34             | 0.82 (0.75 – 0.91)      | 0.000   | 85.7   | 0.052       | 0.971        |
| COPD                              | 3              | 0.82 (0.47 – 1.43)      | 0.002   | 83.6   | 0.194       |              |
| Pneumonia                         | 15             | 0.79 (0.65 – 0.95)      | 0.000   | 86.0   | 0.078       |              |
| Respiratory failure               | 3              | 0.62 (0.38 – 1.00)      | 0.000   | 91.5   | 0.158       |              |
| Respiratory infection             | 2              | 0.95 (0.82 – 1.09)      | 0.085   | 66.3   | 0.007       |              |
| Respiratory mortality             | 6              | 0.79 (0.67 – 0.92)      | 0.016   | 64.3   | 0.022       |              |
| Unspecific respiratory diseases    | 4              | 1.00 (0.90 – 1.11)      | 0.269   | 23.6   | 0.003       |              |
| All-cause mortality               | 43             | 0.57 (0.51 – 0.63)      | 0.000   | 93.6   | 0.090       | 0.235        |
Fig. 2. Forest plot of incident cardiovascular diseases associated with influenza vaccination.
The present study is that we used influenza vaccination as our keyword and did not limit the outcomes, enabling us to increase the chance of detecting all outcomes. Our study has several limitations. First, heterogeneity was evident within individual outcome endpoints. We only performed subgroup analyses according to age, sex, study design, study country or region, and pre-existing specific disease. Second, given the lack of more detailed study parameters such as the type or dose of influenza vaccine administered, we were unable to examine other factors.

Most previous studies have focused on one specific outcome or patient population with a specific disease. A major strength of the present study is that we used influenza vaccination as our keyword and did not limit the outcomes, enabling us to increase the chance of detecting all outcomes. Our study has several limitations. First, heterogeneity was evident within individual outcome endpoints. We only performed subgroup analyses according to age, sex, study design, study country or region, and pre-existing specific disease. Second, given the lack of more detailed study parameters such as the type or dose of influenza vaccine administered, we were unable to examine other factors.
that can potentially account for the observed heterogeneity. Third we extracted the adjusted estimates (OR/RR/HR), but were unable to convert them into a unified format. Finally, as the funnel plot revealed an apparent asymmetry, there are potential publication bias, language bias, and potential risk of inflated estimates by a flawed methodological design in smaller studies and/or a lack of publication of small trials with opposite results. Despite of these limitations, findings from this comprehensive and in-depth meta-analysis suggest significant protective effects of influenza vaccination against cardiovascular and respiratory adverse outcomes as well as all-cause mortality. They also provide strong evidence to support and promote influenza vaccination coverage. In the US, influenza vaccination coverage in the general adult population remains suboptimal (Ji et al., 2019) and the National Institute of Allergy and Infectious Disease (NIAID) of NIH has launch the universal influenza vaccine initiative (Paules et al., 2017). The situation in China is even more concerning as a national survey conducted from 2004 to 2014 reported vaccination coverage in China as low as 1.5–2% (Yan et al., 2016). Therefore, efforts for promoting vaccination coverage (Li and Leng, 2020) and evidence supporting such efforts have profound public health implications, particularly in the era of the ongoing COVID-19 pandemic.

![Fig. 3. Forest plot of incident respiratory diseases associated with influenza vaccination.](image-url)
5. Conclusion

This meta-analysis provides comprehensive summary and synthesis of existing evidence supportive of significant associations between influenza vaccination and reduced risks for cardiovascular diseases and respiratory adverse outcomes as well as all-cause mortality. These beneficial associations are evident not only in older adults and individuals with pre-existing conditions, but also in the general adult population across different countries and regions, indicating the generalizability. The findings also point out the need for more RCTs to further evaluate and confirm the beneficial health effects of influenza vaccination on respiratory health and other important health outcomes beyond influenza prevention. They also provide supportive evidence for promoting influenza vaccination coverage with significant public health implications, particularly in the era of the ongoing COVID-19 pandemic.

Funding

This study was funded by the National Natural Science Foundation of China (NSFC, Grant No. 71910107004, 91746205) to YGW, National Institutes of Health (NIH) of USA (R01 AI108907, R21 AG059742, and U54 AG062333) to SXL, Irma and Paul Milstein Program for Senior Health fellowship award to CJW and funding from Milstein Medical Asian American Partnership (MMAAP) Foundation of USA (www.mmaapf.org) to SXL.

Declaration of Competing Interest

We declare no competing interests.
Appendix A. Supplementary data can be found at the online version, at doi:https://doi.org/10.1016/j.arr.2020.101124.

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