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### Study question:

Outcome of Pneumococcal vaccinated group and Placebo among patients with and without established cardiovascular disease

### PICO Questionnaires

P= patient/population (Patients with and without established cardiovascular disease)

I= Intervention arm (Pneumococcal vaccinated group)

C= Comparison arm (Placebo/control group)

O= outcomes (primary outcome): all-cause mortality. Secondary outcomes: myocardial infarction, cardi mortality, and stroke.

### Search Strategy:

((Pneumococcal Vaccine) OR (PPV)) AND ((Cardiovascular outcomes) OR (Myocardial Infarction )) AND ((Heart failure)) AND ((Acute coronary syndrome)).

Table S1: Definition of Outcomes

Study Variable	Definition
<b>All Cause Mortality</b>	All studies that indicated mortality used a primary endpoint as all-cause mortality. All-cause mortality is defined as death from any cause that occurred during follow-up period among participants in intervention and comparison groups.
<b>MACE</b>	Major adverse cardiovascular events (MACE) is defined as a composite of in-hospital all-cause death, acute myocardial infarction, or any cardiovascular events.
<b>Acute Myocardial Infarction</b>	Presumptive cases of AMI were initially identified on the basis of primary hospital discharge ICD-9 diagnosis codes for acute myocardial infarction (ICD-9 410). AMI was defined as a detection of rise and/or fall in cardiac biomarkers together with at least one of the following: symptoms of ischaemia, ECG changes indicative of new ischaemia (new ST- T changes, new left bundle branch block and/or development of pathological Q waves) and/or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
<b>Stroke</b>	Stroke was defined as an accident which led to loss of neurological function with residual symptoms at least 24 hrs after onset, presumed to be from vascular etiology.
<b>Cardiovascular mortality</b>	Cardiovascular mortality is defined as death occurred due cardiovascular disease such as one of the following: acute myocardial infarction, acute rheumatic fever and chronic rheumatic heart disease, ischemic heart disease,



Ihara 2019	★	★	★	★	★★	★	★		8
Hsieh 2016	★	★	★		★★	★	★		7
Siriwar dena 2014	★	★	★	★	★	★	★		7
Lamont agne 2008	★	★	★	★	★	★	★		7

\*Score >6 was considered as an adequate quality study.

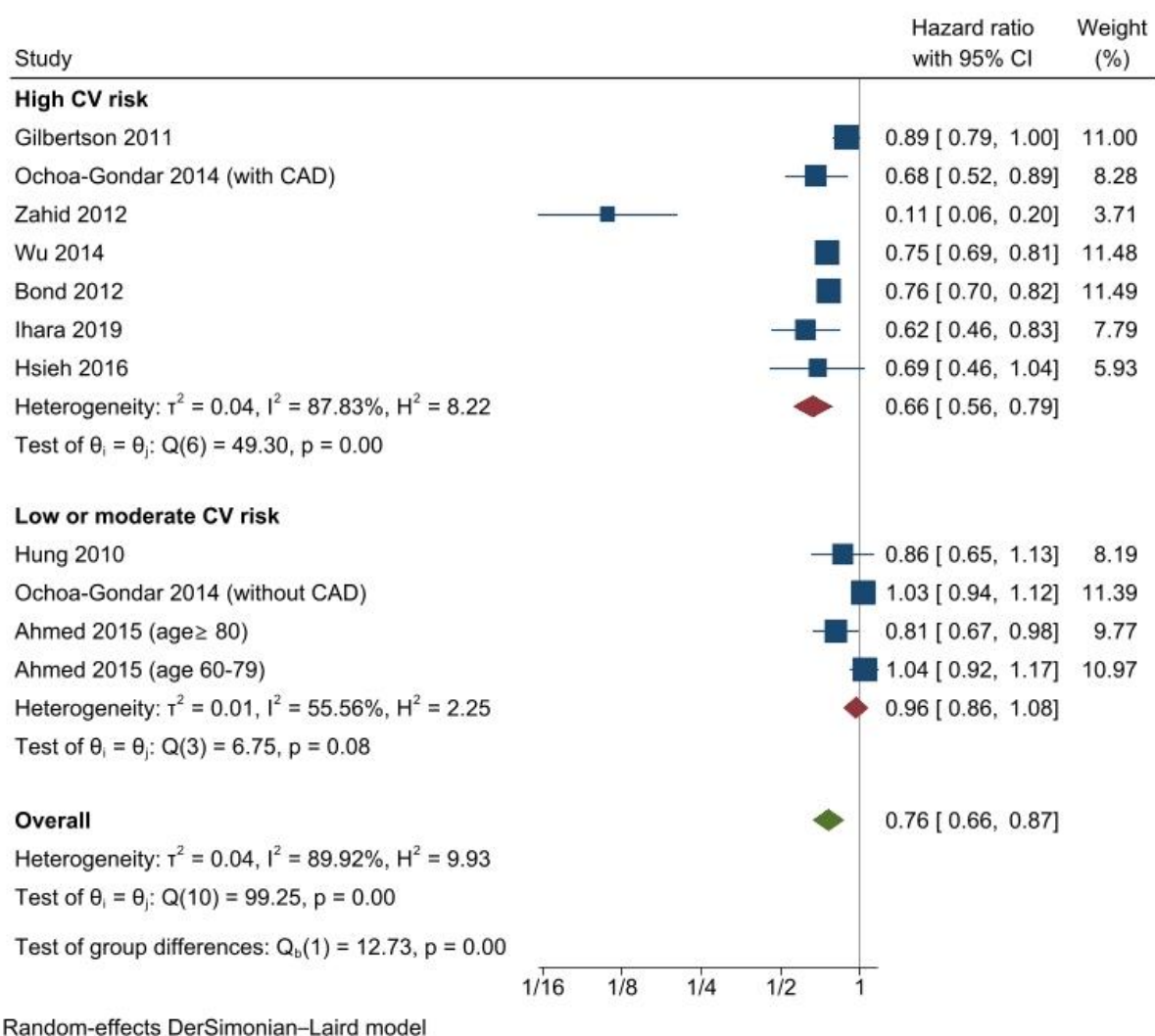


Figure S1: Subgroup analyses based on cardiovascular risk for primary outcome: all-cause mortality

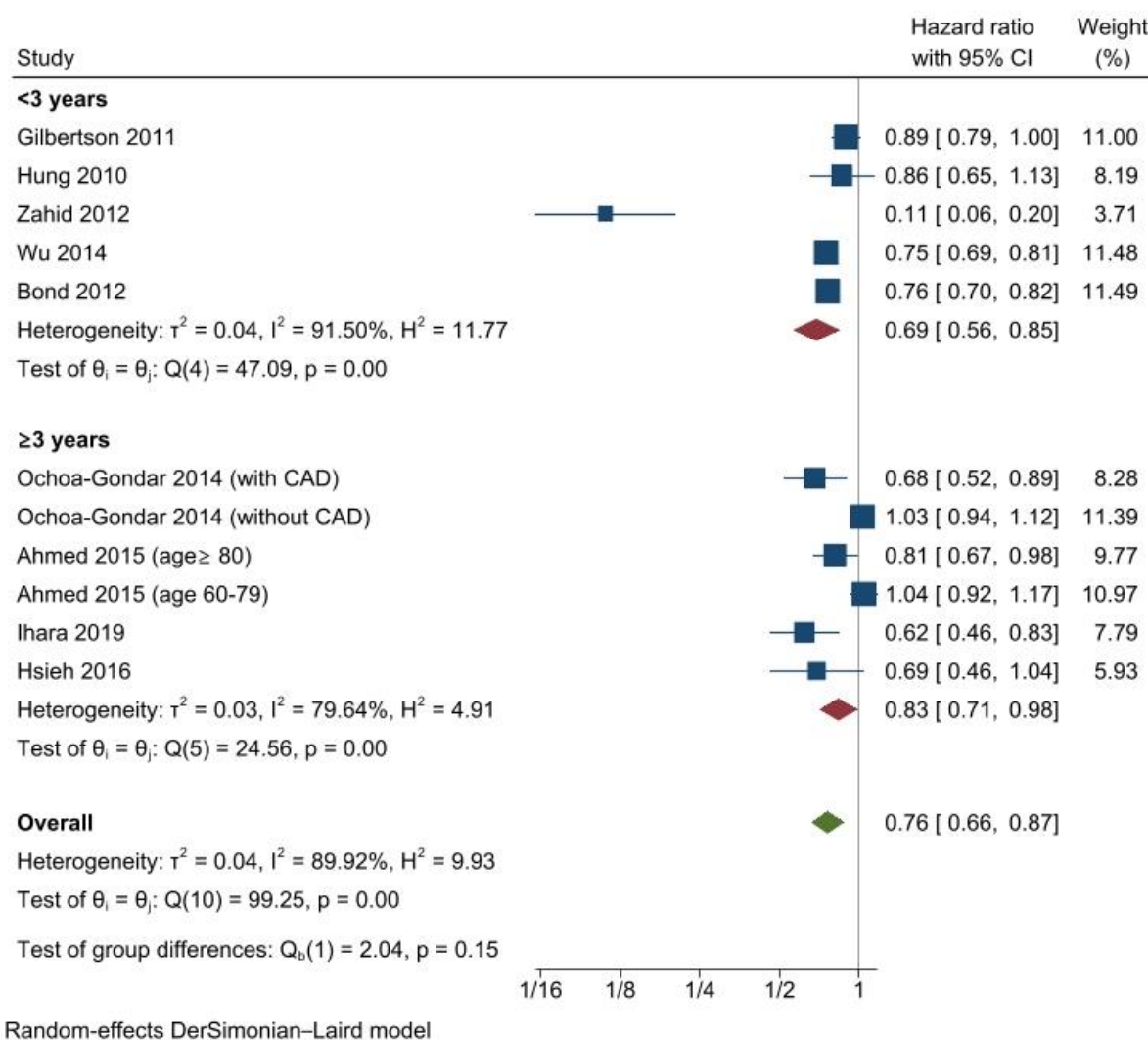


Figure S2: Subgroup analyses based on follow-up duration for primary outcome: all-cause mortality

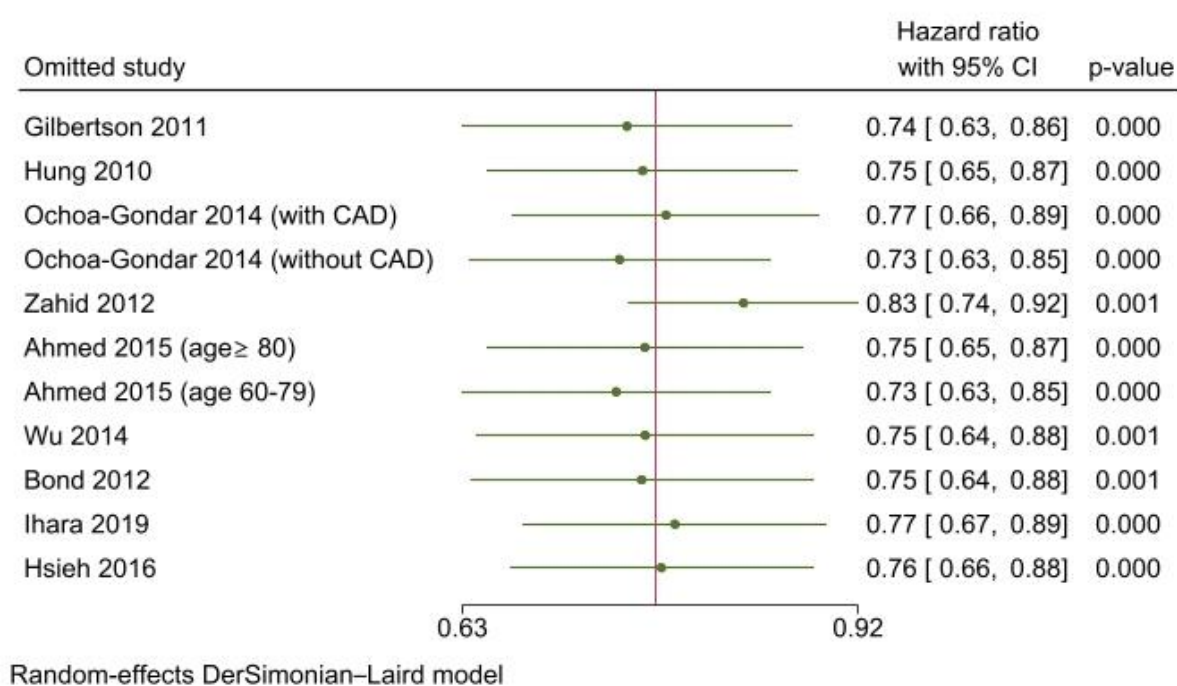


Figure S3: Leave-one-out analysis for primary outcome: all-cause mortality

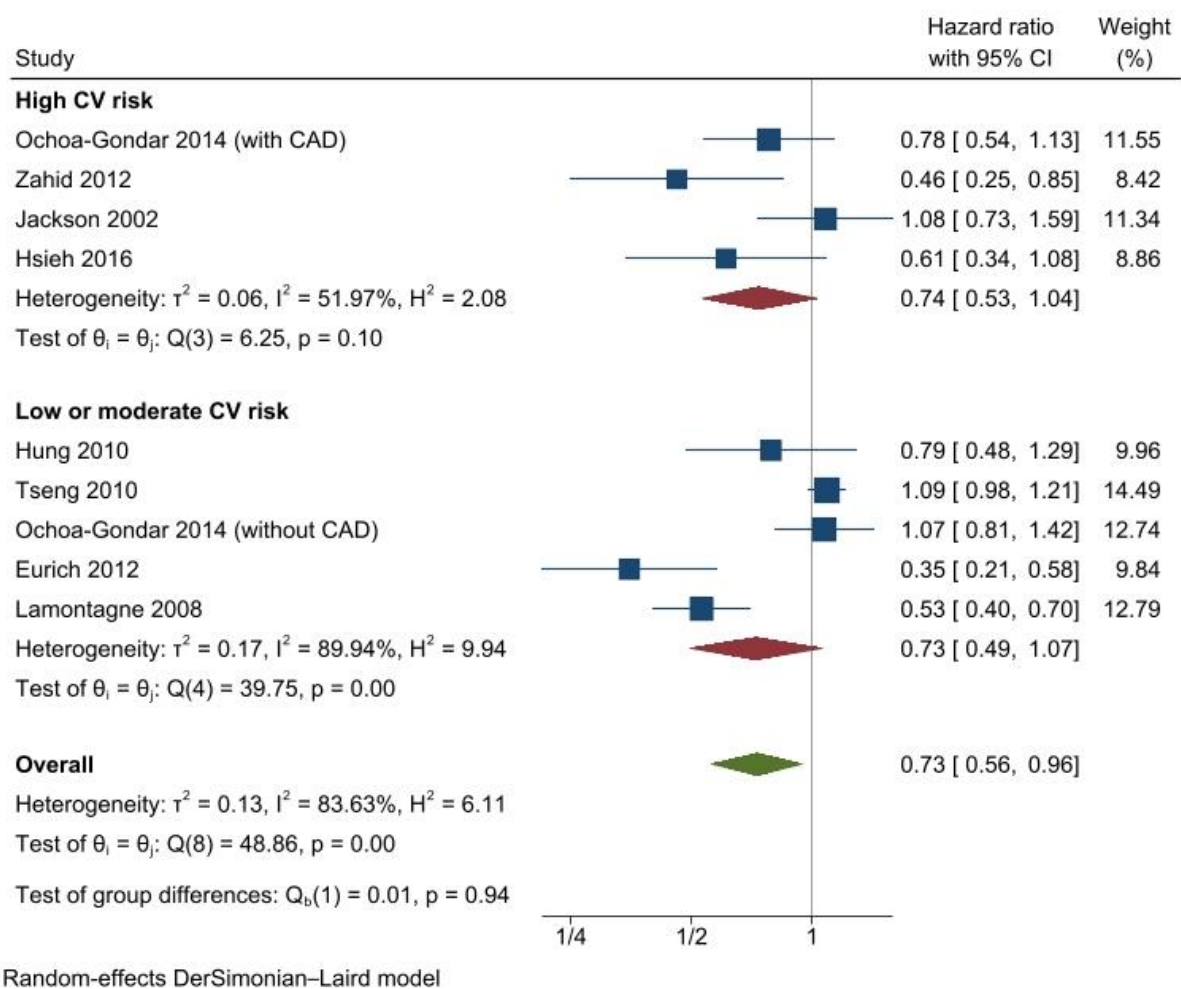


Figure S4: Subgroup analyses based on cardiovascular risk for secondary outcome: MI



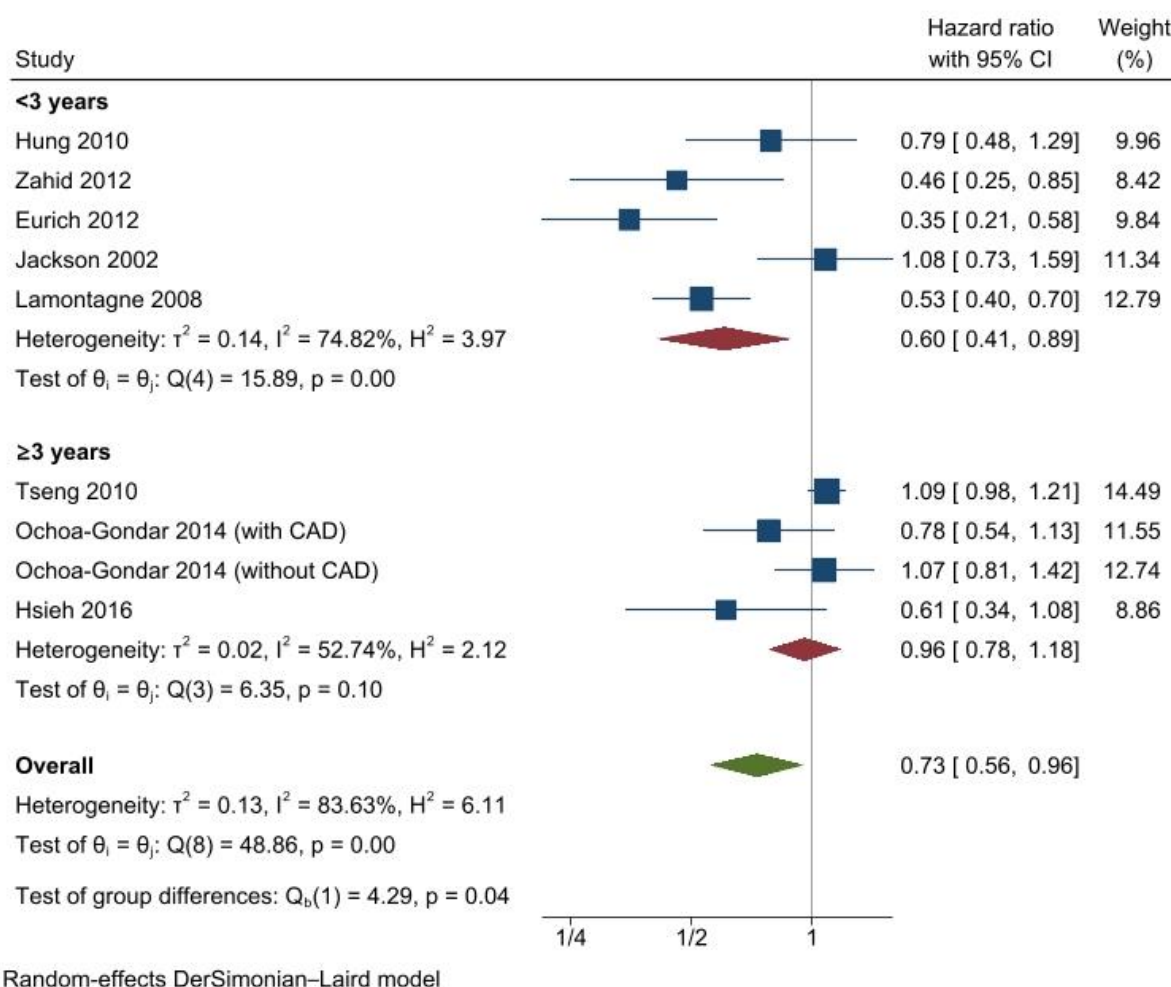


Figure S5: Subgroup analyses based on follow-up duration for secondary outcome: MI

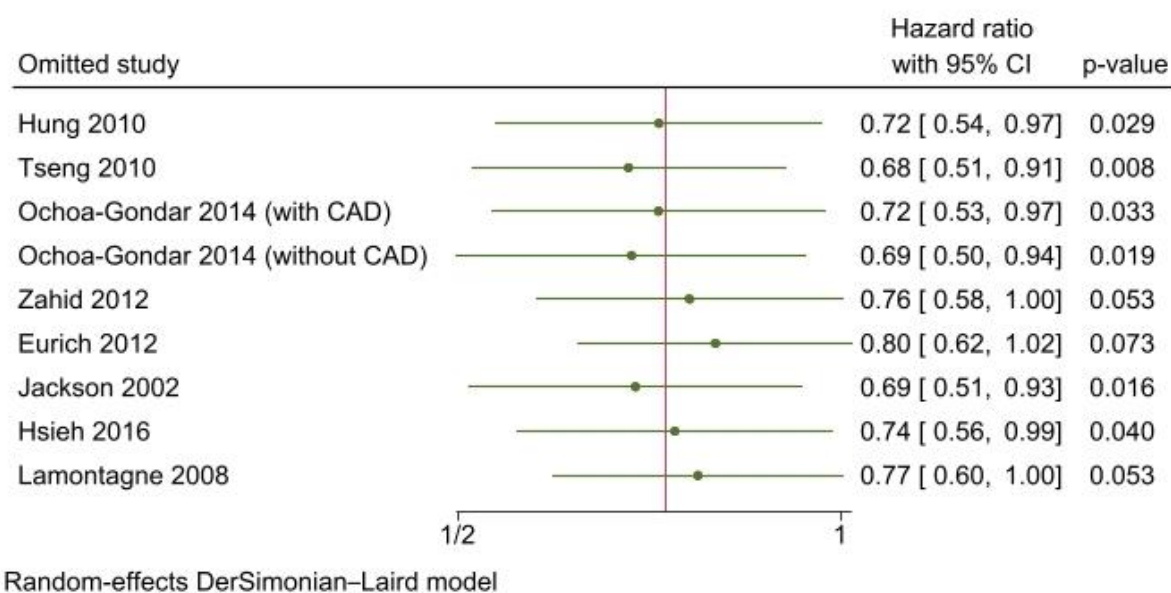
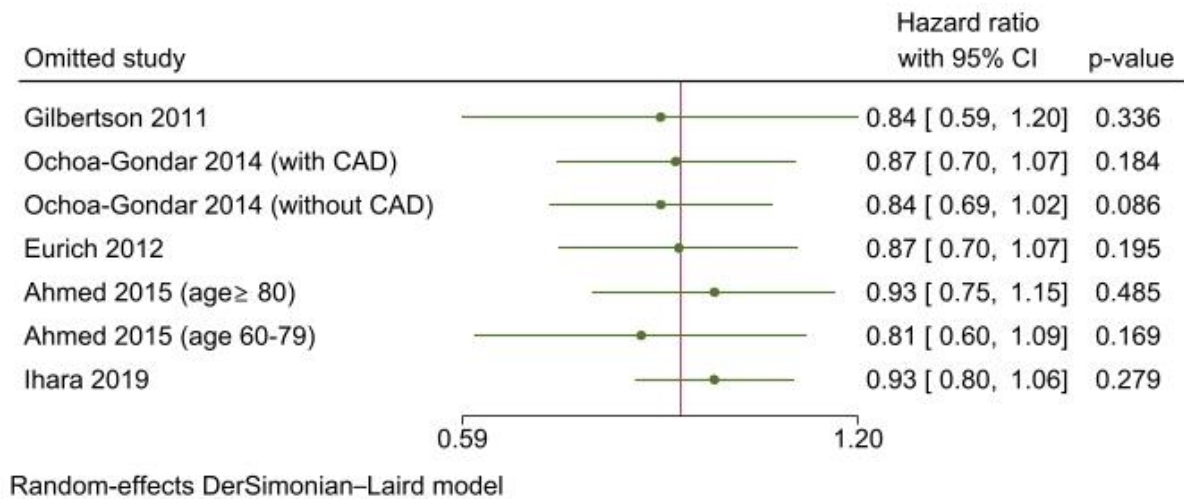


Figure S6: Leave-one-out analysis for secondary outcome: MI

### A) CV mortality



### B) Stroke

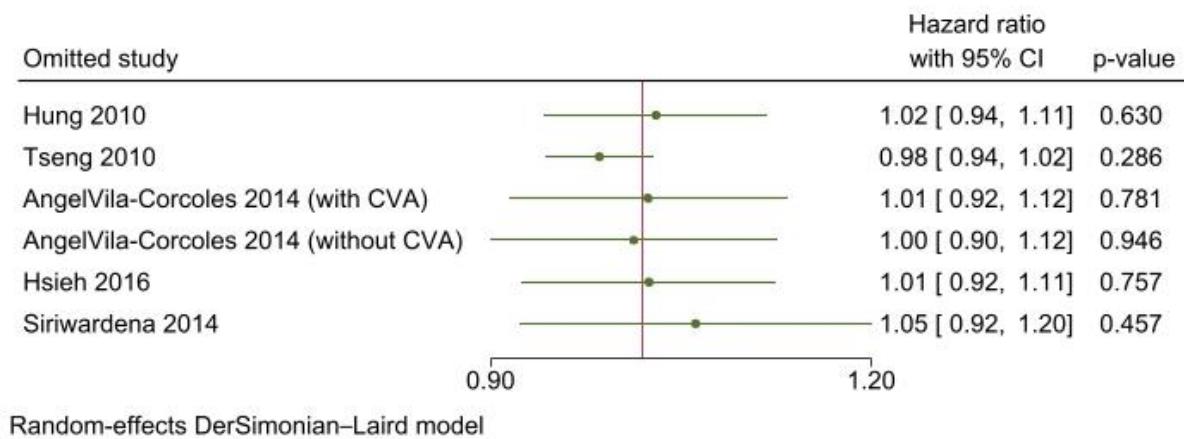


Figure S7: Leave-one-out analysis for secondary outcome: (A) CV mortality (B) Stroke

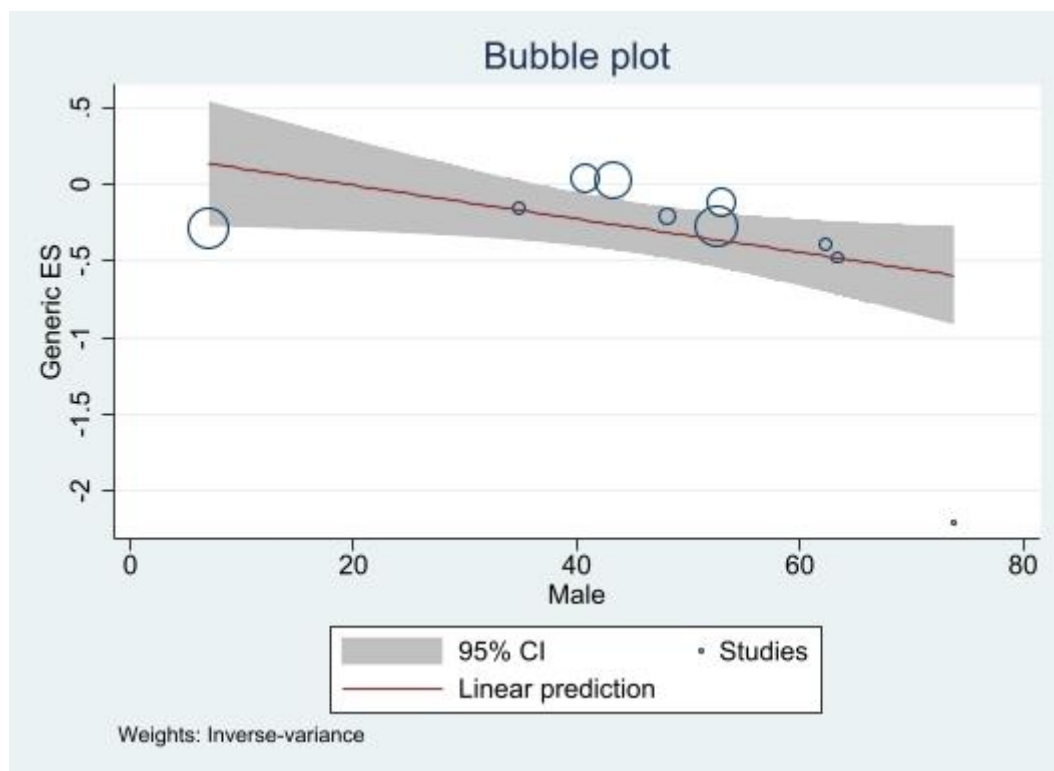


Figure S8: Meta-regression of male as an effect modifier for all-cause mortality

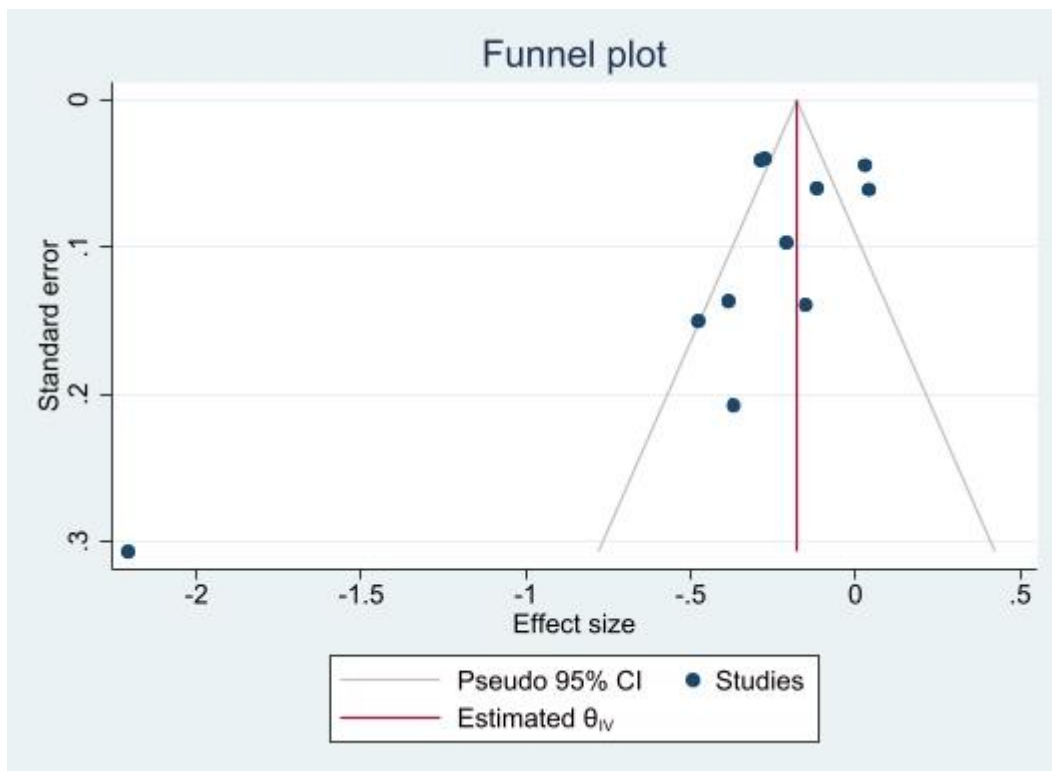
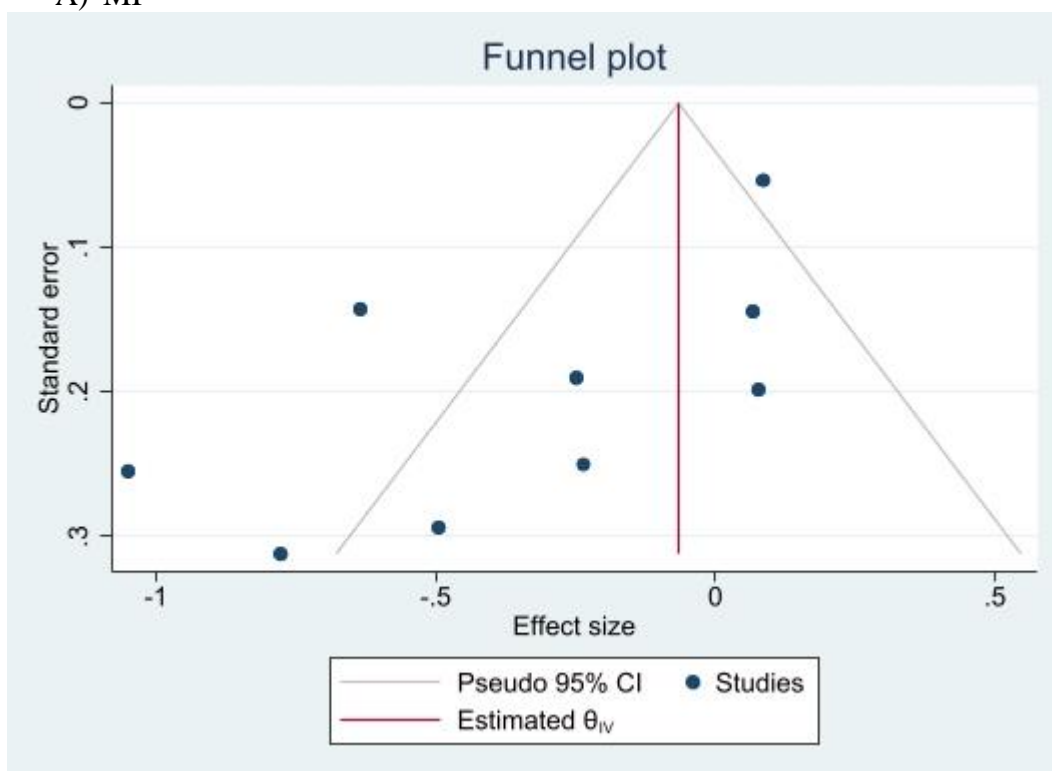
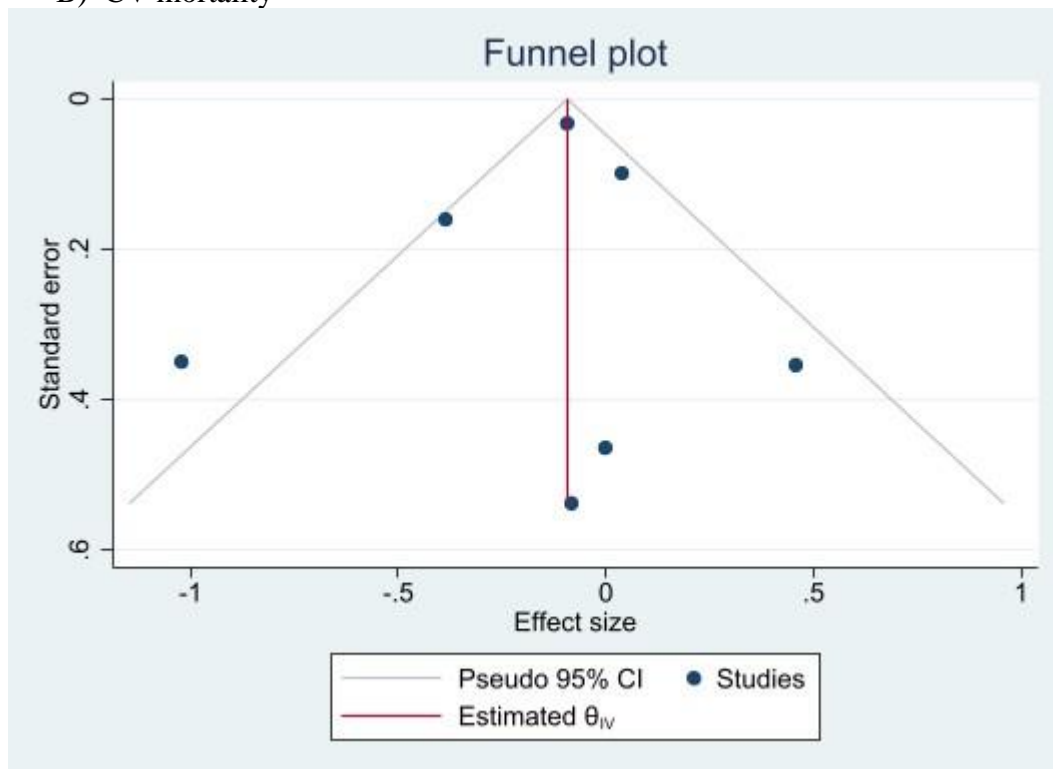


Figure S9: Funnel plots for publication bias for primary outcome including (A) all-cause mortality

A) MI



B) CV mortality



C) Stroke

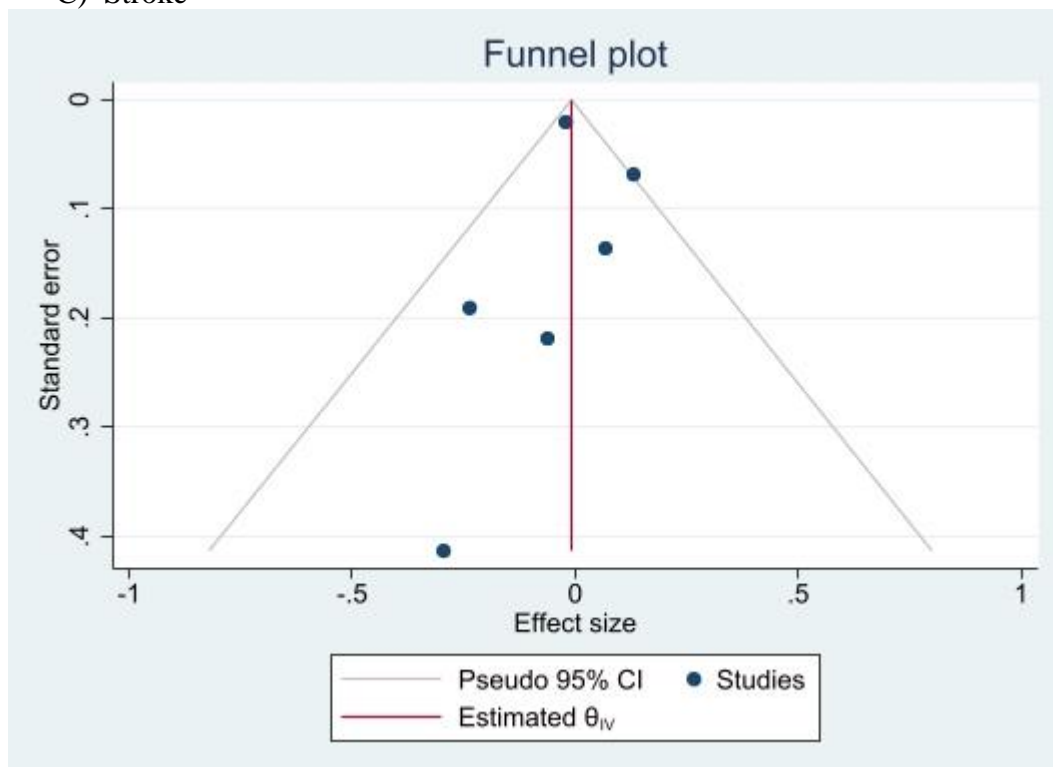


Figure S10: Funnel plots for publication bias for secondary outcomes including A) MI, B) CV mortality, C) Stroke