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

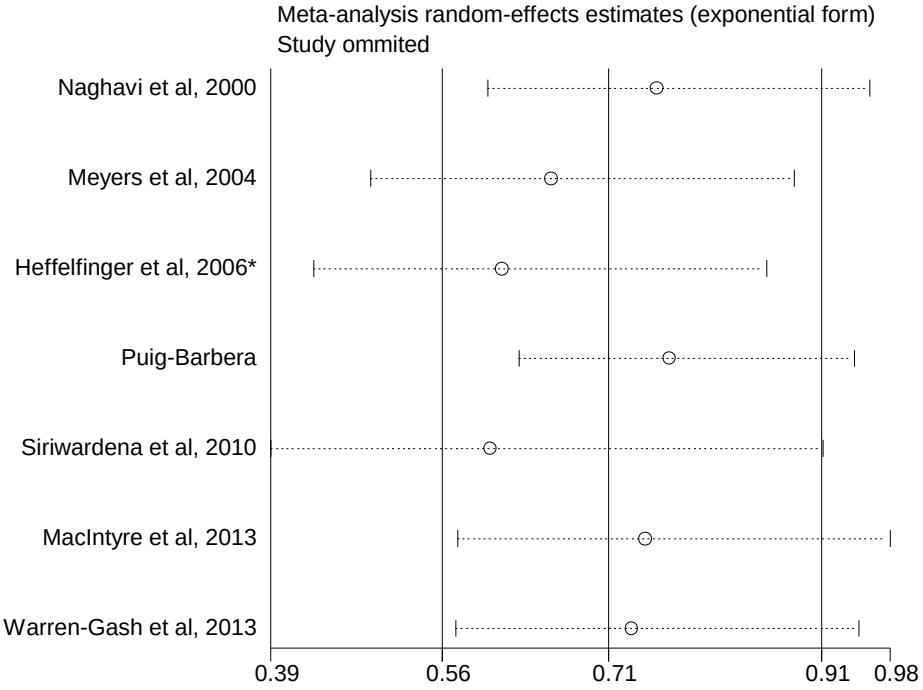
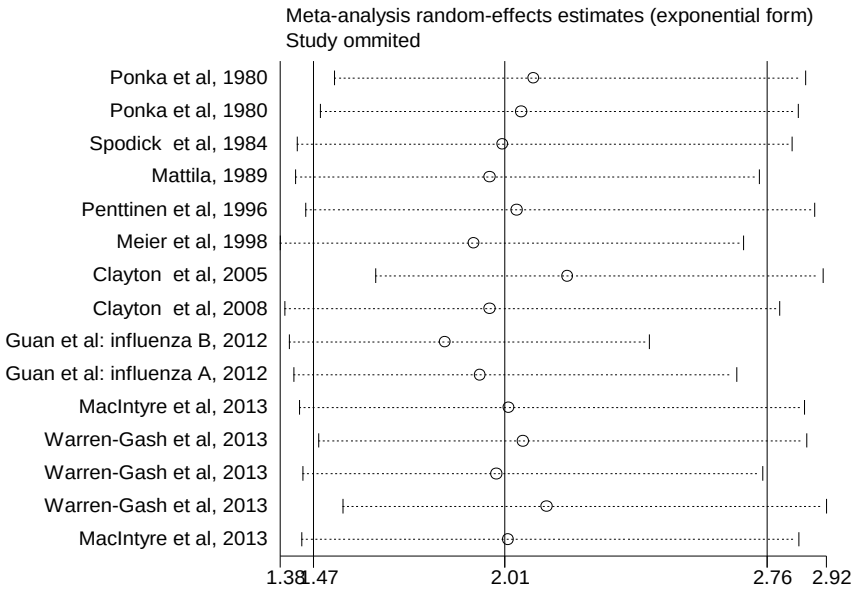


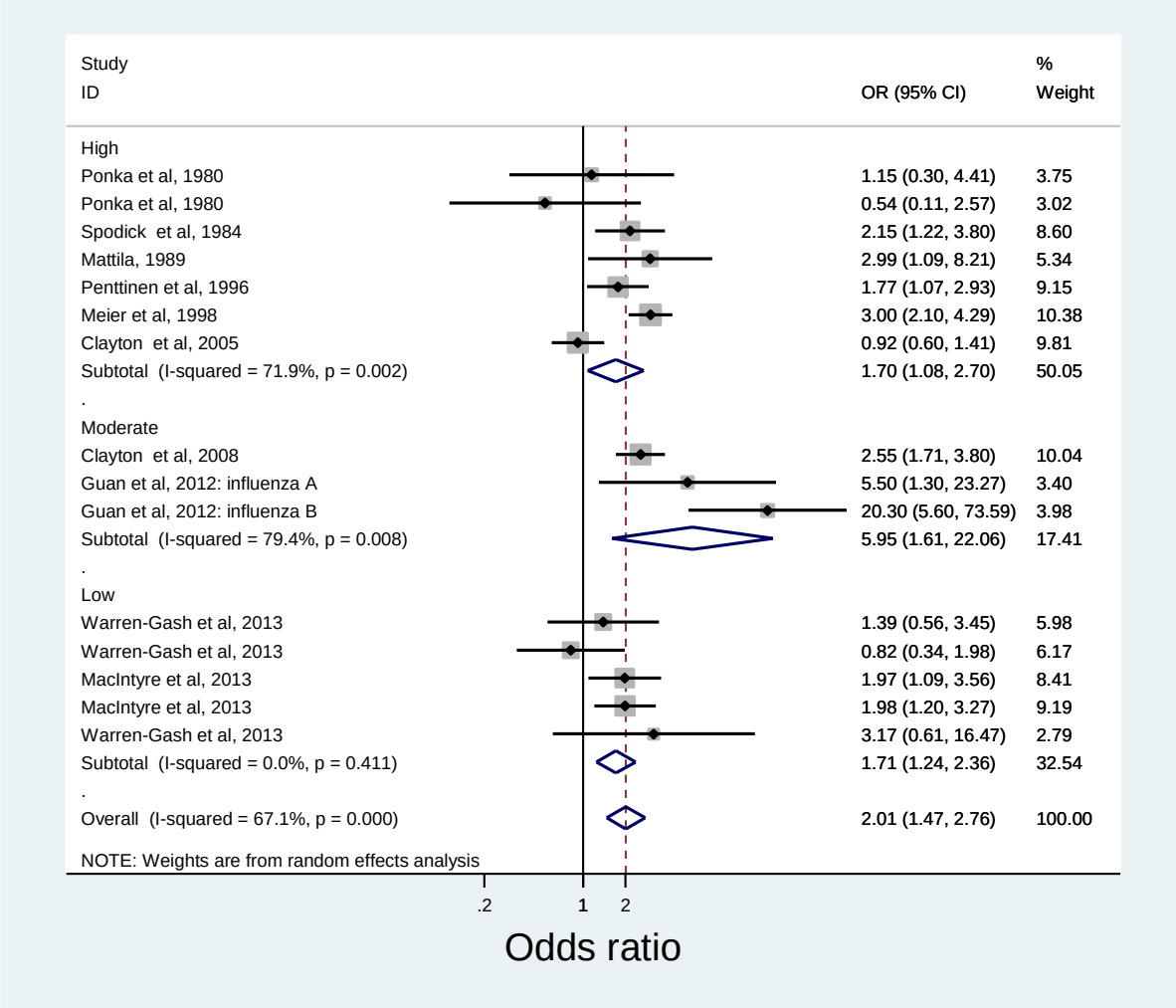
Figure 2: Influence analysis plot for studies of the association between influenza infection and AMI



Study quality

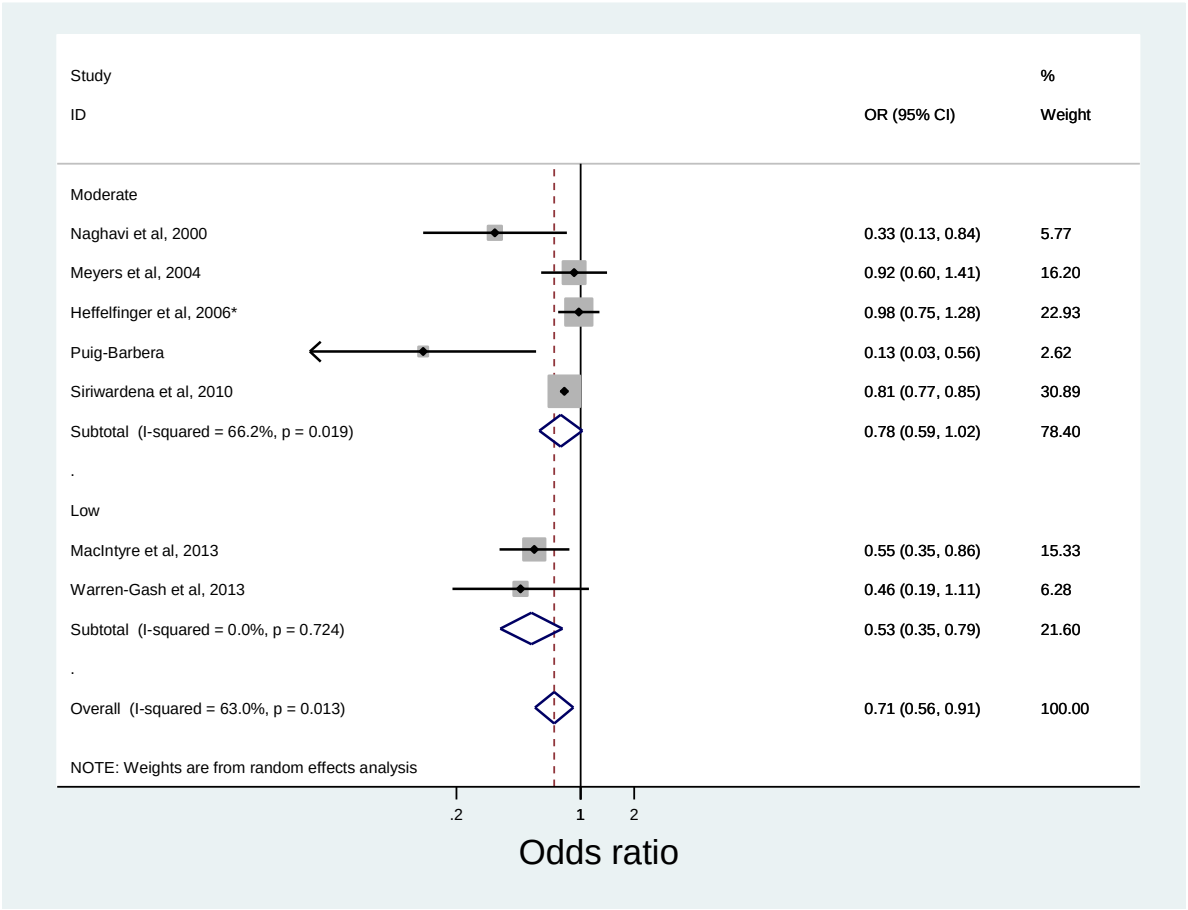
Figure 3 shows the pooled meta-analysis results by assigned study quality for the exposure of influenza infection and **Figure 4** shows the pooled meta-analysis results by assigned study quality for the exposure of influenza vaccination. The pooled estimates were not different among sub-group analyses 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

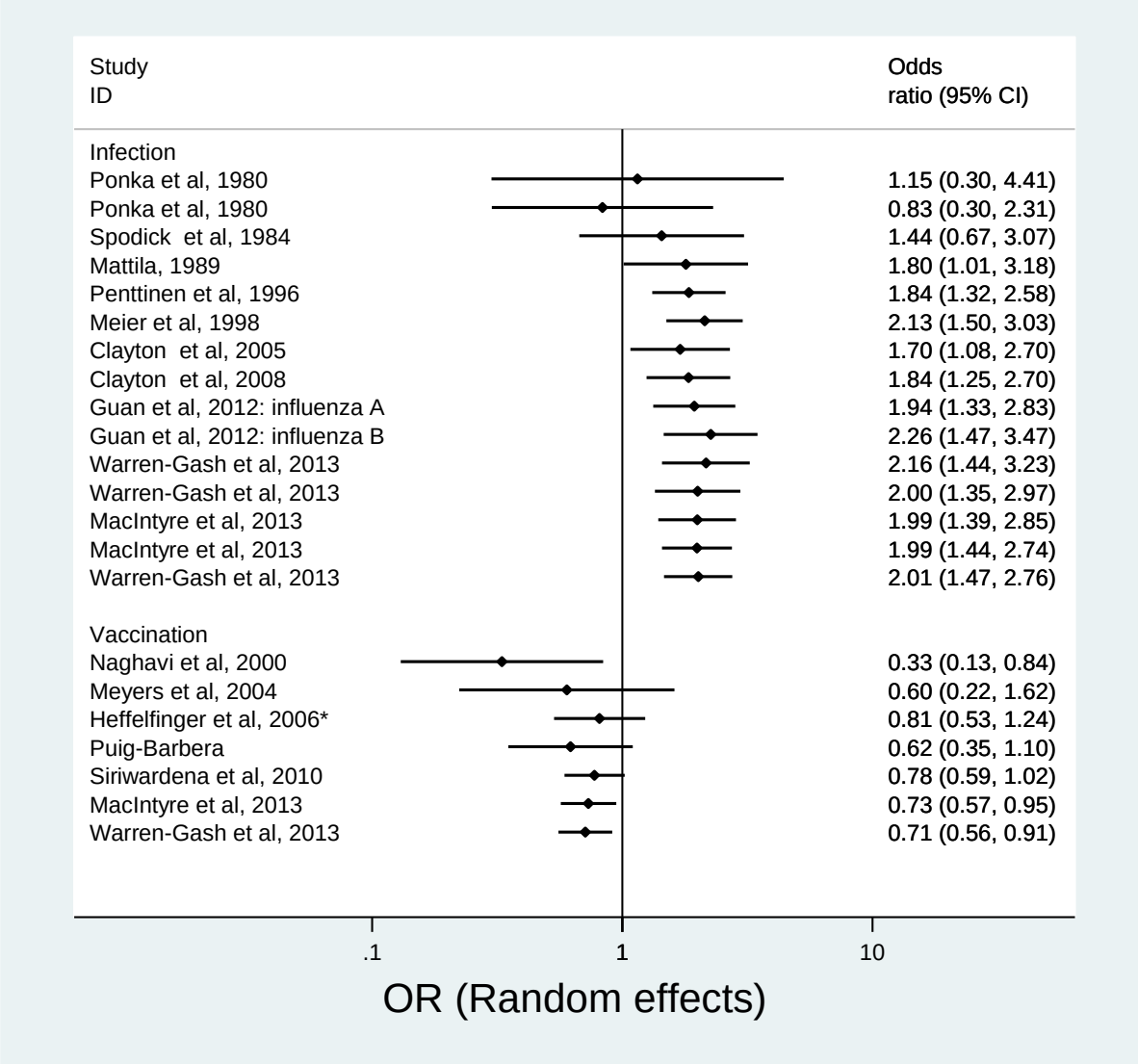


Note: P-value from meta-regression using study quality as explanatory variable = 0.239

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

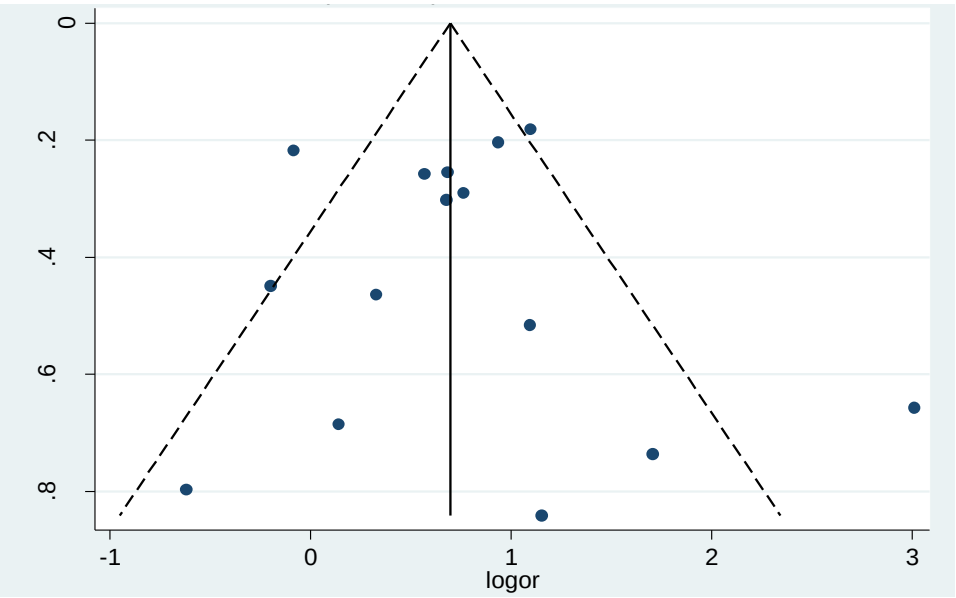
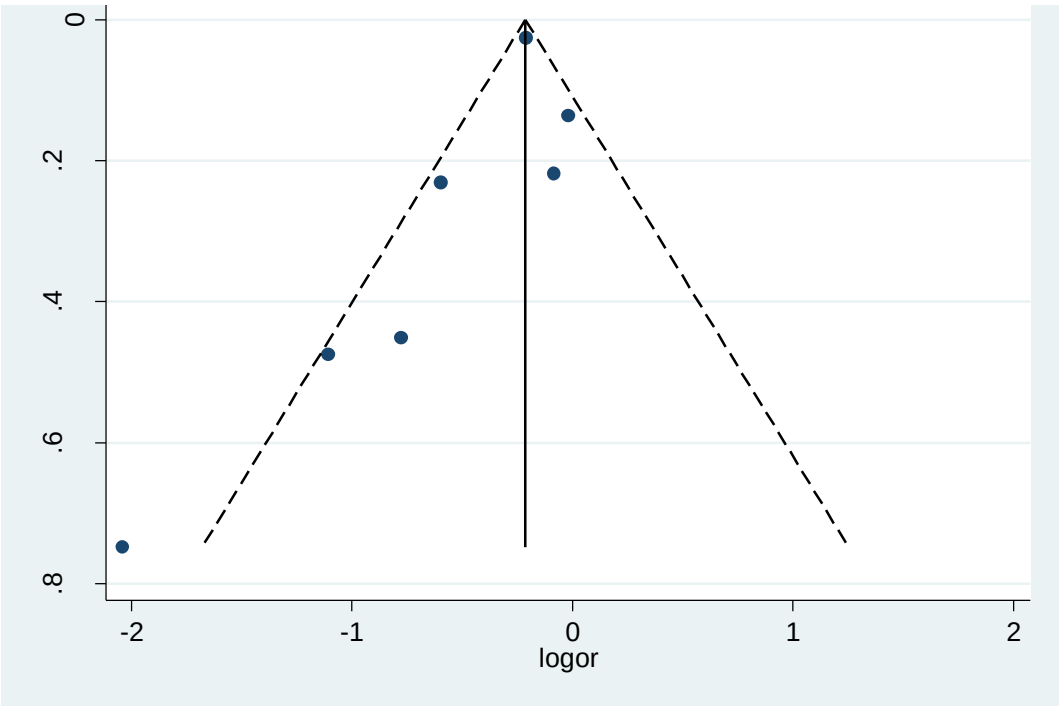


Figure 7: Funnel plot with pseudo 95% CI, for studies assessing association between AMI and influenza vaccination



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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