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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

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 remodeling during aging, leading to immune functional decline in older adults, or immunosenescence (Nikolich-Žugich, 2018). The aging immune system also manifests a chronic low-grade inflammatory phenotype (CLIP) or inflammaging 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

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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 inflammaging 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) (Phrommintikul 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-Barré 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 unspecific heart disease. Similarly, respiratory outcomes were further evaluated as individual conditions, such as COPD, asthma, pneumonia, respiratory failure, respiratory infection, respiratory mortality, and unspecific 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-exiting 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 =

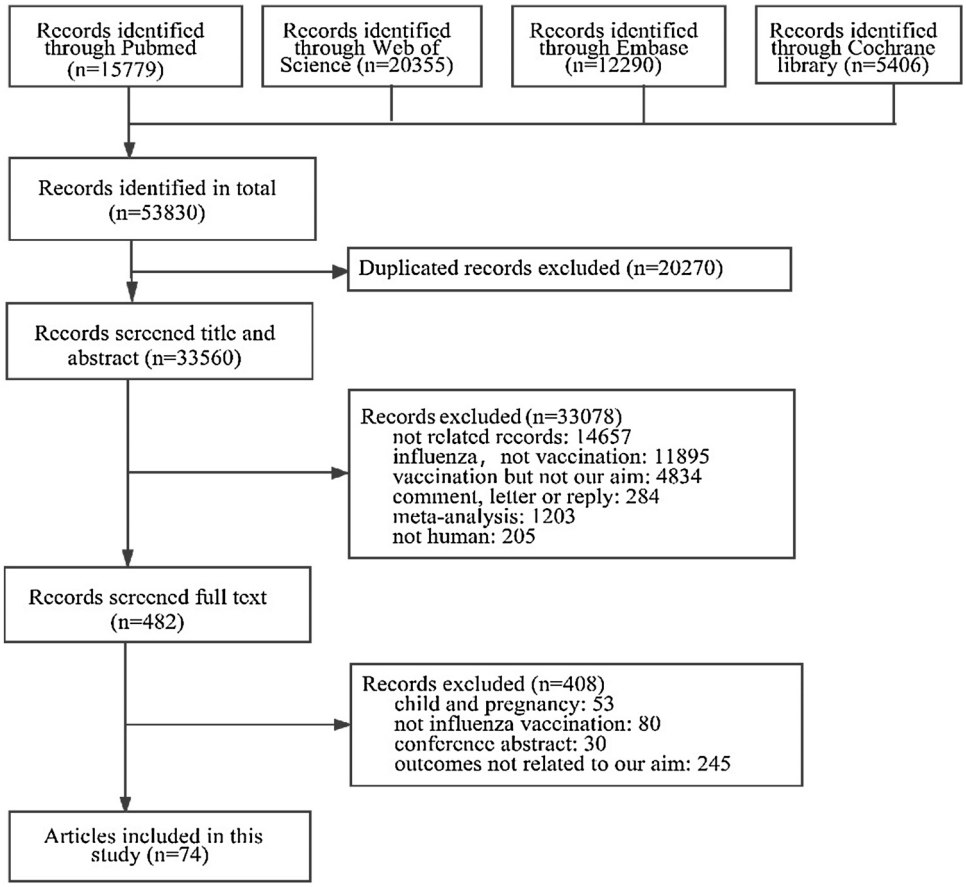

Fig. 1. Details of study selection for meta-analysis.

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, two in France, 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 unspecific 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 unspecific 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	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	12,441	≥55	6 months-5.5 years	Vascular disease	MACEs
(Huang et al., 2013)	Cohort	China-Taiwan	29,178	14,581	6713	All ages	8 years	COPD	IHD
(Kao et al., 2017)	Cohort	China-Taiwan	6570	3470	2547	73.39 ± 9.65	8 years	Atrial fibrillation	Stroke
(Liu et al., 2012)	Cohort	China-Taiwan	6570	3470	2547	73.39 ± 9.65	8 years	Atrial fibrillation	Stroke
(Kopel et al., 2014)	Cohort	Israel	1964	111	501	≥50	1 − 4 years	Acute heart failure	All-cause mortality
(Hsu et al., 2016)	Cohort	China-Taiwan	202,058	101,746	93,051	≥65	1 year	—	Myocardial infarction
(Hung et al., 2010)	Cohort	China-Hong Kong	36,636	—	9368	≥65	64 weeks	—	Pneumonia, COPD, Asthma, Stroke, IHD, Myocardial infarction, Heart failure, All-cause mortality
(Nichol et al., 1999)	Cohort	US	1898	926	1366	≥65	11 months	Chronic lung disease	Respiratory diseases, All-cause mortality
(Campitelli et al., 2010)	Cohort	Canada	25,922	10,569	14,512	≥65	1 year or until date of death	—	All-cause mortality
(Ortqvist et al., 2007)	Cohort	Sweden	260,155	103,620	98,199	≥65	9 month	—	All-cause mortality
(Spaude et al., 2007)	Cohort	US	8251	4544	1590	≥18	—	Community-Acquired Pneumonia	All-cause mortality
(Voordouw et al., 2004)	Cohort	Netherlands	17,822	7178	8911	≥65	6 months	—	All-cause mortality, Pneumonia
(Shapiro et al., 2003)	Cohort	Israel	84,613	—	36,569	≥65	4 months	—	All-cause mortality
(Wang et al., 2016)	Cohort	China-Taiwan	4178	1807	2089	58.8	12 months	Peritoneal dialysis patients	Respiratory failure, Stroke, Heart failure, All-cause mortality
(Rodriguez-Blanco et al., 2012)	Cohort	Spain	2650	1093	1586	≥65	28 months	Diabetes	All-cause mortality
(Heymann et al., 2004)	Cohort	Israel	15,556	7929	8200	≥65	1 year	Diabetes	All-cause mortality
(Chan et al., 2012)	Cohort	China-Hong Kong	286	107	211	≥65	12 months	—	All-cause mortality, Pneumonia mortality, Cardiovascular mortality
(Eurich et al., 2008)	Cohort	Canada	704	381	352	≥17	Until death or patient discharge	Pneumonia	All-cause mortality
(Fang et al., 2016)	Cohort	China-Taiwan	4406	2571	2254	>55	12 years	Chronic Kidney Disease	Heart failure
(Sung et al., 2014)	Cohort	China-Taiwan	7722	4631	3027	≥55	12 years	COPD	ACS
(Nichol et al., 2003)	Cohort	US	140,055	61,218	77,738	≥65	1 year	—	Cardiac disease, IHD, Heart failure, Stroke, All-cause mortality
(Nichol et al., 2003)	Cohort	US	146,328	65,024	87,357	≥65	1 year	—	IHD, Heart failure, Stroke, All-cause mortality
(Chen et al., 2013)	Cohort	China-Taiwan	25,609	13,860	3345	≥55	8 years	COPD	Heart failure
(Arriola et al., 2017)	Cohort	US	4910	2277	1749	≥18	1 year	Hospitalization of influenza	All-cause mortality
(Kaya et al., 2017)	Cohort	Turkey	656	473	265	62 ± 13	15 ± 6 months	Heart failure	Heart failure, Cardiovascular mortality
(Blaya-Nováková et al., 2016)	Cohort	Spain	3229	1211	1468	73.6 ± 13.2	4 years	Heart failure	All-cause mortality
(Voordouw et al., 2006)	Cohort	Netherlands	26,071	15,131	3063	≥65	6 years	—	Respiratory infection, Pneumonia
(Silaporn and Jiamsiri, 2018)	Cohort	Thailand	2,244,594	770,913	874,221	51.5 ± 18.7	1 year	—	Pneumonia
(Chang et al., 2012)	Cohort	China-Taiwan	16,284	7450	8142	≥75	12 months	—	All-cause mortality, Respiratory diseases, COPD, Heart failure
(Christenson et al., 2004)	Cohort	Sweden	163,391	—	134,045	≥65	—	—	Pneumonia, Pneumonia mortality, All-cause mortality
(Su et al., 2016)	Cohort	China-Taiwan	8080	4596	4434	≥20	9 years	Chronic hepatitis B virus infection	Heart disease, Respiratory failure, All-cause mortality
(Herzog et al., 2003)	Cohort	US	12,566	5899	4820	≥65	1 year	—	All-cause mortality
(Landi et al., 2003)	Cohort	Italy	2082	837	1084	78.8 ± 9.5	12 months	—	All-cause mortality

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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
(Armstrong et al., 2004)	Cohort	UK	24,535	—	—	≥75	4 years	—	All-cause mortality, Cardiovascular mortality, Respiratory mortality
(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	3years and 3 months	CHD	All-cause mortality
(Liu et al., 2012)	Cohort	China-Taiwan	5048	2793	2760	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
(Lee et al., 2014)	Cohort	China-Taiwan	5063	2370	3378	Non-vaccinated:78.0 ± 7.6 Vaccinated:77.3 ± 7.1	1 year	—	All-cause mortality, Respiratory diseases
(Castilla et al., 2015)	Cohort	Spain	208,296	—	112,480	≥65	5 months	—	All-cause mortality
(Chang et al., 2016)	Cohort	China-Taiwan	10,125	1172	1765	> 18	1 year	Systemic Lupus Erythematosus	Pneumonia, Heart disease, All-cause mortality
(Poscia et al., 2017)	Cohort	European Union	3510	886	2866	84.6 ± 7.2	1 year	—	All-cause mortality
(Liu et al., 2018)	Cohort	China-Taiwan	33,806	16,340	16,903	≥66	—	Major Surgery	Pneumonia, All-cause mortality
(Ciszewski et al., 2008)	RCT	Poland	658	477	325	59.9 ± 10.3	298 days	CAD/stable angina	MACEs, Cardiovascular mortality
(Ciszewski et al., 2010)	RCT	Poland	658	477	325	59.9 ± 10.3	298 days	CAD/stable angina	Myocardial infarction
Phrommintikul et al., 2011)	RCT	Thailand	439	249	221	66 ± 9	360 days	ACS	MACEs, Cardiovascular mortality, ACS, Heart failure
(Gurfinkel and de la Fuente, 2004)	RCT	Argentina	301	126	151	> 21	2 years	ACS	All-cause mortality
(Gurfinkel et al., 2002)	RCT	Argentina	301	126	151	> 21	6 months	Myocardial Infarction/PCI	All-cause mortality, MACEs
(Gurfinkel et al., 2004)	RCT	Argentina	292	126	151	> 21	1 year	—	Cardiovascular mortality
(Siscovick et al., 2000)	Case-control	US	891	713	255	25−74	6 years	—	Cardiac arrest
(Grau et al., 2005)	Case-control	Germany	740	510	187	60.6 ± 12.8	18 months	Ischemic or hemorrhagic stroke or TIA	Stroke, TIA
(Siriwardena et al., 2010)	Case-control	UK	78,706	30,339	15,575	≥40	—	—	Myocardial infarction
(Huang et al., 2017)	Case-control	China-Taiwan	19,788	11,574	6226	≥45	≥5 years or until date of death	COPD	Respiratory failure
(Tsai et al., 2007)	Case-control	China-Taiwan	1729	906	867	72.93 ± 6.12	1 year	—	Respiratory infection
(Heffelfinger et al., 2006)	Case-control	US	2485	819	1145	≥65	—	—	Myocardial infarction
(Yokomichi et al., 2014)	Case-control	Japan	150	116	52	≥18	—	Idiopathic interstitial pneumonia	All-cause mortality
(Bond et al., 2012)	Case-control	US	20,220	—	14,226	—	1 year	3 End-Stage Renal Disease	All-cause mortality
(Chang et al., 2016)	Case-control	China-Taiwan	56,870	31,676	16,451	70.9 ± 13.4	—	—	Atrial fibrillation
(Chiang et al., 2017)	Case-control	China-Taiwan	160,726	89,474	62,331	≥65	—	—	MACEs, Myocardial infarction, Stroke
(Lavallée et al., 2002)	Case-control	France	270	168	149	≥60	—	—	Stroke
(Lin et al., 2014)	Case-control	China-Taiwan	3120	1692	2890	≥65	—	—	Stroke
(Meyers et al., 2004)	Case-control	US	534	279	303	≥49	—	—	Myocardial infarction

(*continued on next page*)

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	431	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.

Table 2
Characteristics and main findings from the studies reporting pertinent outcomes.

Outcomes	No. of studies	Relative risk (95 % CI)	P value	I^2 (%)	Tau-squared	Egger's test
Cardiovasculardiseases	**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	0.002	
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	
MACEs	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**

0.38 − 1.00), or respiratory infections (RR = 0.95, 95 % CI = 0.82 − 1.09). In contrast, there was a statistically significant reduction in pneumonia and respiratory mortality in those who received the influenza vaccination, with relative risks of 0.79 (95 % CI = 0.65 − 0.95) and 0.79 (95 % CI = 0.67 − 0.92), respectively (Fig. 3).

In the subgroup analysis according to age, the results showed that in the group aged over 65, influenza vaccination reduced the risk of respiratory diseases (RR = 0.86, 95 % CI = 0.77 − 0.96), while in the group younger than 65, influenza vaccination had no significant relationship with the risk of respiratory diseases (RR = 0.92, 95 % CI = 0.70–1.22; Table 3).

3.5. All-cause mortality

We have identified 43 studies that examined the association of influenza vaccination with all-cause mortality. The pooled estimates from these studies showed a significant risk reduction of all-cause mortality for vaccinated compared with unvaccinated individuals (RR = 0.57, 95 % CI = 0.51–0.63; Table 3 and Fig. 4).

In the subgroup analyses, except in Japan, the association of influenza vaccination with all-cause mortality remained statistically significant (Table 3).

3.6. Publication bias

We conducted funnel plot analysis to check for potential publication bias, and the funnel plot was generally symmetric, indicating the absence of publication bias. This was further confirmed by a non-significant Egger's test for respiratory diseases, $P = 0.971$ and all-cause mortality, $P = 0.235$, except for that for cardiovascular outcomes, $P = 0.013$.

3.7. Sensitivity analyses

We did sensitivity analysis excluding any trial from the pooled result. Results for the primary end point were similar when after removal of any trial from the pooled result (details in Supplement Table B).

4. Discussion

This meta-analysis included large cohort and case-control studies 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

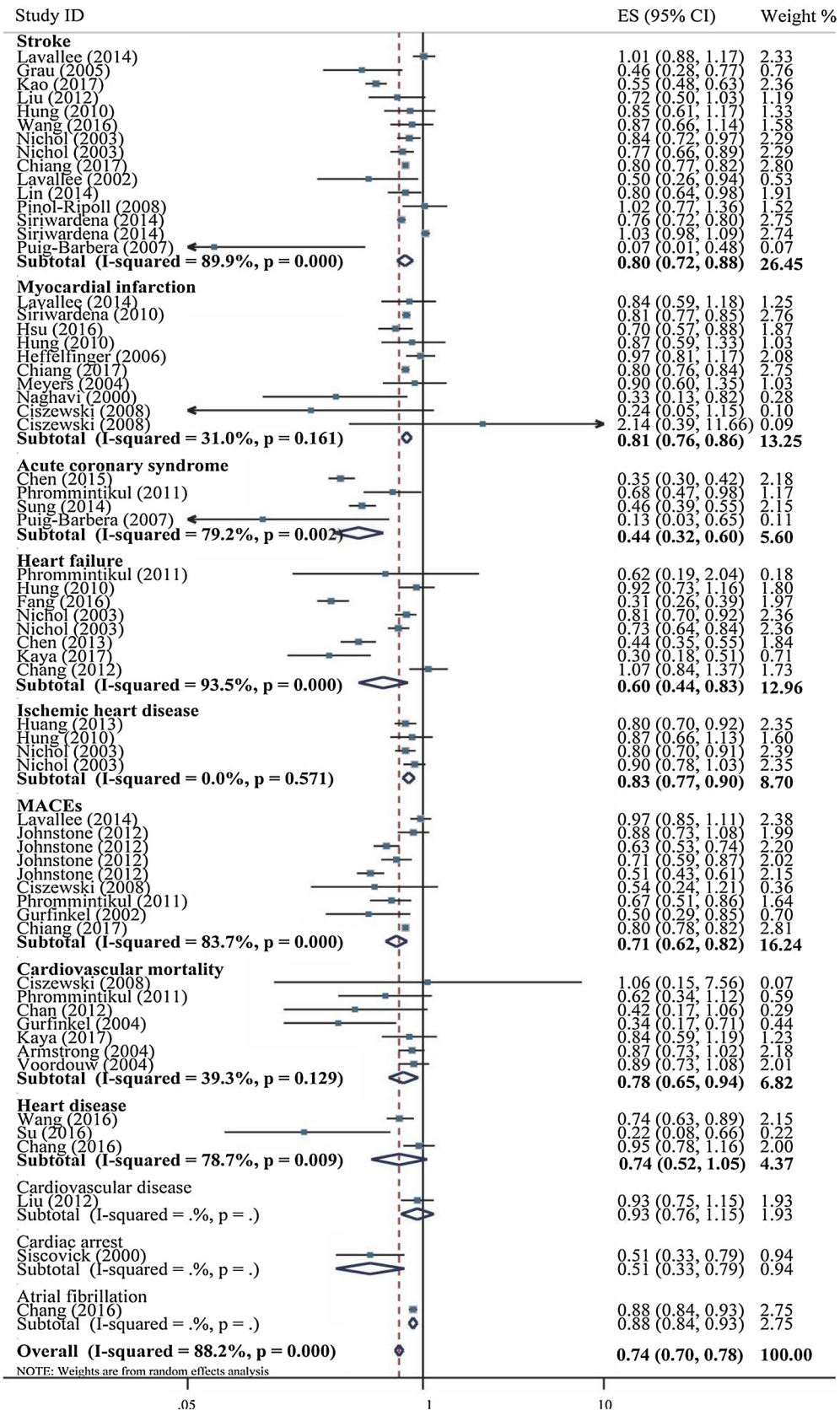

Fig. 2. Forest plot of incident cardiovascular diseases associated with influenza vaccination.

Table 3
Subgroup analyses of the associations between influenza vaccination and risk of cardiovascular diseases, respiratory diseases and all-cause mortality.

Component		Number of entries	RR (95 %CI) random effects
Cardiovascular diseases			
Sex	Men	17	0.66 (0.58, 0.75)
	Women	17	0.66 (0.59, 0.75)
Age (years)	< 65	12	0.76 (0.66, 0.88)
	≥65	32	0.74 (0.70, 0.79)
Seasonality	Influenza	16	0.69 (0.63, 0.76)
	Non-influenza	16	0.63 (0.54, 0.73)
Pre-existing specific diseases	Yes	35	0.62 (0.54, 0.72)
			0.83 (0.80, 0.87)
	No	28	0.83 (0.80, 0.87)
Study design	Cohort	30	0.69 (0.61, 0.79)
	Case-control	23	0.82 (0.78, 0.86)
	RCT	10	0.62 (0.52, 0.73)
Country/Region	International	7	0.77 (0.63, 0.95)
	Germany	1	0.46 (0.28, 0.76)
	China-Taiwan	19	0.68 (0.63, 0.74)
	China-Hong Kong	5	0.87 (0.75, 1.00)
	United States	10	0.81 (0.75, 0.88)
	France	1	0.50 (0.26, 0.95)
	Spain	3	0.25 (0.04, 1.62)
	United Kingdom	4	0.86 (0.74, 1.00)
	Thailand	4	0.67 (0.55, 0.81)
	Turkey	2	0.51 (0.19, 1.40)
	Poland	4	0.64 (0.29, 1.39)
	Argentina	2	0.44 (0.28, 0.67)
	Netherlands	1	0.89 (0.73, 1.08)
Respiratory diseases			
Sex	Men or Women	34	0.82 (0.75, 0.91)
Age (years)	< 65	2	0.92 (0.70, 1.22)
	≥65	23	0.86 (0.77, 0.96)
Pre-existing specific diseases	Yes	8	0.69 (0.56, 0.86)
	No	26	0.88 (0.80, 0.96)
Study design	Cohort	27	0.84 (0.75, 0.94)
	Case-control	7	0.80 (0.66, 0.96)
Country/Region	China-Taiwan	10	0.79 (0.66, 0.94)
	China-Hong Kong	6	0.76 (0.67, 0.87)
	United States	1	0.76 (0.53, 1.09)
	Spain	1	0.31 (0.14, 0.70)
	United Kingdom	3	0.84 (0.59, 1.19)
	Thailand	4	1.28 (1.00, 1.65)
	Netherlands	4	0.94 (0.81, 1.09)
	Japan	2	0.30 (0.12, 0.76)
	Sweden	3	0.91 (0.80, 1.04)
All-cause mortality			
Sex	Men	3	0.47 (0.32, 0.68)
	Women	3	0.53 (0.32, 0.86)
Seasonality	Influenza	5	0.56 (0.45, 0.69)
	Non-influenza	3	0.79 (0.69, 0.90)
Pre-existing specific diseases	Yes	23	0.50 (0.41, 0.62)
	No	20	0.63 (0.56, 0.71)
Study design	Cohort	40	0.56 (0.50, 0.63)
	Case-control	3	0.73 (0.67, 0.80)
Country/Region	China-Taiwan	7	0.47 (0.35, 0.63)
	China-Hong Kong	3	0.74 (0.62, 0.88)
	United States	7	0.54 (0.45, 0.65)
	Israel	6	0.49 (0.31, 0.77)
	Spain	5	0.77 (0.68, 0.87)
	Argentina	2	0.28 (0.10, 0.74)
	Netherlands	2	0.77 (0.71, 0.83)
	Canada	2	0.57 (0.45, 0.73)
	Sweden	3	0.40 (0.24, 0.69)
	Japan	2	0.79 (0.31, 2.03)
	Italy	1	0.73 (0.56, 0.95)
	Europe	1	0.80 (0.65, 0.98)
	United Kingdom	1	0.89 (0.80, 0.98)
	France	1	0.84 (0.76, 0.94)

severe COVID-19 deserves further investigation. In fact, the existing Bacille Calmette-Guérin (BCG) vaccine that is not specific to SARS-CoV-2 is currently in clinical trial evaluating its potential protection against COVID-19 (Curtis et al., 2020). Finally, regulation of tumor necrosis factor-like weak inducer of apoptosis (TWEAK)-Fn14 pathway has been proposed as a novel molecular mechanism mediating cardiovascular protective effects of influenza vaccination (Keshtkar-Jahromi et al., 2018). TWEAK-Fn14 pathway is considered as a critical "immune switch" (Burkly et al., 2011). Studies both in humans and in animal models suggest that activation of TWEAK-Fn14 pathway play an important role in contributing to cardiovascular diseases and their severity (Chorianopoulos et al., 2010; Novoyatleva et al., 2013; Sastre et al., 2014). Keshtkar-Jahromi and colleagues have shown that influenza vaccination significantly reduced circulating TWEAK levels in older adults, providing initial evidence supportive of this molecular mechanism that deserves further investigation (Keshtkar-Jahromi et al., 2018).

Associations of influenza vaccination with reduced risk of overall respiratory adverse outcomes and specific respiratory conditions are not as robust or broad as those with cardiovascular outcomes and conditions. Significant protective effects of influenza vaccination against overall respiratory outcomes, pneumonia and respiratory mortality are most likely secondary to its prevention of influenza infection. These results are consistent with the data reported by Yin et al. that compared to placebo or no vaccination, dual influenza and pneumococcal vaccinations (1-odds ratio) prevents influenza by 35 % and pneumonia by 29 %; it reduces hospitalization by 18 % and respiratory mortality by 38 % (Yin et al., 2018). Our results indicate no significant associations of influenza vaccination with risk reduction of other respiratory infections or diseases after excluding influenza infection, nor with that of COPD and respiratory failure. Factors contributing to the development and worsening of COPD and respiratory failure are complex, and effects of influenza vaccination on these conditions require further investigation.

Data from the subgroup analyses indicate similar or slightly more robust protective effects of influenza vaccination in older adults compared to those younger than 65 years of age. This finding has significant clinical implication because of high prevalence of cardiovascular and pulmonary diseases in older adults. At the same time, this is somewhat counter intuitive, as many studies have shown reduced effectiveness of influenza vaccination in prevention of influenza infection in older adults (Gross et al., 1995; Hak et al., 2002; Nichol et al., 2007; Vu et al., 2002). One likely reason is the immune modulating effects of influenza vaccination on age-related CLIP or inflammaging as described above. It may also be explained by high disease burden of cardiovascular and pulmonary conditions in older adults. Sex difference identified in this study is consistent with evidence on sex differences in immune responses to influenza vaccination reported previously (Fink et al., 2018; Fink and Klein, 2015; Klein et al., 2015) and is currently under active research of our group. Another important point about our subgroup analyses worthwhile mentioning here is that protective effects of influenza vaccination against cardiovascular and respiratory conditions as well as all-cause mortality are also evident in individuals with pre-existing diseases, emphasizing generalizability of our findings. In addition, with very few exceptions, such protective effects are present across different countries and regions.

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

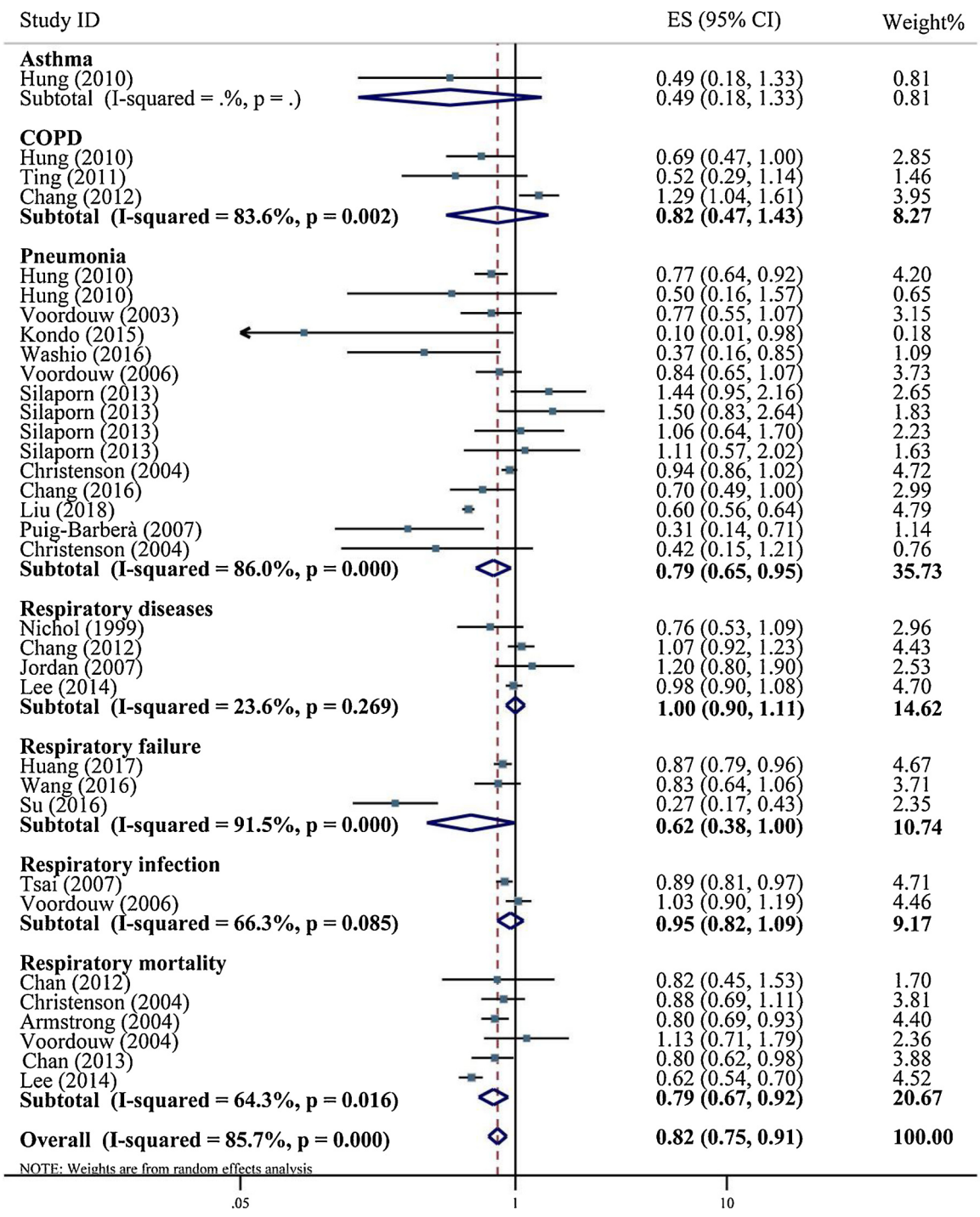

Fig. 3. Forest plot of incident respiratory diseases associated with influenza vaccination.

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 (Lu 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% (Yang 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.

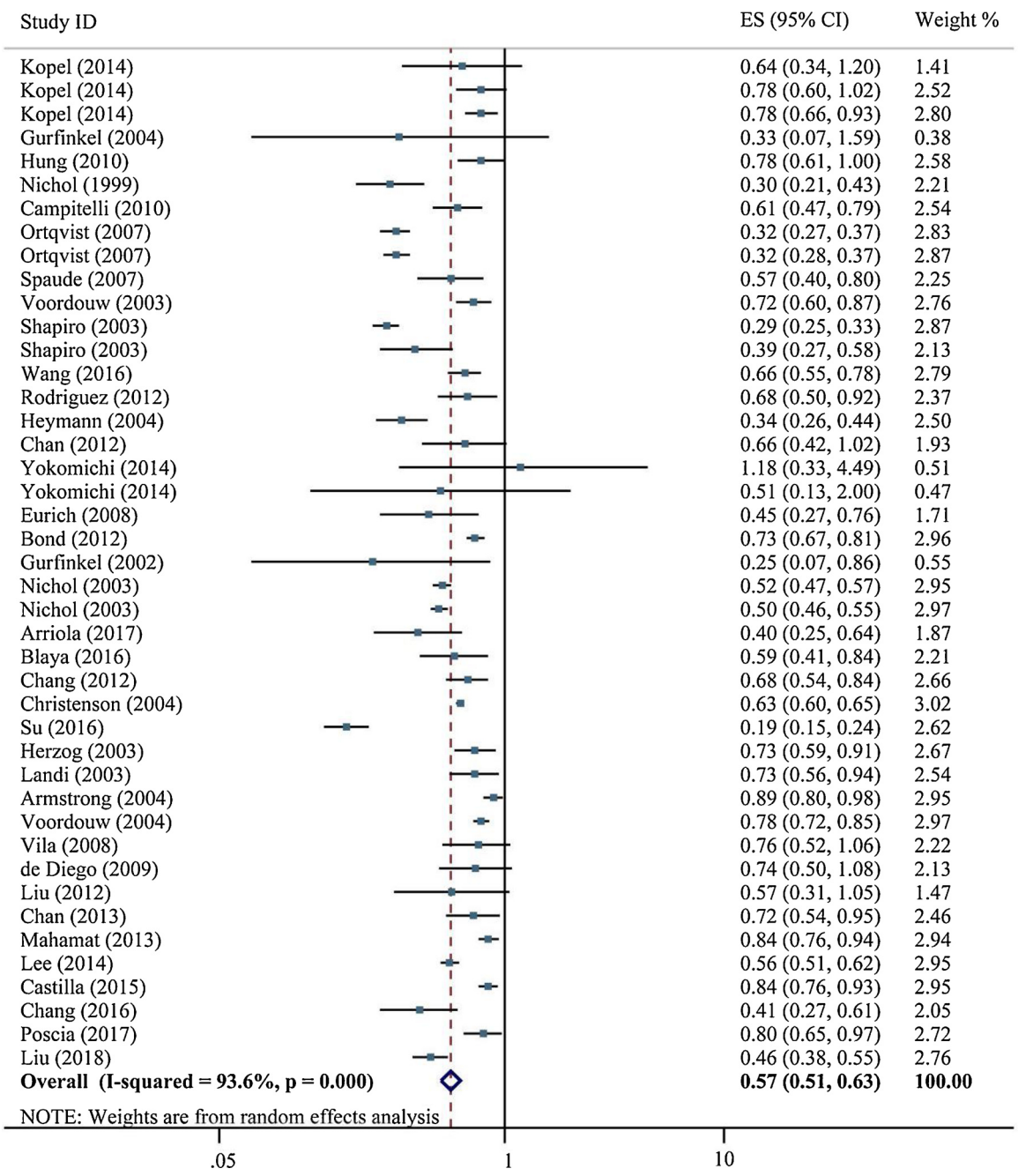

Fig. 4. Forest plot of all-cause mortality associated with influenza vaccination.

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.

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Declaration of Competing Interest

We declare no competing interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2020.101124.

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