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Acute myocardial infarction and influenza: a meta-analysis of case–control studies

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ABSTRACT

Objective Acute myocardial infarction (AMI) is the leading cause of death and disability globally. There is increasing evidence from observational studies that influenza infection is associated with AMI. In patients with known coronary disease, influenza vaccination is associated with a lower risk of cardiovascular events. However, the effect of influenza vaccination on incident AMI across the entire population is less well established.

Method The purpose of our systematic review of case–control studies is twofold: (1) to estimate the association between influenza infection and AMI and (2) to estimate the association between influenza vaccination and AMI. Cases included those conducted with first-time AMI or any AMI cases. Studies were appraised for quality and meta-analyses using random effects models for the influenza exposures of infection, and vaccination were conducted.

Results 16 studies (8 on influenza vaccination, 10 on influenza infection and AMI) met the eligibility criteria, and were included in the review and meta-analysis. Recent influenza infection, influenza-like illness or respiratory tract infection was significantly more likely in AMI cases, with a pooled OR 2.01 (95% CI 1.47 to 2.76). Influenza vaccination was significantly associated with AMI, with a pooled OR of 0.71 (95% CI 0.56 to 0.91), equating to an estimated vaccine effectiveness of 29% (95% CI 9% to 44%) against AMI.

Conclusions Our meta-analysis of case–control studies found a significant association between recent respiratory infection and AMI. The estimated vaccine effectiveness against AMI was comparable with the efficacy of currently accepted therapies for secondary prevention of AMI from clinical trial data. A large-scale randomised controlled trial is needed to provide robust evidence of the protective effect of influenza vaccination on AMI, including as primary prevention.

INTRODUCTION

Globally, coronary heart disease (CHD), particularly acute myocardial infarction (AMI), is the leading cause of death and disability.[1] While there has been a consistent decline in the number of deaths from CHD in high-income countries,[2] deaths in low-income and middle-income countries continue to increase.[2]

The epidemiological relationship between AMI and influenza was first observed in the 1930s[3] with increased cardiovascular deaths during the influenza seasons.[4] It is hypothesised that influenza infection can lead to AMI via acute coronary occlusion through thrombosis of a pre-existing, subcritical atherosclerotic plaque;[5] additionally, infection promotes atherogenesis in mouse models.[6] Infection causes tachycardia, hypoxia, release of inflammatory cytokines and a thrombophilic state, potentially contributing to AMI through multiple mechanisms. This relationship between influenza infection and AMI in humans has been largely studied using observational studies, particularly case–control studies.[7]

There is a growing interest in using seasonal influenza vaccines in AMI prevention, with studies (including three randomised controlled trials (RCTs))[8–10] focusing on secondary prevention in patients with previous AMIs or known CHD. A meta-analysis of six RCTs found an association between influenza vaccination and lower risk of composite cardiovascular events (Relative risk (RR) 0.64, 95% confidence interval (CI) 0.48 to 0.86).[11] However, only observational studies are available to measure the association between influenza infection and AMI. In mouse models, influenza vaccination is protective against AMI outside of the influenza season, with reductions in atherosclerotic plaque size, increased plaque stability with decreased proinflammatory markers.[6]

Many countries recommend influenza vaccination for patients at increased risk of severe complications from influenza, including individuals with cardiovascular disease (CVD).[12–14] However, vaccine coverage remains suboptimal in this vulnerable population.[15–17] We conducted a systematic review and meta-analysis of case–control studies to examine the evidence for the relationship between AMI, influenza infection and influenza vaccination in any population. The purpose of our systematic review of case–control studies is twofold: (1) to estimate the association between influenza infection and AMI and (2) to estimate the association between influenza vaccination and AMI.

METHODS

Search strategy

We performed a literature search combining Medical Subject Headings (MeSH) terms and keyword searches using Medline, EmBase, Cochrane and Index to Theses databases up to 24 June 2014, limited to English-language publications. MeSH terms for Medline and EmBase included 'influenza, human', 'influenza vaccines', 'acute myocardial infarction' and 'respiratory tract infection'. Keyword searches included combinations of 'influenz$/flu', 'vaccin$', 'immun?e$', 'immun?a$', 'ischem$/ischaem$', 'myocardial',

'cardiovascular', 'acute', 'coronary', 'cardi$', 'event', 'syndrome', 'respiratory', 'symptom', 'disease' and 'illness'. Search terms for the Index to Theses and Cochrane databases were 'myocardial', 'infarction', 'acute coronary' 'event' or 'syndrome', 'cardiovascular', 'respiratory tract infection', 'flu', 'influenza', 'vaccine' and 'vaccination'. Reference lists were reviewed for additional relevant studies.

Inclusion and exclusion criteria

We included case–control studies in which the primary outcome was fatal or non-fatal AMI, including first or subsequent episode(s) of AMI. AMI was defined as a constellation of clinical features, including ischaemic symptoms, biochemical and/or electrical evidence of myocardial ischaemia, evidence of critical artery stenosis on coronary angiography or autopsy evidence of myocardial infarction. We included prospective and retrospective case–control studies in which the exposure was either influenza infection or influenza vaccination. Influenza infection broadly included laboratory-confirmed influenza, influenza-like illness (ILI) or respiratory tract infection (RTI) of any definition used by the authors. Influenza vaccination included both self-reported and database records of vaccination status. We excluded self-controlled case–control studies, case cross-over studies, case–control studies in which the cases were not exclusively AMI or case–control studies in which AMI were considered the control group.

Data extraction and quality appraisal

We developed a standardised data extraction tool and study quality grading instrument. Assessment tools of case–control study quality and bias susceptibility have been developed, but have limited generalisability.[18] We developed our own tool, modifying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) risk of bias assessment for observational studies,[19] to assess individual study quality. A simple checklist with a small number of key domains was designed to critically appraise the study biases, including methodological domains of participant selection, outcome measurement, exposure measurement, control for confounding and appropriate analysis.[20] Each study was assessed as low, moderate or high risk of bias based on these domains. Papers were selected from databases by one author (MB). Two researchers (MB and AM) independently graded the included studies with differences resolved by consensus between other investigators (AEH, BR, ATN, CRM).

Statistical analysis

The number of cases and controls by exposure, and the reported adjusted odds ratios (OR) and corresponding 95% CIs for each study were extracted for use in the formal meta-analysis. The ORs from individual studies were pooled using the inverse-variance weighted random effects method.[21] Calculation of vaccine effectiveness (VE) can be done using observational epidemiological data.[22] The OR of the association between influenza vaccination and AMI was used to estimate the pooled VE of influenza vaccine against AMI using the formula: $(1-OR)\times 100$.[22] Between-study heterogeneity was quantified with the I^2 statistic, which describes the proportion of total variation in study estimates due to heterogeneity.[23] Analyses were separated by exposure type (infection and vaccination) and stratified by study type (prospective and retrospective). We conducted a meta-regression of the log of the ORs, weighted by the inverse of their variances, on the categorical variable of risk of bias separately to assess the possible impact of study quality on the effect measures. For these analyses, we fitted a random effects model with two additive variance components (within and between studies). The influence of each study on the combined risk estimate was examined by consecutively omitting each study from the meta-analysis. Finally, we tested for possible publication bias using Begg and Egger's tests and by visual inspection for asymmetry of funnel plots of the natural logarithms of the effect estimates against their SEs.[24 25]

Statistical analysis was performed using Stata SE V.10.1 2007 (Stata, College Station, Texas, USA) and RevMan V.5 2008 (The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Included studies

Of the 2976 publications identified, 14 were relevant with two further articles identified through reference lists of published studies (see figure 1). Ten studies evaluated the association between influenza infection and the risk of AMI, defined as laboratory-diagnosed influenza in four studies,[26–29] clinical ILI in three studies[26 28 30] and RTI in seven studies.[27 28 31–35] Three studies measured multiple exposures. Seven studies examined the association between influenza vaccination and prevention of first AMI, while one[36] assessed prevention of recurrent AMI. Two studies examined the relationship between AMI and both influenza vaccination and infection.[27 28]

Risk estimates

Influenza infection

Two of the four studies reporting serologically diagnosed influenza infection showed a significant association, with only one remaining significant after adjustment for confounders (table 1). Of studies using clinical case definitions, one ILI study[30] (table 2) and two[27 32–35] RTI studies (table 3) were significantly predictive of AMI after adjustment. Figure 2 shows the pooled meta-analysis results by diagnostic technique. Studies of ILI (OR 2.29, 95% CI 1.11 to 4.73) and RTI (OR 1.89, 95% CI 1.35 to 2.65) were significantly associated with AMI, while laboratory-diagnosed influenza studies were non-significant (OR 2.44, 95% CI 0.83 to 7.20). The overall pooled results were significant, with the odds of

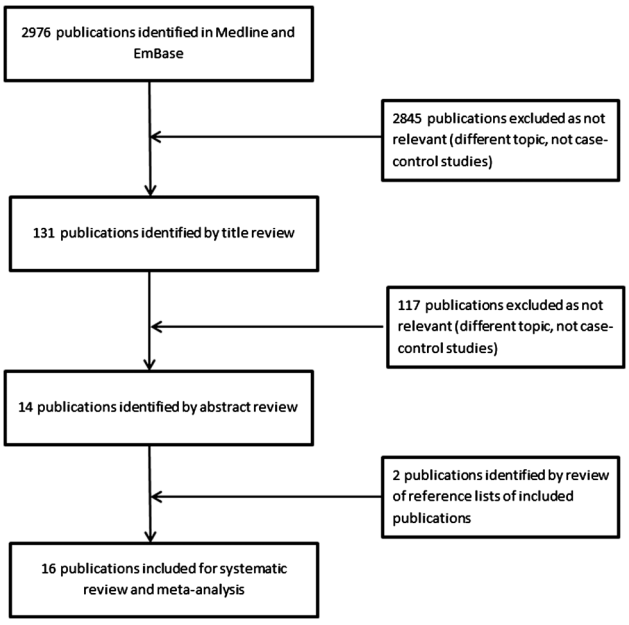

Figure 1 Flow chart of study selection and included studies.

Table 1 Summary table of case–control studies of the association between laboratory-diagnosed influenza infection and AMI

Study	Study location	Study design and study period	Participant age Mean (range) *	Prior AMI in study participants	Influenza in cases n/N (%)	Influenza in controls n/N (%)	OR (95% CI)	Confounders adjusted for	Vaccine coverage	aOR (95% CI)	Risk of bias score
Guan *et al*[29]	China	Prospective hospital-based study; 2005–2006 and 2006–2007 influenza seasons	*Cases:* 57.29 (SD 9.88) *Controls*: 55.54 (SD 10.95)	*Cases:* prior MI and angina pectoris excluded *Controls*: confirmed CAD or indications of CAD on an ECG and CXR excluded	88/102 (86.3) for influenza A 78/102 (76.5) for influenza B	100/150 (66.7) for influenza A 45/150 (30.0) for influenza B	3.1 (1.5 to 6.4) for influenza A 10.2 (5.7 to 20.0) for influenza B	Demographics (age, education, employment, gender, insurance); CAD risk (BMI, HT, DM, family history, current smoking); biochemistry (HDL, LDL, total cholesterol, triglyceride); antibodies (influenza A/B, HSV 1/2, adenovirus, rubella, chlamydia)	Estimated at 2%	5.5 (1.3 to 23.0) influenza A 20.3 (5.6 to 40.8) influenza B	Moderate
MacIntyre *et al*[27]	Sydney, Australia	Prospective hospital-based study; 2008–2010 influenza seasons	Aged ≥40 years	*Cases:* prior AMI eligible (NNR) *Controls*: 12-month history of AMI, TIA or stroke excluded	53/275 (12.4)	19/284 (1.97)	1.97 (1.09 to 3.54)	Age, gender, smoking, high cholesterol, influenza vaccination	33.5% cases 64.8% controls	1.07 (0.53 to 2.19)	Low
Ponka *et al*[26]	Helsinki, Finland	Prospective hospital-based study; 1980 influenza season	*Cases*: 63 (36–82) *Controls*: 68 (33–89)	Exclusion criteria not reported	3/49 (6.1)	4/37 (10.8)	0.54 (0.11 to 2.57)†	Date of hospital admission	Not reported	Not calculated	High
Warren-Gash *et al*[28]	London, England	Prospective hospital-based study; 2009–2010 influenza season	Aged ≥40 years 63.6 (IQR 53.3–72.6)	*Cases:* prior AMI eligible (14/70) *Controls*: 1-month history of AMI excluded (5/64 prior AMI)	25/70 (46.3)	28/64 (54.9)	0.7 (0.33 to 1.54)	Influenza vaccination, personal and family history of AMI	42.9% cases 45.3% controls	0.82 (0.34 to 2.00)	Low

*Unless otherwise reported.
†Calculated from included data (not reported in original paper).
AMI, acute myocardial infarction; aOR, adjusted OR; BMI, body mass index; CAD, coronary artery disease; CXR, chest X-ray; DM, diabetes mellitus; HDL, high-density lipoprotein; HSV, herpes simplex virus; HT, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; NNR, number not reported; TIA, transient ischaemic attack SD, standard deviation.

Table 2 Summary table of case–control studies of the association between ILI and AMI

Study	Study location	Study design and study period	Participant age Mean (range)*	Prior AMI in study participants	ILI in cases n/N (%)	ILI in controls n/N (%)	OR (95% CI)	Adjusted confounders	Vaccine coverage	aOR (95% CI)	Risk of bias score
Mattila[30]	Helsinki, Finland	Prospective hospital-based study; influenza season(s) unknown	*Cases*: 44.5 (34–50) *Controls without CHD*: 41 (28–50) *Controls with CHD*: 39.1 (30–50)	*Cases*: exclusion criteria not reported *Controls*: 30/71 chronic CHD admitted for angiography	11/40 (28)	8/71 (11.3)	2.99 (1.09 to 8.21)†	No adjustment	Not reported	Not calculated	High
Ponka *et al*[26]	Helsinki, Finland	Prospective hospital-based study; 1980 influenza season	*Cases*: 63 (36–82) *Controls*: 68 (33–89)	Exclusion criteria not reported	6/49 (12.2)	4/37 (10.8)	1.15 (0.30 to 4.41)†	Date of hospital admission	Not reported	Not calculated	High
Warren-Gash *et al*[28]	London, England	Prospective hospital-based study; 2009–2010 influenza season	Aged ≥40 years 63.6 (IQR 53.3–72.6	*Cases*: prior AMI eligible (14/70) *Controls*: 1-month history of AMI excluded (5/64 prior AMI)	10/71 (14.3)	3/64 (4.7)	3.39 (0.89 to 12.92)	Influenza vaccination, personal and family history of myocardial infarction	42.9% cases 45.3% controls	3.17 (0.61 to 16.47)	Low

*Unless otherwise reported.
†Calculated from included data (not reported in original paper).
AMI, acute myocardial infarction; CHD, coronary heart disease; ILI, influenza-like illness.

a recent influenza infection, ILI or RTI in AMI subjects being double (OR 2.01, 95% CI 1.47 to 2.76) than that of controls.

There was moderate, but significant, between-study heterogeneity (I^2 67.1%, p<0.001). Influence meta-analysis did not detect any studies exerting undue influence on the pooled estimate (see online supplementary data). None of the study qualities were significantly associated with the effect measure (OR) in the meta-regression (p=0.086), and the pooled estimate from those with a moderate risk of study bias was much higher than that of studies with high or low risk of bias. This was not significant due to the small number of studies with moderate risk of bias (see online supplementary data). Cumulative meta-analysis results by year of publication showed that additional studies would not meaningfully change the pooled estimates (see online supplementary data). Funnel plots showed no evidence of publication bias (p=0.898, Egger's test, see online supplementary data).

Influenza vaccination

Table 4 summarises the seven studies examining the association between influenza vaccination and AMI prevention with four studies showing significant negative association[27 36–38] after adjustment. Pooled meta-analysis results are shown in figure 3. Overall, odds of influenza vaccination was significantly lower in those with AMI (OR 0.71, 95% CI 0.56 to 0.91) compared with controls, translating to an estimated influenza VE against AMI of 29% (95% CI 9% to 44%).

Between-study heterogeneity was moderate (I^2 63.0%, p=0.013). There was no undue influence of a single study on the pooled estimate. A cumulative meta-analysis by year of publication showed the pooled estimates were not stable, and additional studies may influence results (see online supplementary data). The sub-group analysis showed that studies with low risk of bias had stronger effects of vaccination (see online supplementary data), although this difference was not significant in the meta-regression of effect measure (OR) on study quality (p=0.239). No vaccination studies had a high risk of study bias. A funnel plot found no evidence of publication bias (p=0.17, Egger's test, see online supplementary data).

Quality assessment and study description

We assessed the quality of the included studies with individual study quality assessments available in the online supplementary data.

Influenza infection

Of the 10 studies investigating the association between influenza infection and AMI, 2[27 28] were categorised as low risk of methodological bias, 2[29 32] at moderate risk and 6[26 30 31 33–35] at high risk (tables 1–3). Of the three retrospective studies using GP or hospital databases to identify subjects, three used medical coding (Read codes,[32] Oxford Medical Indexing System (OXMIS)[33] and International Classification of Diseases 9 (ICD-9)[34]) with study quality reliant on database accuracy. Of the seven prospective studies recruiting cases from hospital admissions, two recruited community controls from GP practices[32 33] and five recruited controls from inpatients with non-cardiac diagnoses[26 28 35] or non-cardiac outpatient clinics.[27 29] Representativeness of these control groups is unclear, with few reporting baseline characteristics, only three reporting response rates (ranging from 65% to 67%[27 28 30]) and three studies of unmatched design, with significant[27 29] or unknown[30] differences in baseline demographic characteristics.

Table 3 Summary table of case–control studies of the association between RTI and AMI

Study	Study location	Study design and study period	Participant age Mean (range)*	Prior AMI in study participants	RTI in cases n/N (%)	RTI in controls n/N (%)	OR (95% CI)	Adjusted confounders	Vaccine coverage	aOR (95% CI)	Risk of bias score
Clayton *et al*[31]	Kansas, USA	Prospective hospital-based study; influenza season(s) unknown	63 (NNR)	Exclusion criteria not reported	177/335 (52.8)	126/199 (63.3)	1.0 (0.5 to 1.9)	Gender, age, BMI, area deprivation score, smoking status and history of angina	Not reported	0.92 (0.60 to 1.42)	High
Clayton *et al*[32]	UK	Retrospective GP database study; 1994–1996, not restricted to influenza season	72 (SD 13)	*Cases/controls*: prior MI excluded	84/11 155 (0.8)†	34/11 155 (0.3)†	2.48 (1.67 to 3.70)‡	Hypertension, hyperlipidaemia, diabetes, CVA, coronary heart disease in first-degree relatives, peripheral vascular disease and chronic obstructive pulmonary disease, smoking status and BMI	35.6% cases 31.7% controls	2.55 (1.71 to 3.80)	Moderate
MacIntyre *et al*[27]	Sydney, Australia	Prospective hospital-based study; 2009–2010 influenza seasons§	Aged ≥40 years	*Cases:* prior AMI eligible. (NNR) *Controls*: 12-month history of AMI, TIA or stroke excluded	52/275 (31.1)	32/284 (18.6)	1.98 (1.2 to 3.3)	Age, gender, smoking, high cholesterol	33.5% cases 64.8% controls	Not calculated	Low
Meier *et al*[33]	UK	Retrospective GP database study; 1994–1996, not restricted to influenza season	Aged ≤75 years	*Cases/controls*: prior MI, angina pectoris and other cardiovascular conditions excluded	54/1922 (2.8)¶	72/7649 (0.94)¶	3.0 (2.1 to 4.4)	Smoking status, BMI, history of asthma, calendar year, fatal AMI	Not reported	3.0 (2.1 to 4.4)	High
Penttinen and Valonen[34]	Finland	Nested case–control study; 1980–1992 not restricted to influenza season	NNR (38–61)	*Cases*: exclusion criteria not reported *Controls*: prior MI excluded	50/83 (60.3)	115/249 (46.1)	1.77 (1.07 to 2.93)‡	Age, smoking status, social status and county of residence	Not reported	Not calculated	High
Spodick *et al*[35]	Massachusetts, USA	Prospective hospital-based study; influenza season(s) unknown	*Cases*: males 63 (SD 13), females 73 (SD 11) *Controls*: males 63 (SD 13), females 73 (SD 11)	Exclusion criteria not reported	42/150 (28)	23/150 (15.3)	2.15 (1.22 to 3.80)‡	Gender	Not reported	Not calculated	High
Warren-Gash *et al*[28]	London, England	Prospective hospital-based study; 2009–2010 influenza season	Aged ≥40 years 63.6 (IQR 53.3–72.6	*Cases:* prior AMI eligible (14/70) *Controls*: 1-month history of AMI excluded (5/64 prior AMI)	17/70 (24.3)	12/64 (18.8)	1.39 (0.60 to 3.19)	Influenza vaccination, personal and family history of AMI	42.9% cases 45.3% controls	1.39 (0.56 to 3.47)	Low

*Unless otherwise reported.
†RTI occurring 1–7 days before AMI.
‡Calculated from included data (not reported in original paper).
§RTI questionnaires conducted over the 2009 and 2010 influenza seasons only.
¶RTI occurring 1–10 days before AMI.
AMI, acute myocardial infarction; BMI, body mass index; CVA, cerebrovascular accident; IQR, interquartile range; MI, myocardial infarction; NNR, number not reported; RTI, respiratory tract infection; TIA, transient ischaemic attack; SD, standard deviation.

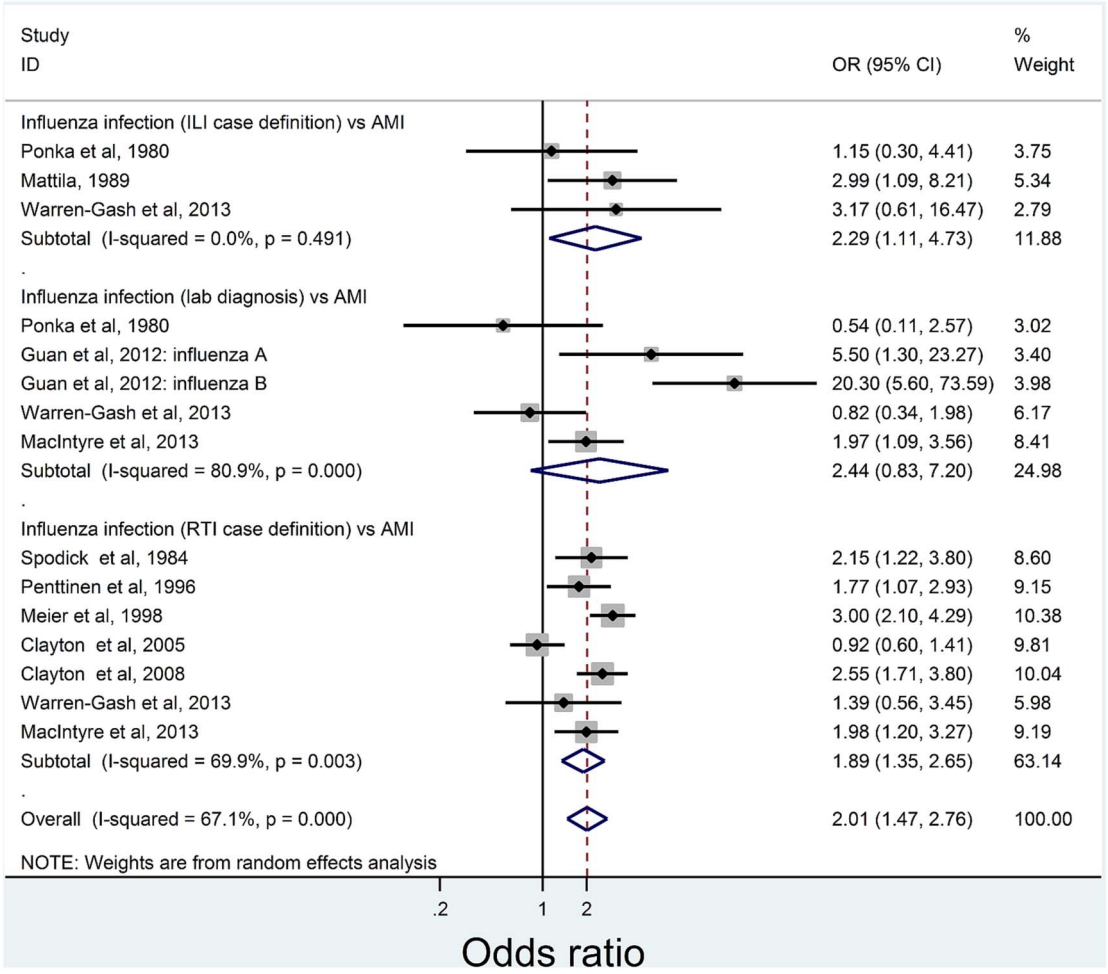

Figure 2 Pooled results for analysis of infection studies by the type of measure and AMI diagnosis. AMI, acute myocardial infarction; ILI, influenza-like illness; RTI, respiratory tract infection.

Four studies reported laboratory-diagnosed influenza-based exposure on influenza antibody titres, two relying on single-point estimates[28 29] either correlated with self-reported symptoms and adjusted for vaccination,[28] or conducted in China (vaccination unlikely).[29] The remaining two studies[26 27] defined exposed as a fourfold rise in paired acute-convalescent antibody titres, including a single high antibody titre in unvaccinated subjects or a positive PCR from nasopharyngeal swabs in one study,[27] and are likely indicative of recent infection. Exposure was measured by ILI in three[26 28 30] and RTI in seven[27 28 31–35] studies with RTI differentiated from ILI by inclusion of fever as a necessary criterion in ILI studies. All prospective studies included self-reported ILI/RTI with variable timing of exposure[30 32 33] prior to AMI with only one[28] including medical record validation.

Appropriate adjustment for potential confounders was determined in three of nine studies[27 29 32] by either matching or logistic regression analysis. Only two studies adjusted for prior influenza vaccination[27 28] while a third assumed low vaccination coverage.[29] Four studies[26–29] restricted their study period to the influenza season, covering one,[26 28] two[29] or three[27] seasons.

Influenza vaccination

Of the seven studies assessing the association between influenza vaccination and prevention of AMI, two were categorised as low[27 28] and five as moderate[36–40] risk of methodological bias (table 4). Four were prospective studies defining cases as consecutively admitted patients with AMI[27 28 37 39] and controls as non-cardiac outpatients[27 39] or inpatients[28 37] with participant rates between 66% and 91%. Prespecified AMI diagnostic criteria and chart review[27 28 39] or ICD-9 coding[37] identified cases with controls through self-reported absence of previous AMI,[28 39] or absence of AMI on medical records[27 37] with low risk of misclassification. Retrospective studies identified cases and controls as presence or absence of AMI on hospital[36] or health maintenance[40] billing records or hospital discharge letters on general practice[38] databases. Two studies[36 40] validated this with medical chart review of identified cases. One study[36] assessed recurrent AMI events in a single population of cardiology outpatients.

Influenza vaccination included self-report in all four prospective studies, two validated against GP records[27] or a population-based immunisation register.[37] Of the retrospective studies, two[38 40] included vaccination status from database records with a chart review of vaccination-negative participants in one.[40] All studies adequately adjusted for potential confounders through either matching or multivariable analysis. Two studies did not restrict timing of AMI events to the influenza season.[38 40]

DISCUSSION

This is the first meta-analysis of influenza infection and AMI, and shows that influenza infection is significantly associated

Table 4 Summary table of case–control studies of the association between influenza vaccination and AMI

Paper, year	Study location	Study design	Participant age Mean (range)*	Prior AMI in study participants	Vaccination of cases n/N (%)	Vaccination of controls n/N (%)	OR (95% CI)	Adjusted confounders	aOR (95% CI)	Risk of bias score
Meyers[39]	Kansas City, USA	Hospital-based retrospective study with patient follow-up	*Cases*: 66±11 *Controls*: 74±11	Exclusion criteria not reported	177/335 (52.8)	126/199 (63.3)	0.65 (0.45 to 0.93)	Gender, age, BMI, ever smoked, positive family history, previous heart disease, number of URTI, URTI within 2 weeks before AMI	0.92 (0.60 to 1.42)	Moderate
Heffelfinger *et al*[40]	Seattle, USA	Retrospective HMO database study	*Cases*: 72.9 *Controls*: 73.7	*Cases*: Prior MI excluded *Controls*: males hypertensive	494/750 (65.8)	1145/1735 (66.0)	0.99 (0.83 to 1.19)†	Age, gender, history of treated hypertension, index year, pre-existing cardiovascular disease, presence of treated hyperlipidaemia, DM, current smoking and COPD/asthma	0.98 (0.75 to 1.30)	Moderate
Macintyre *et al*[27]	Sydney, Australia	Prospective hospital-based study	Aged ≥40 years	*Cases:* prior AMI eligible (NNR) *Controls*: 12-month history of AMI, TIA or stroke excluded	92/275 (33.5)	184/284 (64.8)	0.27 (0.19 to 0.39)†	Age, gender, smoking, high cholesterol	0.55 (0.35 to 0.85)	Low
Naghavi *et al*[36]	Houston, USA	Prospective study based in cardiology outpatient department in a university hospital	*Cases:* 62.9±11.9 *Controls:* 64.6 ±13.5	*Cases/controls*: All with prior history of MI	50/109 (45.8)	73/109 (67.0)	0.42 (0.24 to 0.72)†	Current smoking, current hypertension, current hypercholesterolaemia, multivitamin, physical activity (20–30 min 3–4 times/week), history of influenza vaccine in previous years, age ≥60 years	0.33 (0.13 to 0.82)	Moderate
Puig-Barbera *et al*[37]	Valencia Autonomous Region, Spain	Prospective hospital-based study in three health districts	*Cases:* 75.7 (6.8) *Controls:* 78.8 (7.6)	Prior MI not an exclusion criteria (NNR)	114/144 (79.2)	181/258 (70.2)	1.61 (1.0 to 2.62)†	Propensity score, at least 3 cardiovascular risk factors	0.13 (0.03 to 0.65)	Moderate
Siriwardena *et al*[38]	UK	Retrospective study of representative GP database	Aged ≥40 years	*Cases*: prior MI excluded *Controls:* exclusion not reported	8472/16 012 (52.9)	32 081/62 694 (51.2)	1.07 (1.04 to 1.11)†	Age, gender, smoking, DM, hypertension, previous cardiovascular disease, hyperlipidaemia, family history of AMI	0.81 (0.77 to 0.85)	Moderate
Warren-Gash *et al*[28]	London, England	Prospective hospital-based study; 2009–2010 influenza season	Aged ≥40 years 63.6 (IQR 53.3–72.6)	*Cases:* prior AMI eligible (14/70) *Controls*: 1-month history of AMI excluded (5/64 prior AMI)	30/70 (42.9)	29/64 (45.3)	0.91 (0.46 to 1.79)†	Age, gender, month of admission and history of AMI	0.46 (95% CI 0.19 to 1.12)	Low

*Unless otherwise reported.
†Calculated from included data (not reported in original paper).
AMI, acute myocardial infarction; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HMO, health maintenance organisation; IQR, interquartile range; MI, myocardial infarction; NNR, number not reported; URTI, upper respiratory tract infection; TIA, transient ischaemic attack.

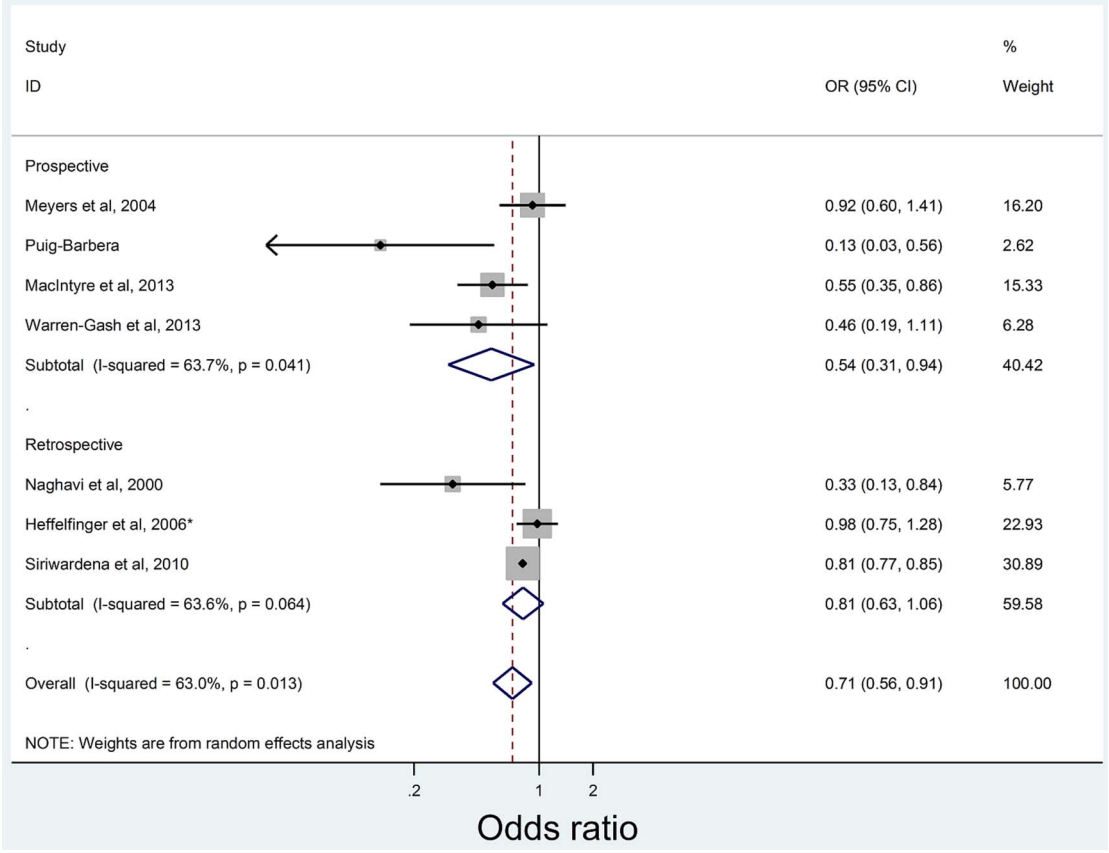

Figure 3 Pooled results for the analysis of vaccination studies by study type and acute myocardial infarction diagnosis.

with AMI, with cases having double the risk of influenza infection or RTI compared with controls. Our study also provides estimates of VE against AMI. Data show that vaccination is associated with a significantly lower rate of AMI. We calculated a pooled VE of 29% (95% CI 9% to 44%) in preventing AMI, on a par with or better than accepted AMI preventive measures, with the estimates of the efficacy of statins for secondary prevention of 36%,[41] antihypertensives of 15%–18%[42] and smoking cessation interventions of 26%.[43] Given the high global burden of AMI, and ischaemic heart disease being the leading cause of death and disability in the world, influenza vaccination could be added to other preventive strategies and confer additional population health benefits on AMI prevention. Vaccination is inexpensive, safe and effective. Patients with ischaemic heart disease are identified as a risk group for serious influenza infection, with many countries recommending vaccination for people with CVD. However, vaccination is underused in this population,[15 16] particularly in those under 65.[17] With increasing incidence of AMI after 50 years,[1] our findings add to the evidence base supporting influenza vaccination for middle-aged adults. Influenza vaccination has already been estimated to be cost-effective when used for influenza prevention in older adults, without direct consideration for cardiac protection.[44] However, it should be noted that interpretation of VE is complex, as influenza vaccination may not be equally protective against AMI during the entire year, with four of the six included vaccination studies performed during the influenza season.

Observational studies are subject to methodological biases, with case–control studies being prone to biases from participant selection and measurement of exposure. However, we found no differences in overall results when stratified by study quality and no undue influence by individual studies included in the analysis. Further, observational studies are the only ethical study type to measure the association between influenza infection and AMI, with the majority of published studies being of case–control design. The specificity of the case definition of influenza appeared important when comparing ILI with RTI.[34] Laboratory-confirmed diagnoses were not significantly associated with AMI, probably because of reduced statistical power due to small numbers and technical limitations of the current diagnostic tools. Our pooled VE concurs with a meta-analysis of published RCTs assessing the efficacy of influenza vaccination on recurrent ischaemic events. This meta-analysis found that influenza vaccine given to high-risk patients reduced their risk of AMI by 0.64, equating to a vaccine efficacy of 36% (95% CI 14% to 52.8%).[11] To expand the body of evidence supporting an association between influenza vaccination and AMI, we did not include previously pooled RCTs on influenza vaccine and AMI. Currently published RCTs are limited to recurrent events in high-risk patients, have heterogeneous outcome measures and are performed in low-income and middle-income countries without established influenza vaccination recommendations.[8–10] The generalisability of these RCTs to high-income countries with well-resourced health systems and better AMI outcomes[2] is unclear. While we provide pooled estimates of published observational case–control studies, a large-scale RCT is needed to provide the necessary evidence of the protective efficacy of influenza vaccination on AMI, including as primary prevention.

The effectiveness of annual influenza vaccines varies depending on the vaccine match to circulating strains.[45] The timing of vaccination is also important, with vaccination status being a valid predictor of AMI risk only if the vaccine was administered

prior to the AMI event. The majority of included vaccination studies examined vaccination prior to AMI, but no study analysed matching between circulating and vaccine strains. We found a variable quality in studies, with lower-quality studies tending to be older. However, no single study had a large influence on the results. While it appears that study quality was not a factor, variations in study-participant characteristics and differences in the measurement of exposures may explain this heterogeneity.

Despite advances in rapid revascularisation, public health campaigns and risk factor management, AMI remains the leading cause of death in the world. Influenza vaccination may offer another strategy to prevent AMI, and we have shown VE against AMI similar to accepted preventive measures such as statins, antihypertensives and smoking cessation interventions. It is postulated that influenza triggers an acute thrombosis in an already-diseased coronary artery with a subcritical level of stenosis.[5] This supports influenza vaccination as secondary prevention of AMI. Physicians should be aware of the need to offer vaccination to patients with CVD. Cardiologists should consider offering vaccination following an AMI, prior to hospital discharge or during cardiac rehabilitation/follow-up. Cost-effectiveness studies are needed to compare influenza vaccination as primary and secondary prevention for AMI, to further inform preventive health policy.

Key messages

What is already known on this subject?
Acute myocardial infarction (AMI) continues to cause significant morbidity and mortality on a global scale despite coronary prevention programmes and rapid revascularisation technology. Influenza infection is associated with an increased risk of AMI, and vaccination lowers that risk in patients with previous AMI or known cardiovascular disease. However, the potential benefit of influenza vaccination in preventing AMI across the entire population is less well established.

What might this study add?
This systematic review of published case–control study data found that influenza infection was significantly associated with AMI, with a pooled OR 2.01 (95% CI 1.47 to 2.76). Influenza vaccination was negatively associated with AMI, with a pooled OR of 0.71 (95% CI 0.56 to 0.91), equating to a vaccine effectiveness of 29% (95% CI 9% to 44%) against AMI.

How might this impact on clinical practice?
Influenza vaccination is a readily available, inexpensive, straightforward and safe intervention, which may reduce the risk of AMI in people even in patients without predetermined heart disease.

Correction notice Since this article was first published online figure 1 has been updated. The middle box on the right hand side of the chart now includes the number 117 and not 15 as previously stated.

Contributors CRM conceived the study. CRM, MB, AEH, BR and ATN designed the study. MB, AEH and AM conducted the literature search and data extraction. BR performed the meta-analysis. CRM, MB, AEH, BR and ATN interpreted the data. MB and AEH wrote the first draft of the manuscript, and all mentioned coauthors critically revised the manuscript and provided final approval of the manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

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SUPPLEMENTAL MATERIAL

This appendix contains additional sensitivity analyses and the individual study quality assessments.

Additional meta-analyses results

Sensitivity analyses include influence analysis by individual included studies, analysis by assigned study quality, cumulative meta-analysis and assessment of publication bias.

Influence analysis

Influence meta-analyses were performed for both exposure types with the results shown in **Figures 1 and 2** below. Neither plot shows evidence of undue influence on the pooled estimate from individual included studies.

Figure 1: Influence analysis plot for studies of the association between vaccination and AMI

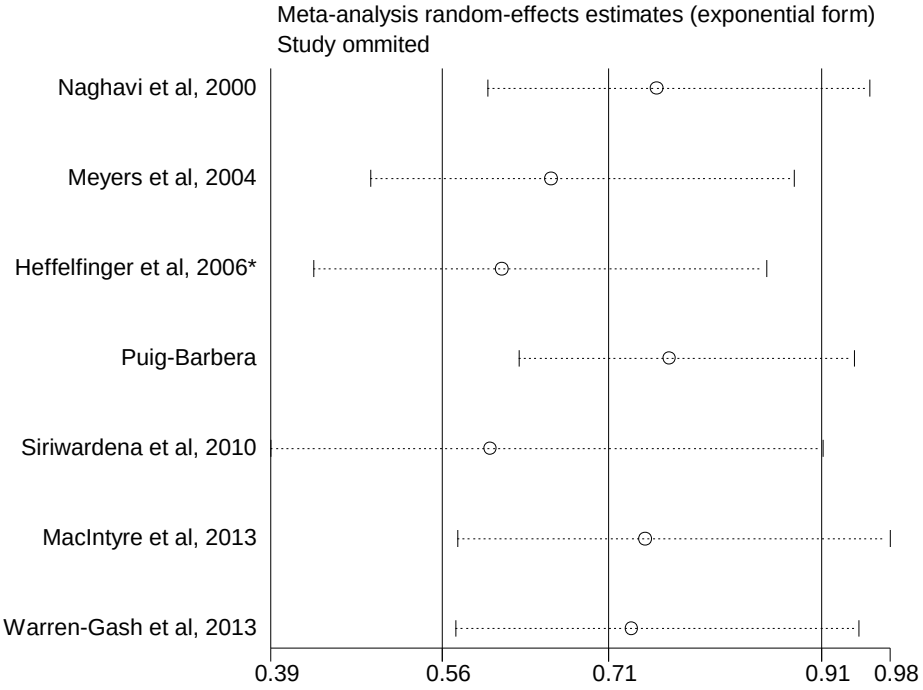
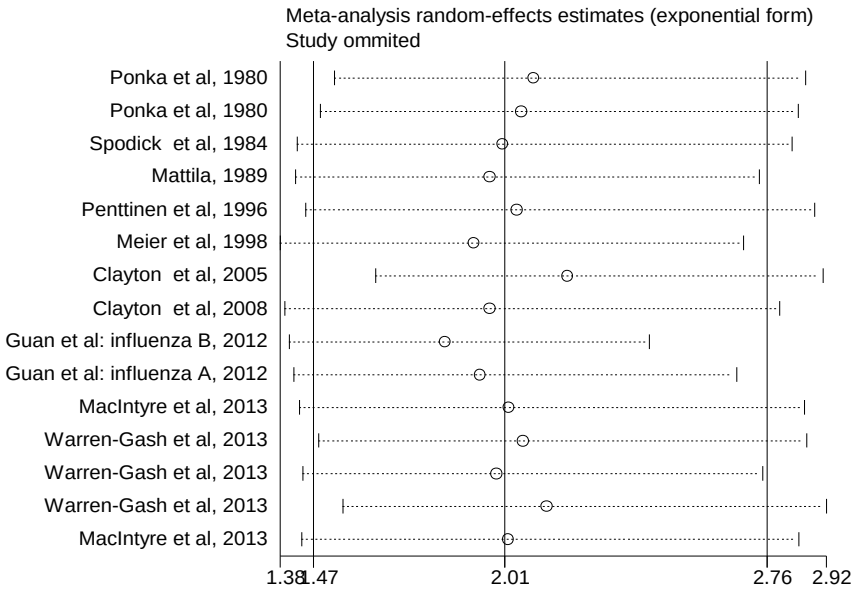


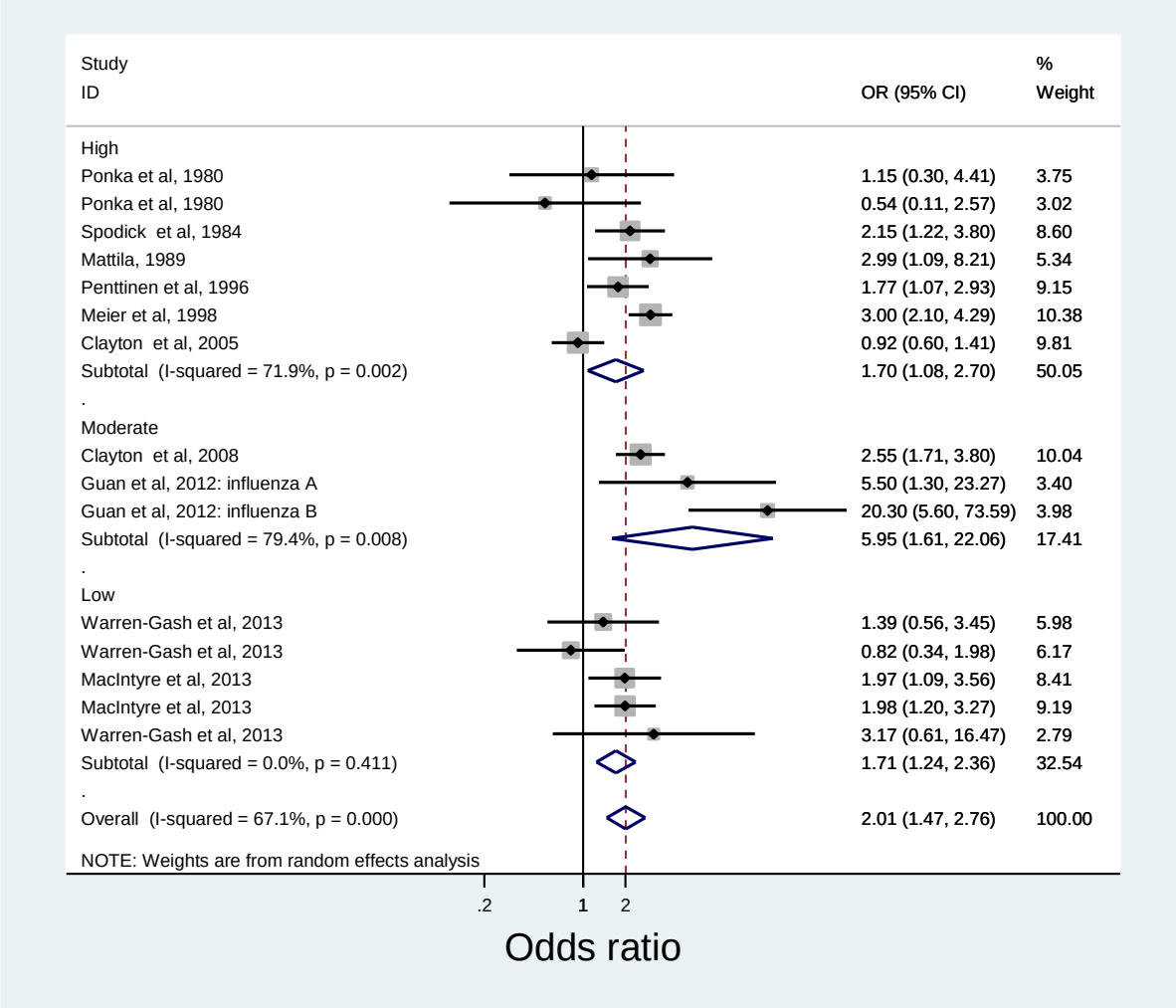
Figure 2: Influence analysis plot for studies of the association between influenza infection and AMI



Study quality

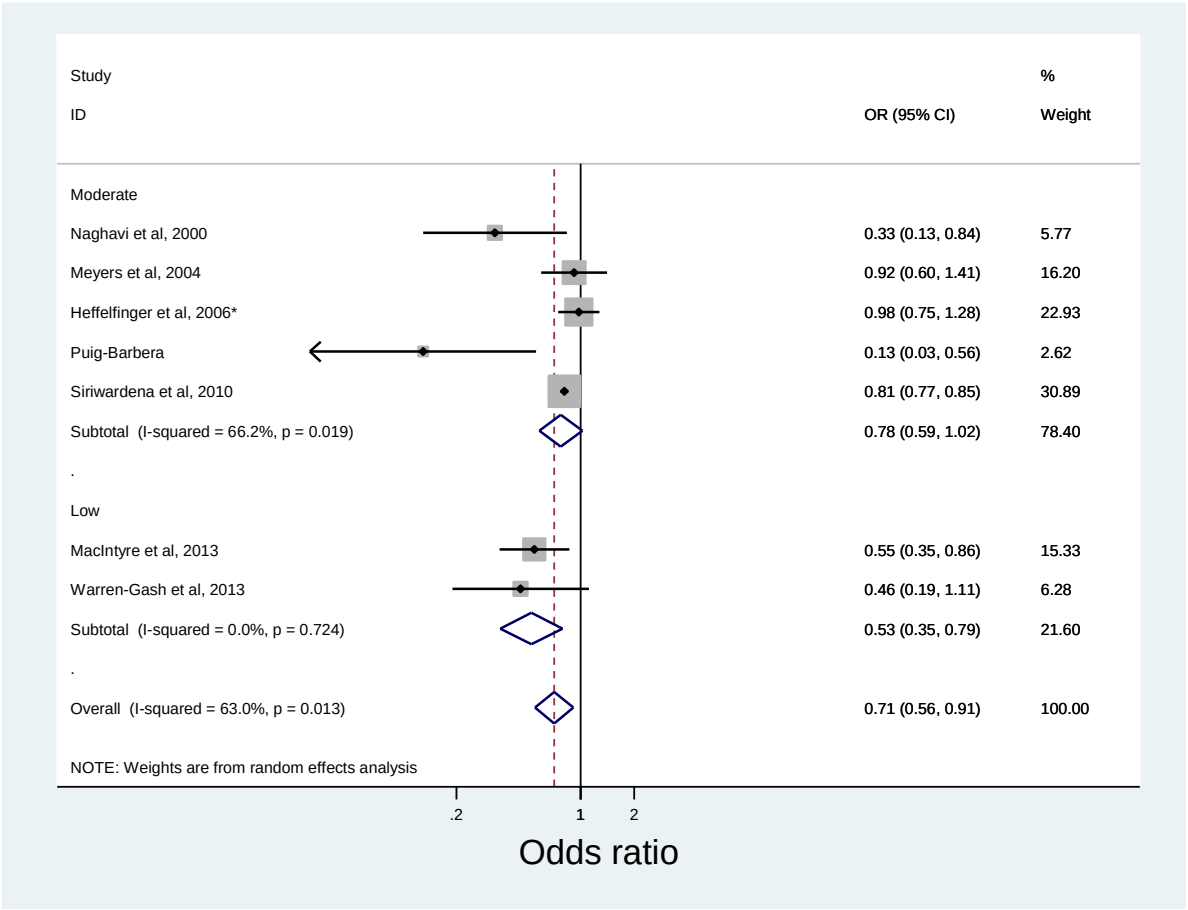
Figure 3 shows the pooled meta-analysis results by assigned study quality for the exposure of influenza infection and **Figure 4** shows the pooled meta-analysis results by assigned study quality for the exposure of influenza vaccination. The pooled estimates were not different among sub-group analyses by study quality. None of the coefficients from the meta-regressions using study quality as the explanatory variable were significant, for vaccination studies or for the infection studies.

Figure 3: Pooled results for analysis of infection studies by risk of study bias



Note: Overall P-value from meta-regression using study quality as explanatory variable = 0.086

Figure 4: Pooled results for analysis of vaccination studies by risk of study bias

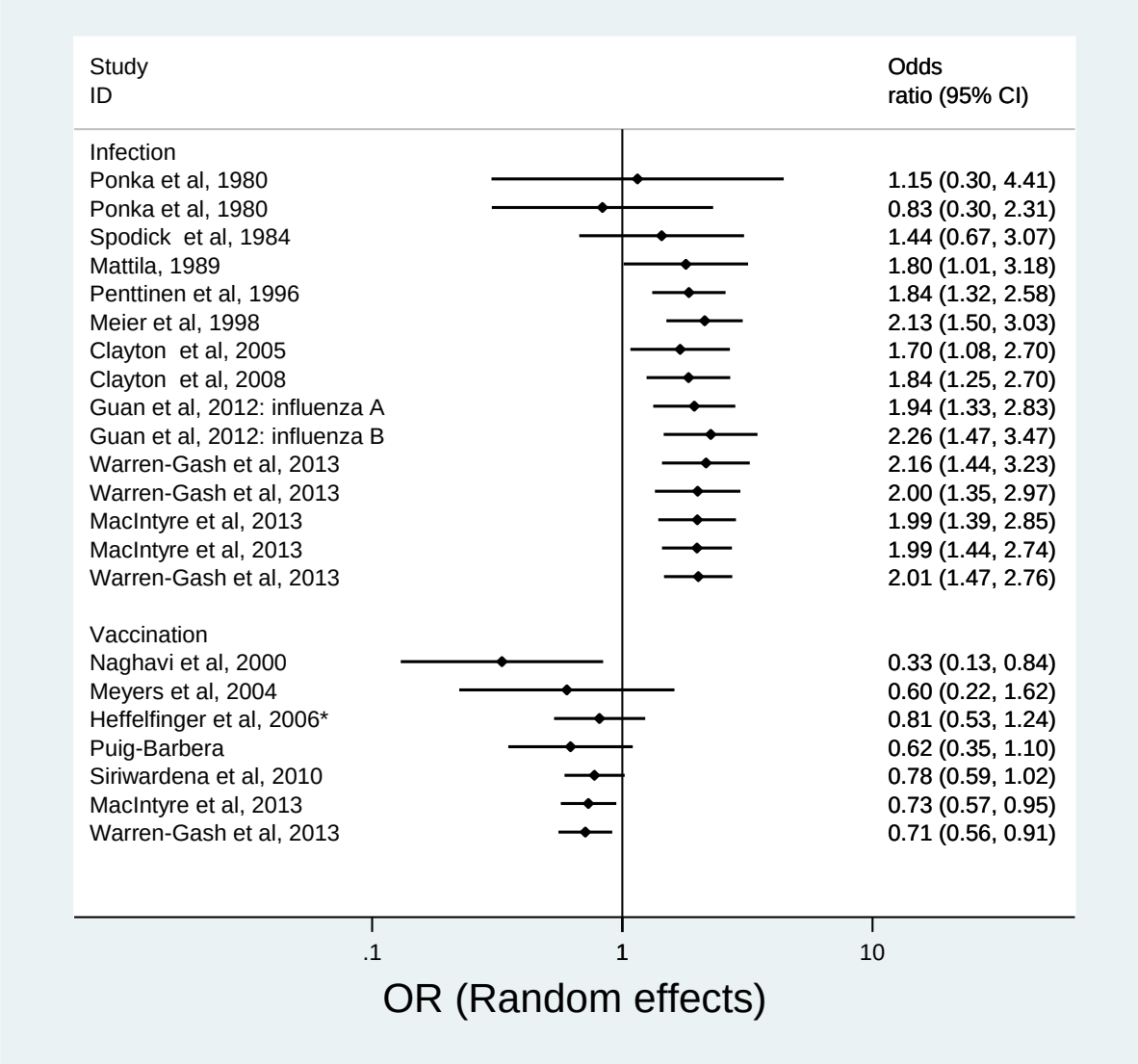


Note: P-value from meta-regression using study quality as explanatory variable = 0.239

Cumulative meta-analysis

For the infection studies, visual inspection (**Figure 5**) indicates that the pooled estimate is close to stabilised with additional studies not meaningfully changing the pooled estimate. However, for the vaccination studies, the pooled estimate is not close to stabilised (**Figure 5**).

Figure 5: Cumulative meta-analysis by year of publication



Publication bias

Tests found no evidence of publication bias. For the studies with infection the funnel plot (**Figure 6**) looks symmetrical and both the statistical tests are highly non-significant (Begg's test for small-study effects P=0.843; Egger's test for small-study effects P=0.898). For the vaccination studies, although the funnel plot (**Figure 7**) shows a little asymmetry, mainly due to small number of studies. Although Begg's test, which is a non-parametric test and very sensitive to sample size, for small-study effects is significant (P=0.035) the Egger's test is highly non-significant (P=0.167). Thus, it would be reasonable to conclude that publication bias is unlikely with the vaccination studies.

Figure 6: Funnel plot with pseudo 95% CI, for studies assessing association between AMI and influenza infection

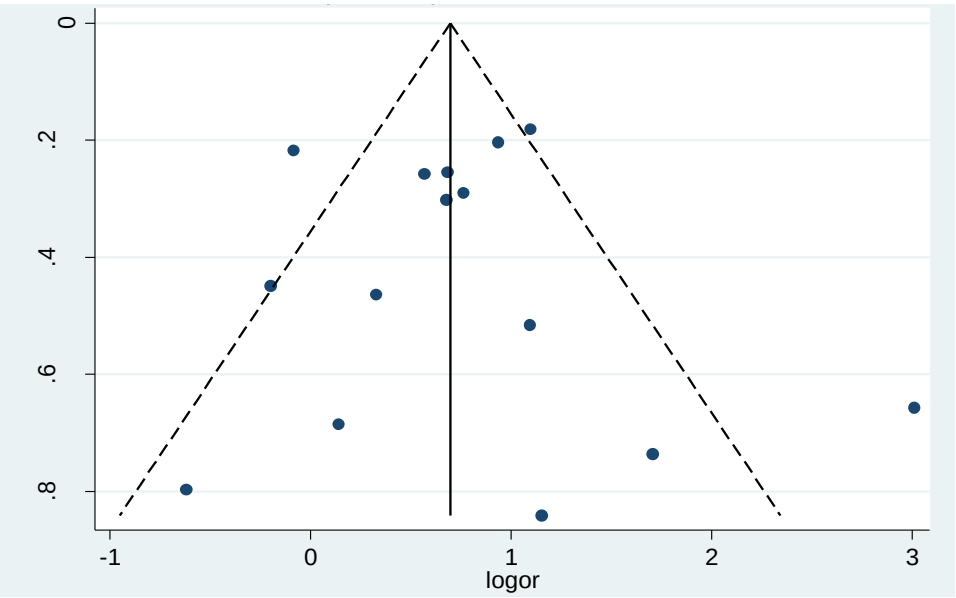
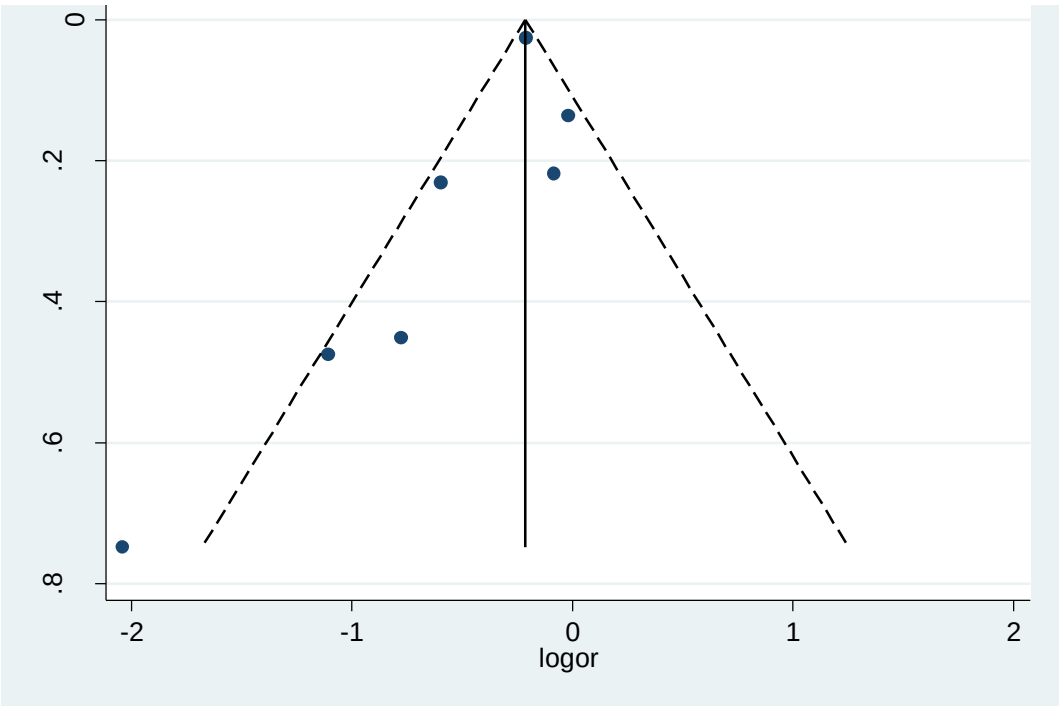


Figure 7: Funnel plot with pseudo 95% CI, for studies assessing association between AMI and influenza vaccination



Results – individual study quality assessment

Case control studies – AMI and influenza infection/RTI

Table1.1: Clayton 2005 [1]

Quality domain	*Summary*
Selection of Cases /Controls	• Prospective population-based study • No study period given; restriction to influenza season - unknown • Prevention of AMI: unknown if first and/or subsequent episode • Cases: Patients admitted with AMI to coronary units, two hospitals; exclusion criteria not reported • Controls: Matched patients registered at neighbouring GP practices; exclusion criteria not reported • Method of control selection – not reported • Participation rate – not reported • Baseline demographic information of cases or controls – not reported
Risk of bias	***High***
Measurement of Outcome	• Presence of AMI (cases): Criteria used to diagnose AMI – clinician diagnosis, no further information • Absence of AMI (controls): Not reported • Validation of outcome measures – not reported for absence of AMI
Risk of bias	***High***
Measurement of Exposure	• Exposure RTI: self-reported respiratory symptoms; consistent measurement between cases and controls • RTI definition: Clinical case definition: 1) any two of runny nose, stuffy or blocked nose, sore throat, hoarseness or general cold symptoms; or 2) any two of cough, sputum, or sputum colour change • Time of exposure to AMI: within one month • Validation of exposure measures – not reported
Risk of bias	***Moderate***
Controlling for confounding	• Influenza vaccination status – not reported; no adjustment • Matching: age, gender and area deprivation score • Adjustment: smoking status and history of angina • Measured but not adjusted: cardiovascular disease, including BMI, hypercholesterolaemia, hypertension • Unknown differences between cases and controls in demographic information and cardiovascular factors
Risk of bias	***High***
Analysis	• Cases and controls matched, conditional logistic regression used (appropriate analysis) • Unclear if analysis was restricted to influenza season(s) • Did not adjust for influenza vaccination
Risk of bias	***Moderate***
Overall risk of bias	**HIGH**

Table 1.2: Clayton 2008 [2]

Quality domain	Summary
Selection of Cases /Controls	• Retrospective population-based study • Study period: 1994-2004; Restriction to influenza season – No • Prevention of AMI: first AMI episode • Cases: Patients ≥18 years at time of first AMI diagnosis; registered on database for ≥2 years prior to AMI; exclusion criteria not reported • Controls: Matched selected patients ≥18 years; registered on database for ≥2 years; excluded if prior AMI documented • Method of control selection: Random • Baseline demographic information: Reported
Risk of bias	***Low***
Measurement of Outcome	• Presence of AMI (cases): Documented AMI diagnosis using the READ clinical criteria (symptoms, ECG findings and biomarkers) • Absence of AMI (controls): No documented diagnosis of AMI whilst patient has been listed on database • Validation of outcome measure: Not reported
Risk of bias	***Moderate***
Measurement of Exposure	• Exposure RTI: database diagnosis; consistent measurement between cases and controls • RTI definition: from GP consults and/or hospital discharge letters; extracted from database using READ codes (terms: "acute bronchitis", "pneumonia" and "productive cough"). • Time of exposure to AMI: within one year, not same day • Validation of exposure measures: Not reported
Risk of bias	***Moderate***
Controlling for confounding	• Influenza vaccination status – reported; not validated; not adjusted for in analysis • Matching: age, gender, GP practice and calendar year • Adjustment: major cardiovascular risk factors - hypertension, hyperlipidaemia, diabetes, CVA, coronary heart disease in first degree relatives, peripheral vascular disease, and chronic obstructive pulmonary disease, smoking status and BMI • No significant differences between cases and controls in demographic information provided
Risk of bias	***High***
Analysis	• Cases and controls matched, conditional logistic regression used (appropriate analysis) • Not restricted to influenza season • Did not adjust for influenza vaccination
Risk of bias	***Moderate***
Overall risk of bias	**MODERATE**

Table 1.3: Guan 2012 [3]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • Study period: 2005-2007 influenza seasons; restriction to influenza season - Yes • Prevention of AMI: First AMI episode • Cases: Consecutive admissions for new AMI diagnosis to cardiac unit, 1 hospital; excluding those with previous AMI or angina • Controls: Employees or retirees attending outpatient clinics for routine physical examination; excluding those with CAD (ECG/CXR evidence) • Method of control selection: Random • Participation rate: not reported • Baseline demographic information of cases and controls - reported
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Diagnosis by pre-specified criteria (ischaemic symptoms, cardiac biomarkers, ECG findings) • Absence of AMI (controls): Negative history and ECG/CXR evidence of CAD • Validation of outcome measures – not reported for absence of AMI
Risk of bias	**Low**
Measurement of Exposure	• Exposure laboratory diagnosed influenza: serologic assay; Consistent measurement between cases and controls • Serologic definition: Single point assay of antibodies (IgG) against influenza A and B performed by blinded laboratory staff • Time of exposure to AMI: Unable to determine timing of infection based on IgG • Validation of exposure measures: No validation by clinical or other laboratory-based techniques
Risk of bias	**High**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. Low population vaccine coverage (<2%) (low risk of confounding) • Matching: none reported • Adjustment: demographic information (age, education, employment, gender, insurance); CHD risk factors (BMI, HT, DM, positive family history, current smoking), biochemistry (HDL, LDL and total cholesterol, triglyceride) and antibodies to infections (influenza A and B, HSV 1 and 2, adenovirus, rubella, chlamydia) separately and combined • Cases and controls significantly different all measured CHD risk factors
Risk of bias	**Low**
Analysis	• No information on matching, or logistic regression tool used (use of appropriate analysis unknown) • Analysis restricted to influenza season • Did not adjust for influenza vaccination
Risk of bias	**Low**
Overall risk of bias	**MODERATE**

Table 1.4: Macintyre 2013 [4]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • Study period: 2008-2010; restriction to influenza season - Yes • Prevention of AMI: first and subsequent AMI episode • Cases: Consecutive AMI patients aged ≥40 years admitted to cardiac unit, 1 hospital, able to provide specimen within 72 hours of admission, lived in Sydney, available for follow-up; exclusion criteria not reported • Controls: Outpatients (orthopaedic/ophthalmic), 1 hospital, aged ≥40 years able to provide specimen, lived in Sydney, available for follow-up**;** excluded if history of AMI, TIA/CVA in previous 12 months • Method of control selection: Not reported • Participation rate: 67% • Baseline demographic information - reported
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Pre-specified diagnostic criteria (characteristic rise and fall of cardiac biomarkers with ≥1 of: symptoms of ischaemia, new Q waves or ST shift on ECG, coronary artery intervention, pathological MI findings) • Absence of AMI (controls): Negative history of cardiovascular event in the 12 months preceding recruitment • Validation of outcome measures: not reported for absence of AMI
Risk of bias	**Low**
Measurement of Exposure	• Exposure laboratory-confirmed influenza: paired serology and nucleic acid detection, consistent measurement between cases and controls • Exposure RTI: self-report for 2009/ 2010; consistent measurement between cases and controls • Laboratory definition: Four-fold rise in IgG titres paired sera in any or high titre in vaccine negative participants or NAT positive nasopharyngeal swab specimen • RTI definition: self-report, structured questionnaire RTI symptoms • Time of exposure to AMI: acute sera at admission, convalescent sera at 4-6 weeks; nasopharyngeal swab within 72 hours; within 1 week for RTI • Validation of exposure measures – not reported for RTI symptoms
Risk of bias	**Low**
Controlling for confounding	• Influenza vaccination status – reported and adjusted in analysis; self-report validated with GP records • Matching: no • Adjustment: age, gender and major cardiovascular risk factors (smoking, high cholesterol, hypertension, alcohol consumption, DM) • Cases and controls differ significantly in multiple variables (demographics and cardiovascular risk factors)
Risk of bias	**Moderate**
Analysis	• Controls and cases not matched, unconditional logistic regression used (appropriate analysis) • Analysis restricted to influenza seasons • Analysis adjusted for influenza vaccination
Risk of bias	**Low**
Overall risk of bias	**LOW**

Table 1.5: Mattila 1989 [5]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • No study period given; restriction to influenza season - unknown • Prevention of AMI: unknown if first and/or subsequent AMI episode • Cases: Consecutive males with verified AMI patients aged ≥50 years, lived in Helsinki or immediate surrounds, presented within 36 hours of symptom onset; exclusion criteria not reported • Controls: recruited within 1-3 weeks of case AMI, two groups used: 1. "Chronic coronary heart disease" (CCHD): male patients admitted to hospital for coronary angiography; ≥50 years of age and lived in Helsinki or immediate surrounds; exclusion criteria not reported 2. "Control population": males selected from Helsinki inhabitant database; excluded if chronic disease or medication (one treated for HT) • Method of controls selection: CCHD consecutive; "control" random • Overall participation rate: 65% (no breakdown by case or control group) • Baseline demographic information: Not reported
Risk of bias	**Moderate**
Measurement of Outcome	• Presence of AMI (cases): Diagnosis based on ECG changes, elevation of CK-MB isozyme activity • Absence of AMI (controls): Negative history • Validation of outcome measure: Not reported for absence of AMI
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure laboratory-confirmed influenza: paired serology; consistent measure between cases and controls • Exposure ILI: self-reported respiratory symptoms; consistent measurement of between cases and controls • ILI definition: fever and one or more of- sore throat, nasal congestion, cough • Serology definition: Four-fold rise in paired sera titres and/or a high titre (at least 98-99th percentile in a healthy Finnish population) • Time of exposure to AMI: acute sera at admission, convalescent sera at 4 weeks; ILI within 3 months • Validation of exposure measure: Not reported
Risk of bias	**Moderate**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. • Matching: no • Adjustment: Used the CCHD control group as proxy for confounding for AMI risk factor • No information on baseline demographic characteristics or cardiovascular risk factors for cases and controls
Risk of bias	**High**
Analysis	• Univariate analysis only, no logistic regression (no adjusted odds ratio reported) (incomplete analysis) • Unclear if analysis was restricted to influenza season • No adjustment for influenza vaccine status
Risk of bias	**High**
Overall risk of bias	**HIGH**

Table 1.6: Meier 1998 [6]

Quality domain	Summary
Selection of Cases /Controls	• Retrospective population-based study • Study period: 1994-1996; restriction to influenza season - No • Prevention of AMI: first AMI episode • Cases: Diagnosis of first time AMI; patients ≤75 years of age at date of diagnosis; no history of metabolic or cardiovascular risk factors for AMI; ≥3 years on database; excluded if history of previous AMI, angina, undiagnosed chest pain, arrhythmias, heart failure, peripheral vascular disease, CVA, connective tissue disease in the 60 days before AMI diagnosis, or cystic fibrosis • Controls: Absence of AMI diagnosis recorded on database; same exclusion criteria as for cases (see above) • Method of control selection: Not reported • Baseline demographic information: Not reported
Risk of bias	**Moderate**
Measurement of Outcome	• Presence of AMI (cases): Presence of OXMIS code for AMI in database • Absence of AMI (controls): Absence of OXMIS code for AMI in database • Validation of outcome measure: Not reported
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure RTI: Database diagnosis; consistent measurement between cases and controls • RTI definition: Recorded as non-specific acute RTI, bronchitis, pneumonia, chesty productive cough leading to a GP visit before AMI diagnosis • Time of exposure to AMI: 4 specific time periods: 1-10, 11-30, 31-90 and 91-365 days before AMI • Validation of exposure measure: Not reported
Risk of bias	**Moderate**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. • Matching: age, gender, and GP practice attended • Adjusted: smoking status, BMI, history of asthma, calendar year, fatal AMI • Did not adjust for significant risk factors for AMI (including hypertension, hypercholesterolaemia, DM) • Cases differ significantly from controls in multiple AMI risk factors • Unknown differences between cases and controls in baseline demographic information
Risk of bias	**High**
Analysis	• Cases matched to controls, conditional logistic regression analysis (appropriate analysis) • Analysis not restricted to influenza season • Analysis not adjusted for vaccination status
Risk of bias	**High**
Overall risk of bias	**HIGH**

Table 1.7: Penttinen 1996 [7]

Quality domain	Summary
Selection of Cases /Controls	• Nested case-control study, Finnish farmers • Study period: 02/1980 – 12/1992; restriction to influenza season - No • Prevention of AMI: first AMI episode • Cases: Diagnosis of first time AMI; excluded if previous AMI • Controls: Selected from through absence of inpatient hospital care and visits to the local health care unit for IHD; excluded if previous AMI • Method of control selection: Controls selected from non-AMI participants of cohort study, no further information • Participation rate: Not reported • Baseline demographic information: Not reported
Risk of bias	**High**
Measurement of Outcome	• Presence of AMI (cases): Presence of ICD-9 code for AMI in Hospital Discharge Register or death certificates from the Finnish Statistics Bureau • Absence of AMI (controls): Absence of ICD-9 coding in Hospital Discharge Register, local medical health care unit or death certificate • Validation of outcome measure: Not reported
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure RTI: medical record review; consistent measure between cases and controls • RTI definition: Medical record review for upper and lower RTI before AMI diagnosis; knowingly included suspected non-influenza viral and bacterial aetiologies • Time of exposure to AMI: Not reported • Validation of exposure measure: Not reported
Risk of bias	**High**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. • Matching: age, smoking status, social status and county of residence • Adjustment: none • Unknown differences between cases and controls in demographic or cardiovascular risk factors); Significant cardiovascular risk factors not provided (including hypertension, hypercholesterolaemia, DM)
Risk of bias	**High**
Analysis	• Cases and controls matched, conditional logistic regression used (appropriate analysis) • Analysis not restricted to influenza season • Analysis not adjusted for vaccination status
Risk of bias	**High**
Overall risk of bias	**HIGH**

Table 1.8: Ponka 1981 [8]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • Study period: 01-03/1980; restriction to influenza season - Yes • Prevention of AMI: first AMI episode • Cases: Consecutive patients admitted with new diagnosis of AMI • Controls: Matched patients admitted simultaneously as cases with an acute non-cardiac process; excluded if recent history of chest pain or other cardiac-suggestive symptom • Method of control selection: Simultaneous admission to hospital as cases • No information about participation rate • Baseline demographic information: Not reported
Risk of bias	**Moderate**
Measurement of Outcome	• Presence of AMI (cases): Consistent clinical history, typical ECG changes and rise in CK-MB • Absence of AMI (controls): No information given regarding process of exclusion • Validation of outcome measure: Not reported for absence of AMI
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure laboratory confirmed influenza: paired sera; consistent measure between cases and controls • Exposure ILI: no further information; consistent measure between cases and controls • Laboratory definition: Four-fold rise in pair sera titres (IgG) for Influenza A • ILI definition: not reported • Time of exposure to AMI: Acute sera at admission, convalescent sera 2 weeks later, ILI within 3 weeks • Validation of exposure measure: Not reported for ILI
Risk of bias	**Moderate**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. • Matched: day of hospital admission • Adjustment: none • Unknown differences between cases and controls in demographic information and cardiovascular risk factors provided
Risk of bias	**High**
Analysis	• No multivariate analysis performed (incomplete analysis) • Analysis restricted to influenza season • Analysis not adjusted for vaccination status
Risk of bias	**High**
Overall risk of bias	**HIGH**

Table 1.9: Spodick 1984 [9]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • No study period given; restriction to influenza season - Unknown • Prevention of AMI: unknown if first and/or subsequent epsidode • Cases: Consecutive patients admitted to hospital with AMI; exclusion criteria not reported • Controls: Matched patients admitted to hospital with diagnoses involving systems other than the chest and respiratory systems; exclusion criteria not reported • Method of control selection: Not reported • Participation rate: not reported • Baseline demographic information: Not reported
Risk of bias	**High**
Measurement of Outcome	• Presence of AMI (cases): Not reported • Absence of AMI: Admission with a diagnosis other than involving the chest or respiratory systems • Validation of outcome measure: Not reported
Risk of bias	**High**
Measurement of Exposure	• Exposure RTI: self-reported respiratory symptoms; Consistent measurement between cases and controls • RTI definition: respiratory symptoms elicited though questionnaire: nasal congestion, rhinorrhoea, sore throat, head cold and cough with or without fever • Time of exposure to AMI; within 2 weeks • Validation of exposure measure: Not reported
Risk of bias	**Moderate**
Controlling for confounding	• Influenza vaccination status: not reported; not adjusted in analysis. • Matching: age (+/- 3 years), gender and day (+/-1 day) of AMI admission • Adjustment: No adjustment for demographic information or significant cardiovascular risk factors for AMI • Unknown differences between cases and control of demographics or cardiovascular risk factors
Risk of bias	**High**
Analysis	• No multivariate analysis performed (incomplete analysis) • Unclear if analysis was restricted to influenza season(s) • Analysis not adjusted for vaccination status
Risk of bias	**High**
Overall risk of bias	**HIGH**

Table 1.10: Warren-Gash 2013 [10]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study; • Study period: 2009 – 2010; restriction to influenza season - Yes • Prevention of AMI: unknown if first and/or subsequent episode • Cases: Patients ≥40 years of age admitted with AMI; exclusion criteria not reported • Controls: Patients ≥40 years of age admitted with acute surgical diagnosis; excluded if history of AMI in the last month • Method of control selection: Not reported • Participation rate: cases 66%, controls 67% • Baseline demographic information: Reported
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Diagnosed on pre-specified criteria (rise in TnT associated with ischaemic symptoms +/- typical ECG changes, or coronary artery stenosis diagnosed by angiography), medical record review • Absence of AMI (controls): absence of AMI on current medical record • Validation of outcome measure: Absence of AMI validated by review of medical records from current admission
Risk of bias	**Low**
Measurement of Exposure	• Exposure laboratory-confirmed influenza: serological assay and PCR; consistent measurement between cases and controls • Exposure ILI and RTI: self-reported respiratory symptoms; consistent measure between cases and controls • Laboratory definition: NPA for influenza RNA testing by PCR; single serological assay to detect antibodies (IgA) against pandemic H1N1 influenza A • ILI/RTI definitions: elicited by questionnaire; ILI – feeling feverish with a cough or sore throat in the last month; RTI – fever, chills, cough, myalgia, nasal symptoms, sore throat, wheeze, ear ache or fatigue that does not meet the diagnosis of ILI • Time of exposure to AMI: ILI/RTI within 1 month • Validation of exposure measure: ILI/RTI by medical record review
Risk of bias	**Moderate**
Controlling for confounding	• Influenza vaccination status: self-reported; not validated; adjusted in analysis. • Matching: age-group, gender and week of admission • Adjustment: personal and family history of myocardial infarction • Did not adjust for significant cardiovascular risk factors (hypertension, hypercholesterolaemia, DM • Cases and controls had few significant differences on baseline characteristics
Risk of bias	**Low**
Analysis	• Cases and controls matched, conditional logistic regression used (appropriate analysis) • Analysis restricted to influenza season • Analysis adjusted for vaccination status
Risk of bias	**Low**
Overall risk of bias	**LOW**

Table1:11: Summary table of quality domains assigned to included studies of the association between influenza infection and risk of AMI

Domain	**Clayton 2005** [1]	**Clayton 2008** [2]	**Guan 2012** [3]	**Macintyre 2013** [4]	**Mattila 1989** [5]	**Meier 1998** [6]	**Penttinen 1996** [7]	**Ponka 1981** [8]	**Spodick 1984** [9]	**Warren-Gash 2013** [10]
Selection	High	Low	Low	Low	Moderate	Moderate	High	Moderate	High	Low
Outcome	High	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	High	Low
Exposure	Moderate	Moderate	High	Low	Moderate	Moderate	High	Moderate	Moderate	Moderate
Confounding	High	High	Low	Moderate	High	High	High	High	High	Low
Analysis	Moderate	Moderate	Low	Low	High	High	High	High	High	Low
OVERALL	**HIGH**	**MODERATE**	**MODERATE**	**LOW**	**HIGH**	**HIGH**	**HIGH**	**HIGH**	**HIGH**	**LOW**

Case control studies – AMI and influenza vaccination

Table 2.1: Meyers 2004 [11]

Quality domain	Summary
Selection of Cases /Controls	• Prospective hospital based study; 9 hospitals in 2001; 2 hospitals in 2002 • Prevention of AMI - unknown if first and/or subsequent episode • Study period: 11/ 2001 – 03/2002; Recruitment restricted to influenza season - Yes • Cases: all patients with diagnosis of nonfatal AMI, >49 years of age, excluded dementia patients. • Controls: all patients with diagnosis of new bone fracture, >49 years of age, excluded dementia patients. • Method of control selection: recruited through mail and telephone contact • Participation rate: 88% • Baseline demographic information of cases and controls provided
Risk of bias	**Moderate**
Measurement of Outcome	• Presence of AMI (cases): Diagnosed by pre-specified criteria (≥2 of: ischaemic chest pain of ≥15 minutes; >1 mm ST segment shift or new Q waves in 2 leads electrically contiguous; any cardiac biomarker (TnT, TnI, CK-MB, myoglobin); coronary artery occlusion on angiogram) • Absence of AMI (controls): Absence of ICD-9 diagnosis on medical discharge and interview • Validation of outcome measure: no further validation of control self-report
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure: self-reported influenza vaccination; consistent measurement between cases and controls • Vaccination definition: standardised questionnaire; Date/location of vaccination included to improve accuracy • Validation of exposure measure: not reported
Risk of bias	**Moderate**
Controlling for confounding	• Respiratory tract infection information collected; adjusted in analysis • Matching: no • Adjustment: demographics: gender, age, BMI; cardiovascular risk factors: ever smoked, timing of AMI, positive family history of AMI, previous heart disease; recent RTI: number of upper RTI and upper RTI within 2 weeks before AMI • Cases and controls differ significantly for multiple demographic variables; did not adjust for significant cardiovascular risk factors (hypertension, hypercholesterolaemia, DM)
Risk of bias	**Moderate**
Analysis	• Unmatched study, used conditional logistic regression (inappropriate analysis) • Analysis restricted to influenza season • Adjusted for RTI infection; study reports relatively low influenza season during study period when majority of participants recruited
Risk of bias	**Low**
Overall risk of bias	**MODERATE**

Table 2.2: Heffelfinger 2006 [12]

Quality domain	Summary
Selection of Cases /Controls	• Retrospective population-based study • Prevention of AMI: first episode • Study period: 11/1992 – 12/1998; Restricted to influenza season - No • Cases: first diagnosis AMI during study period on GHC hospitalisations, billing records, including fatal cases. Aged 65-79 years; either female or hypertensive males. GHC member ≥12 months with ≥4 GHC recorded visits • Controls: absence of AMI during study period on GHC hospitalisations, billing records. Randomly selected and matched to cases by sex, age group, calendar year, presence of medicated hypertension aged 65-79 years; either female or hypertensive males. GHC member ≥12 months with ≥4 GHC recorded visits. • Method of control selection: random matched selection from database • Baseline demographic information of cases and controls provided
Risk of bias	**Moderate**
Measurement of Outcome	• Presence of AMI (cases): Pre-specified diagnostic criteria (ischaemic symptoms, cardiac biomarkers, ECG findings) medical notes and discharge summaries • Absence of AMI (controls): Absence of ICD-9 codes on GHC database • Validation of outcome: none reported for the absence of AMI
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure: influenza vaccination on medical records; consistent measurement between cases and controls • Vaccination definition: GHC vaccine registry • Validation of exposure measure: all vaccine registry negative participants validated by chart review
Risk of bias	**Low**
Controlling for confounding	• No information on recent RTI/ILI syndrome collected; not adjusted in analysis • Matching: age, gender, calendar year, presence of medicated hypertension. • Adjustment: adjusted for matching variables (sex, age category, history of treated hypertension and index year as well as significant cardiovascular disease: treated hyperlipidaemia, DM, current smoking and COPD/asthma • Cases and controls differ significantly for multiple demographic variables
Risk of bias	**Moderate**
Analysis	• Matched study; used of unconditional logistic regression (inappropriate analysis) • Analysis restricted to influenza season • No adjustment for recent RTI/ILI syndromes
Risk of bias	**Moderate**
Overall risk of bias	**MODERATE**

Table 2.3: Macintyre 2013 [4]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study • Study period: 2008-2010; restriction to influenza season - Yes • Prevention of AMI: first and subsequent AMI episode • Cases: Consecutive AMI patients aged ≥40 years admitted to cardiac unit, 1 hospital, able to provide specimen within 72 hours of admission, lived in Sydney, available for follow-up; exclusion criteria not reported • Controls: Outpatients (orthopaedic/ophthalmic), 1 hospital, aged ≥40 years able to provide specimen, lived in Sydney, available for follow-up**;** excluded if history of AMI, TIA/CVA in previous 12 months • Method of control selection: Not reported • Participation rate: 67% • Baseline demographic information – reported
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Pre-specified diagnostic criteria (characteristic rise and fall of cardiac biomarkers with ≥1 of: symptoms of ischaemia, new Q waves or ST shift on ECG, coronary artery intervention, pathological MI findings) • Absence of AMI (controls): Negative history of cardiovascular event in the 12 months preceding recruitment • Validation of outcome measures: not reported for absence of AMI
Risk of bias	**Low**
Measurement of Exposure	• Exposure self-reported influenza vaccination; consistent measurement between cases and controls • Vaccination definition: Self-reported • Validation of exposure: GP validation in 76.6% of cases; Self-report used in absence of GP validation
Risk of bias	**Low**
Controlling for confounding	• Influenza symptoms: laboratory-confirmed influenza all years; RTI for 2009 and 2010; adjusted in analysis • Matching: no • Adjustment: age, gender and major cardiovascular risk factors (smoking, high cholesterol, hypertension, alcohol consumption, DM) • Cases and controls differ significantly in multiple variables (demographics and cardiovascular risk factors)
Risk of bias	**Moderate**
Analysis	• Controls and cases not matched, unconditional logistic regression used (appropriate analysis) • Analysis restricted to influenza seasons • Adjusted for recent RTIs
Risk of bias	**Low**
Overall risk of bias	**LOW**

Table 2.4: Naghavi 2000 [13]

Quality domain	Summary
Selection of Cases /Controls	• Retrospective hospital-based study • Study period: 10/1997- 03/1998; Restricted to influenza season – Yes • Prevention of AMI: subsequent AMI episode • Cases: new AMI in cardiology outpatients • Controls: randomly selected routine follow-up cardiology outpatients with no new AMI or deterioration in cardiovascular disease during study period • Method of control selection: random • Participation rate 92% • Baseline demographic information of cases and controls provided
Risk of bias	**Low**
Measurement of Outcome	• Presence of new AMI (cases): Presence of ICD-10 code in medical records; chart review for documentation of AMI diagnostic criteria (≥2 of: ECG changes, cardiac enzyme changes and clinical presentation) • Absence of AMI (controls): Absence of ICD-10 code for AMI in medical records • Validation of outcome measure: no further validation of medical records
Risk of bias	**Low**
Measurement of Exposure	• Exposure: self-reported influenza vaccination; consistent measurement between cases and controls • Vaccination definition: Self-reported • Validation of exposure measures: none
Risk of bias	**Moderate**
Controlling for confounding	• Influenza symptoms: none collected; no adjustment • Matching: no • Adjustment: age ≥60 years; cardiovascular risk factors: current smoking, current hypertension, current hypercholesterolaemia, multivitamins, physical activity (20-30 mins 3-4 times/week), history of influenza vaccine in previous years • Cases and controls differ significantly for a few cardiovascular risk factors but not for demographic variables
Risk of bias	**Moderate**
Analysis	• No information on the type of logistic regression tool used (appropriateness of analysis unclear) • Analysis restricted to influenza season • No adjustment for recent RTI/ILI syndromes
Risk of bias	**Moderate**
Overall risk of bias	**MODERATE**

Table 2.5: Puig-Barbera 2007 [14]

Quality domain	Summary
Selection of Cases /Controls	• Prospective multiple hospital-based study; 3 hospitals • Prevention of AMI: unknown if first and/or subsequent episode • Study period: 11/2004 – 03/2005; Restricted to influenza season – Yes • Cases: All consecutive hospital admissions with a diagnosis of acute coronary syndrome (ACS); ≥64 years; non-institutionalised, lived in the hospital catchment area for the last 6 months and hospitalised ≥72 hours • Controls: Hospital admissions for an acute surgical issue or trauma; admitted on same day (or up to 10 days) of the case admission; ≥64 years; non-institutionalised, lived in the hospital catchment area for the last 6 months and hospitalised ≥72 hours • Method of control selection: Not reported • Participation rate: cases 90.6%; no information for controls • No baseline demographic information of cases and controls provided
Risk of bias	**Low**
Measurement of Outcome	• Presence of ACS (cases): Presence of by ICD-9 coding for AMI in medical records**;** no specified diagnostic criteria provided • Absence of ACS (controls): No information on exclusion of AMI • Validation of outcome measure: None reported
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure: self-reported influenza vaccination; consistent measurement between cases and controls • Vaccination definition: Self-reported • Validation of exposure measure: population vaccination register including month, year and nurse administering vaccination; Propensity score for likelihood of vaccination calculated
Risk of bias	**Low**
Controlling for confounding	• No information collected on recent RTI/ILI syndromes; not adjusted • Matching: gender and hospital of admission • Adjustment: propensity score, at least 3 cardiovascular risk factors (details not specified); No adjustment for demographic characteristics • Unknown differences between cases and control in demographic and cardiovascular risk factors
Risk of bias	**Moderate**
Analysis	• Matched study using conditional logistic regression (appropriate analysis) • Analysis was restricted to influenza season • No adjustment for recent RTI/ILI syndromes
Risk of bias	**Moderate**
Overall risk of bias	**MODERATE**

Table 2.6: Siriwardena 2010 [15]

Quality domain	Summary
Selection of Cases /Controls	• Retrospective population-based study • Prevention of AMI: first episode • Study period: 11/2001 – 05/2007; Restricted to influenza season – No • Cases: first AMI diagnosis in patients ≥40 years with ≥5 years of records prior to AMI/index date • Controls: randomly selected controls ≥40 years of age with ≥5 years of records prior to AMI/index date • Method of control selection: random • Baseline demographic information provided
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Presence of Read and OXMIS codes in GPRD database**;** no specified diagnostic criteria • Absence of AMI (controls): No information on exclusion of AMI • Validation of outcome measure: No validation by review of medical records
Risk of bias	**Moderate**
Measurement of Exposure	• Exposure: medical records of influenza vaccination; consistent measurement between cases and controls • Vaccination definition: extracted from GPRD database; no information of the time of receipt in relation to AMI • Validation of exposure measure: No validation reported
Risk of bias	**Moderate**
Controlling for confounding	• No information collected on recent RTI/ILI syndromes; not adjusted • Matching: gender, age, GP practice and calendar time • Adjustment: for cardiovascular risk factors: smoking, DM, hypertension, previous cardiovascular disease, hyperlipidaemia, family history of AMI; No adjustment for demographic factors: age, gender • Cases and controls differ significantly for multiple demographic variables
Risk of bias	**Moderate**
Analysis	• Matched study using conditional logistic regression (appropriate analysis) • Analysis not restricted to influenza season; • No adjustment for recent RTI/ILI syndromes
Risk of bias	**High**
Overall risk of bias	**MODERATE**

Table 2.7: Warren-Gash 2013 [10]

Quality domain	Summary
Selection of Cases /Controls	• Prospective single hospital-based study; • Study period: 2009 – 2010; restriction to influenza season - Yes • Prevention of AMI: unknown if first and/or subsequent episode • Cases: Patients ≥40 years of age admitted with AMI; exclusion criteria not reported • Controls: Patients ≥40 years of age admitted with acute surgical diagnosis; excluded if history of AMI in the last month • Method of control selection: Not reported • Participation rate: cases 66%, controls 67% • Baseline demographic information: Reported
Risk of bias	**Low**
Measurement of Outcome	• Presence of AMI (cases): Diagnosed on pre-specified criteria (rise in TnT associated with ischaemic symptoms +/- typical ECG changes, or coronary artery stenosis diagnosed by angiography), medical record review • Absence of AMI (controls): absence of AMI on current medical record • Validation of outcome measure: Absence of AMI validated by review of medical records from current admission
Risk of bias	**Low**
Measurement of Exposure	• Exposure: self-reported influenza vaccination; consistent measurement between cases and controls • Vaccination definition: Self-reported • Validation of exposure measures: none
Risk of bias	**Moderate**
Controlling for confounding	• Matching: age-group, gender and week of admission • Adjustment: personal history of myocardial infarction • Did not adjust for significant cardiovascular risk factors (hypertension, hypercholesterolaemia, DM • Cases and controls had few significant differences on baseline characteristics
Risk of bias	**Low**
Analysis	• Cases and controls matched, conditional logistic regression used (appropriate analysis) • Analysis restricted to influenza season
Risk of bias	**Low**
Overall risk of bias	**LOW**

Table 2.6: Summary table of quality domains assigned to included studies of the association between influenza vaccination and protection from AMI

Domain	**Meyers 2004** [11]	**Heffelfinger 2006** [12]	**Macintyre 2013** [4]	**Naghavi 2000** [13]	**Puig-Barbera 2007** [14]	**Siriwardena 2010** [15]	**Warren-Gash 2013** [10]
Selection	Moderate	Moderate	Low	Low	Low	Low	Low
Outcome	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
Exposure	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Confounding	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Low
Analysis	Low	Moderate	Low	Moderate	Moderate	High	Low
OVERALL	**MODERATE**	**MODERATE**	**LOW**	**MODERATE**	**MODERATE**	**MODERATE**	**LOW**

Abbreviations used in tables:

AMI = acute myocardial infarction

BMI = body mass index

CAD = Coronary artery disease

CVA = cerebrovascular accident

CXR = chest x-ray

DM = diabetes myelitis

ECG = electrocardiograph

GP = general practitioner

HSV = herpes simplex virus

HT = hypertension

ILI = influenza-like illness

NAT = nucleic acid test

RTI = respiratory tract infection

TIA = transient ischaemic attack

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