

Supplementary Material for Online Publication

Appendix 1

Search strategy for RCTs of PPV on Medline, Embase and CENTRAL

- #1 MeSH descriptor: [Pneumococcal Vaccines] explode all trees
- #2 pneumococc* near vaccin*
- #3 pneumococc* near immuni*
- #4 MeSH descriptor: [Streptococcus pneumoniae] explode all trees
- #5 streptococc* near pneumon*
- #6 MeSH descriptor: [Vaccination] explode all trees
- #7 vaccin* or immuni*
- #8 (#4 or #5) and (#6 or #7)
- #9 (#1 or #2 or #3 or #8)

Limit for “Randomised Controlled Trials” applied at end of search.

Appendix 2

PPV and ischaemic events observational studies search strategy on Embase

- 1. exp pneumococcal vaccines/
- 2. (pneumococc\$ adj3 vaccin\$).tw.
- 3. (pneumococc\$ adj3 immuni\$).tw.
- 4. exp streptococcus pneumoniae/
- 5. (streptococc\$ adj pneumon\$).tw.
- 6. immuni\$.tw.
- 7. vaccin\$.tw.
- 8. exp vaccination/
- 9. (4 or 5) and (6 or 7 or 8)
- 10. or/1-3,9
- 11. exp Cardiovascular Diseases/
- 12. myocardial.tw.
- 13. angina.tw.
- 14. coronary.tw.
- 15. heart.tw.
- 16. cardiac.tw.
- 17. cardiovascular.tw.
- 18. or/11-17
- 19. 10 and 18
- 20. Cerebrovascular Disease/
- 21. Basal Ganglion Hemorrhage/
- 22. cerebral artery disease/
- 23. Cerebrovascular Accident/
- 24. stroke/
- 25. stroke patient/ or stroke unit/
- 26. Vertebrobasilar Insufficiency/
- 27. exp Carotid Artery Disease/
- 28. exp Brain Hemangioma/
- 29. exp Brain Hematoma/
- 30. exp Brain Hemorrhage/

31. brain infarction/ or brain infarction size/ or brain stem infarction/ or cerebellum infarction/
32. exp Brain Ischemia/
33. exp Cerebrovascular Malformation/
34. exp intracranial aneurysm/
35. exp occlusive cerebrovascular disease/
36. brain injury/
37. brain stem injury/ or artery dissection/
38. cerebellum injury/
39. exp carotid artery/
40. exp carotid artery surgery/
41. carotid endarterectomy/
42. *heart atrium septum defect/ or heart foramen ovale/
43. *heart atrium fibrillation/
44. paradoxical embolism/
45. exp aphasia/ or hemiplegia/ or hemiparesis/ or paresis/ or spastic paresis/ or pseudobulbar palsy/ or hemianopia/ or homonymous hemianopia/ or dysphagia/ or dysarthria/ or dysphasia/ or spasticity/ or apraxia/ or dyspraxia/ or hemiballism/
46. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vascul\$ or cerebral vascul\$ or cva\$ or apoplex\$ or isch?emi\$ attack\$ or tia\$1 or neurologic\$ deficit\$ or SAH or AVM).tw.
47. ((brain\$ or cerebr\$ or cerebell\$ or cortical or vertebrobasilar or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypox\$ or vasospasm or obstruction or vasculopathy)).tw.
48. ((lacunar or cortical) adj5 infarct\$).tw.
49. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
50. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
51. (vertebral artery dissection or cerebral art\$ disease\$).tw.
52. ((brain or intracranial or basal ganglia or lenticulostriate) adj5 (vascular adj5 (disease\$ or disorder or accident or injur\$ or trauma\$ or insult or event))).tw.
53. ((isch?emic or apoplectic) adj5 (event or events or insult or attack\$)).tw.
54. ((cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo\$).tw.
55. (CVDST or CVT).tw.
56. ((intracranial or cerebral art\$ or basilar art\$ or vertebral art\$ or vertebrobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero\$ or atherosclero\$ or occlus\$)).tw.
57. ((venous or arteriovenous or brain vascul\$) adj5 malformation\$).tw.
58. ((brain or cerebral) adj5 (angioma\$ or hemangioma\$ or haemangioma\$)).tw.
59. carotid\$.hw.
60. (patent foramen ovale or PFO).tw.
61. ((atrial or atrium or auricular) adj fibrillation).tw.
62. asymptomatic cervical bruit.tw.
63. (aphasi\$ or apraxi\$ or dysphasi\$ or dysphagi\$ or deglutition disorder\$ or swallow\$ disorder\$ or dysarthri\$ or hemipleg\$ or hemipar\$ or paresis or paretic or hemianop\$ or hemineglect or spasticity or anomi\$ or dysnomi\$ or acquired brain injur\$ or hemiball\$).tw.
64. ((unilateral or visual or hemispatial or attentional or spatial) adj5 neglect).tw.

65. or/20-64
66. 10 and 65
67. 19 or 66
68. Clinical study/
69. case control study/
70. Family study/
71. Longitudinal study/
72. Retrospective study/
73. Prospective study/
74. Randomized controlled trials/
75. 73 not 74
76. Cohort analysis/
77. (Cohort adj (study or studies)).mp.
78. (Case control adj (study or studies)).tw.
79. (follow up adj (study or studies)).tw.
80. (observational adj (study or studies)).tw.
81. (epidemiologic\$ adj (study or studies)).tw.
82. (cross sectional adj (study or studies)).tw.
83. or/68-72,75-82
84. 67 and 83

PPV and ischaemic events observational studies search strategy on Medline

1. exp pneumococcal vaccines/
2. (pneumococc\$ adj3 vaccin\$).tw.
3. (pneumococc\$ adj3 immuni\$).tw.
4. exp streptococcus pneumoniae/
5. (streptococc\$ adj pneumon\$).tw.
6. immuni\$.tw.
7. vaccin\$.tw.
8. exp vaccination/
9. (4 or 5) and (6 or 7 or 8)
10. or/1-3,9
11. exp Cardiovascular Diseases/
12. myocardial.tw.
13. angina.tw.
14. coronary.tw.
15. heart.tw.
16. cardiac.tw.
17. cardiovascular.tw.
18. or/11-17
19. 10 and 18
20. cerebrovascular disorders/
21. exp basal ganglia cerebrovascular disease/
22. exp brain ischemia/
23. exp carotid artery diseases/
24. stroke/
25. exp brain infarction/
26. exp cerebrovascular trauma/
27. Hypoxia-Ischemia, Brain/
28. exp intracranial arterial diseases/
29. exp intracranial arteriovenous malformations/

30. exp "Intracranial Embolism and Thrombosis"/
31. exp intracranial hemorrhages/
32. vasospasm, intracranial/
33. vertebral artery dissection/
34. aneurysm, ruptured/ and exp brain/
35. brain injuries/
36. brain injury, chronic/
37. exp carotid arteries/
38. endarterectomy, carotid/
39. *heart septal defects, atrial/ or foramen ovale, patent/
40. *atrial fibrillation/
41. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or isch?emi\$ attack\$ or tia\$1 or neurologic\$ deficit\$ or SAH or AVM).tw.
42. ((brain\$ or cerebr\$ or cerebell\$ or cortical or vertebrobasilar or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypox\$ or vasospasm or obstruction or vasculopathy)).tw.
43. ((lacunar or cortical) adj5 infarct\$).tw.
44. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracran\$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli\$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
45. ((brain or cerebral or intracranial or communicating or giant or basilar or vertebral artery or berry or saccular or ruptured) adj5 aneurysm\$).tw.
46. (vertebral artery dissection or cerebral art\$ disease\$).tw.
47. ((brain or intracranial or basal ganglia or lenticulostriate) adj5 (vascular adj5 (disease\$ or disorder or accident or injur\$ or trauma\$ or insult or event))).tw.
48. ((isch?emic or apoplectic) adj5 (event or events or insult or attack\$)).tw.
49. ((cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo\$).tw.
50. (CVDST or CVT).tw.
51. ((intracranial or cerebral art\$ or basilar art\$ or vertebral art\$ or vertebrobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero\$ or atherosclero\$ or occlus\$)).tw.
52. ((venous or arteriovenous or brain vasc\$) adj5 malformation\$).tw.
53. ((brain or cerebral) adj5 (angioma\$ or hemangioma\$ or haemangioma\$)).tw.
54. carotid\$.tw.
55. (patent foramen ovale or PFO).tw.
56. ((atrial or atrium or auricular) adj fibrillation).tw.
57. asymptomatic cervical bruit.tw.
58. exp aphasia/ or anomia/ or hemiplegia/ or hemianopsia/ or exp paresis/ or deglutition disorders/ or dysarthria/ or pseudobulbar palsy/ or muscle spasticity/
59. (aphasi\$ or apraxi\$ or dysphasi\$ or dysphagi\$ or deglutition disorder\$ or swallow\$ disorder\$ or dysarthri\$ or hemipleg\$ or hemipar\$ or paresis or paretic or hemianop\$ or hemineglect or spasticity or anomi\$ or dysnomi\$ or acquired brain injur\$ or hemiball\$).tw.
60. ((unilateral or visual or hemispatial or attentional or spatial) adj5 neglect).tw.
61. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. 10 and 61
63. 19 or 62
64. Epidemiologic studies/
65. exp case control studies/

66. exp cohort studies/
67. Case control.tw.
68. (cohort adj (study or studies)).tw.
69. Cohort analy\$.tw.
70. (Follow up adj (study or studies)).tw.
71. (observational adj (study or studies)).tw.
72. Longitudinal.tw.
73. Retrospective.tw.
74. Cross sectional.tw.
75. Cross-sectional studies/
76. or/64-75
77. 63 and 76

PPV and ischemic events search strategy on CENTRAL

#1	MeSH descriptor: [Cerebrovascular Disorders] this term only	1357	
#2	MeSH descriptor: [Basal Ganglia Cerebrovascular Disease] explode all trees		21
#3	MeSH descriptor: [Brain Ischemia] explode all trees	1985	
#4	MeSH descriptor: [Carotid Artery Diseases] explode all trees	883	
#5	MeSH descriptor: [Stroke] this term only	3605	
#6	cerebral small vessel disease	256	
#7	lacunar near/3 stroke	74	
#8	MeSH descriptor: [Brain Infarction] explode all trees	647	
#9	MeSH descriptor: [Cerebrovascular Trauma] explode all trees	23	
#10	MeSH descriptor: [Hypoxia-Ischemia, Brain] this term only	95	
#11	MeSH descriptor: [Intracranial Arterial Diseases] explode all trees	807	
#12	MeSH descriptor: [Intracranial Arteriovenous Malformations] explode all trees		44
#13	MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees		239
#14	MeSH descriptor: [Intracranial Hemorrhages] explode all trees	1145	
#15	MeSH descriptor: [Vasospasm, Intracranial] this term only	94	
#16	MeSH descriptor: [Vertebral Artery Dissection] this term only	3	
#17	MeSH descriptor: [Aneurysm, Ruptured] this term only	94	
#18	MeSH descriptor: [Brain] explode all trees	7188	
#19	#17 and #18	10	
#20	MeSH descriptor: [Brain Injuries] this term only	801	
#21	MeSH descriptor: [Brain Injury, Chronic] this term only	26	
#22	MeSH descriptor: [Carotid Arteries] explode all trees	926	
#23	MeSH descriptor: [Endarterectomy, Carotid] this term only	446	
#24	MeSH descriptor: [Heart Septal Defects, Atrial] this term only	99	
#25	MeSH descriptor: [Foramen Ovale, Patent] explode all trees	21	
#26	MeSH descriptor: [Aphasia] explode all trees	144	
#27	MeSH descriptor: [Anomia] this term only	12	
#28	MeSH descriptor: [Hemiplegia] this term only	394	
#29	MeSH descriptor: [Hemianopsia] this term only	21	
#30	MeSH descriptor: [Paresis] explode all trees	297	
#31	MeSH descriptor: [Deglutition Disorders] this term only	434	
#32	MeSH descriptor: [Dysarthria] this term only	36	
#33	MeSH descriptor: [Pseudobulbar Palsy] this term only	4	
#34	MeSH descriptor: [Muscle Spasticity] this term only	437	
#35	stroke or poststroke or post-stroke or cerebrovasc* or "brain vasc*" or "cerebral vasc*" or cva* or apoplex* or "ischemi* attack*" or "ischaemi* attack*" or TIA or TIAs or "neurologic* deficit*" or SAH or AVM	30771	

#36 (brain* or cerebr* or cerebell* or cortical or vertebrobasilar or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or MCA or "anterior circulation" or "posterior circulation" or "basal ganglia") near/5 (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus* or hypox* or vasospasm or obstruction or vasculopathy) 5562

#37 (lacunar or cortical) near/5 infarct* 140

#38 (brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or "basal gangli*" or subarachnoid or putaminal or putamen or "posterior fossa") near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*) 3848

#39 (brain or cerebral or intracranial or communicating or giant or basilar or "vertebral artery" or berry or saccular or ruptured) near/5 aneurysm* 843

#40 "vertebral artery dissection" or "cerebral art* disease*" 112

#41 (brain or intracranial or "basal ganglia" or lenticulostriate) near/5 vascular near/5 (disease* or disorder or accident or injur* or trauma* or insult or event) 84

#42 (ischemic or ischaemic or apoplectic) near/5 (event or events or insult or attack*) 2286

#43 ("cerebral vein" or "cerebral venous" or sinus or sagittal) near/5 thrombo* 81

#44 CVDST or CVT 40

#45 (intracranial or "cerebral art*" or "basilar art*" or "vertebral art*" or vertebrobasilar or "vertebral basilar") near/5 (stenosis or ischemia or ischaemia or insufficiency or arteriosclero* or atherosclero* or occlus*) 575

#46 (venous or arteriovenous or brain vasc*) near/5 malformation* 186

#47 (brain or cerebral) near/5 (angioma* or hemangioma* or haemangioma*) 6

#48 carotid* 3613

#49 patent foramen ovale 93

#50 PFO 68

#51 asymptomatic cervical bruit 12

#52 aphasi* or apraxi* or dysphasi* or dysphagi* or "deglutition disorder*" or "swallow* disorder*" or dysarthri* or hemipleg* or hemipar* or paresis or paretic or hemianop* or hemineglect or spasticity or anomi* or dysnomi* or "acquired brain injur*" or hemiball* 5024

#53 (unilateral or visual or hemispatial or attentional or spatial) near/5 neglect 201

#54 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53) 38723

#55 MeSH descriptor: [Cardiovascular Diseases] explode all trees 67103

#56 heart (Word variations have been searched) 62011

#57 coronary (Word variations have been searched) 26651

#58 cardiac (Word variations have been searched) 28319

#59 myocardial 21229

#60 cardiovascular 31785

#61 angina 8388

#62 {or #55-#61} 122772

#63 MeSH descriptor: [Pneumococcal Vaccines] explode all trees 460

#64 pneumococc* near vaccin* 800

#65 pneumococc* near immuni* 207

#66 MeSH descriptor: [Streptococcus pneumoniae] explode all trees 442

#67 streptococc* near pneumon* 1111

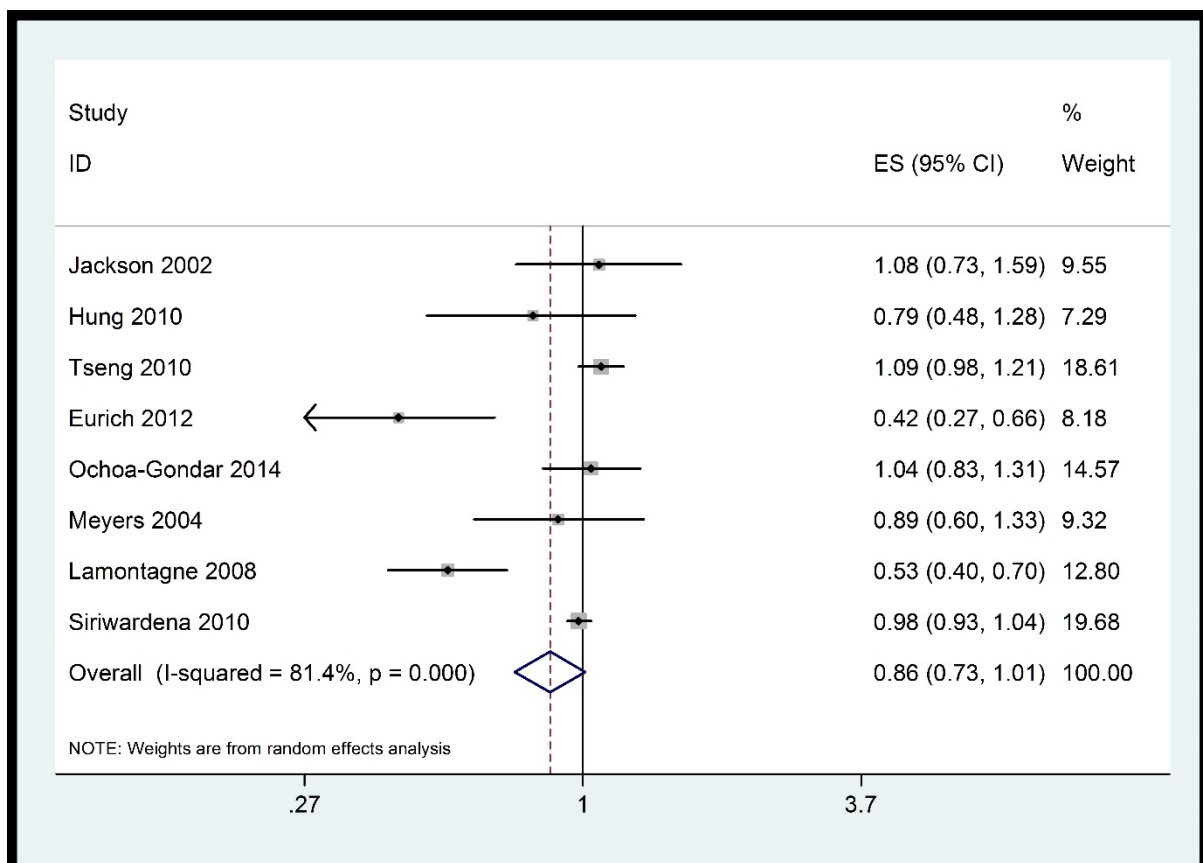
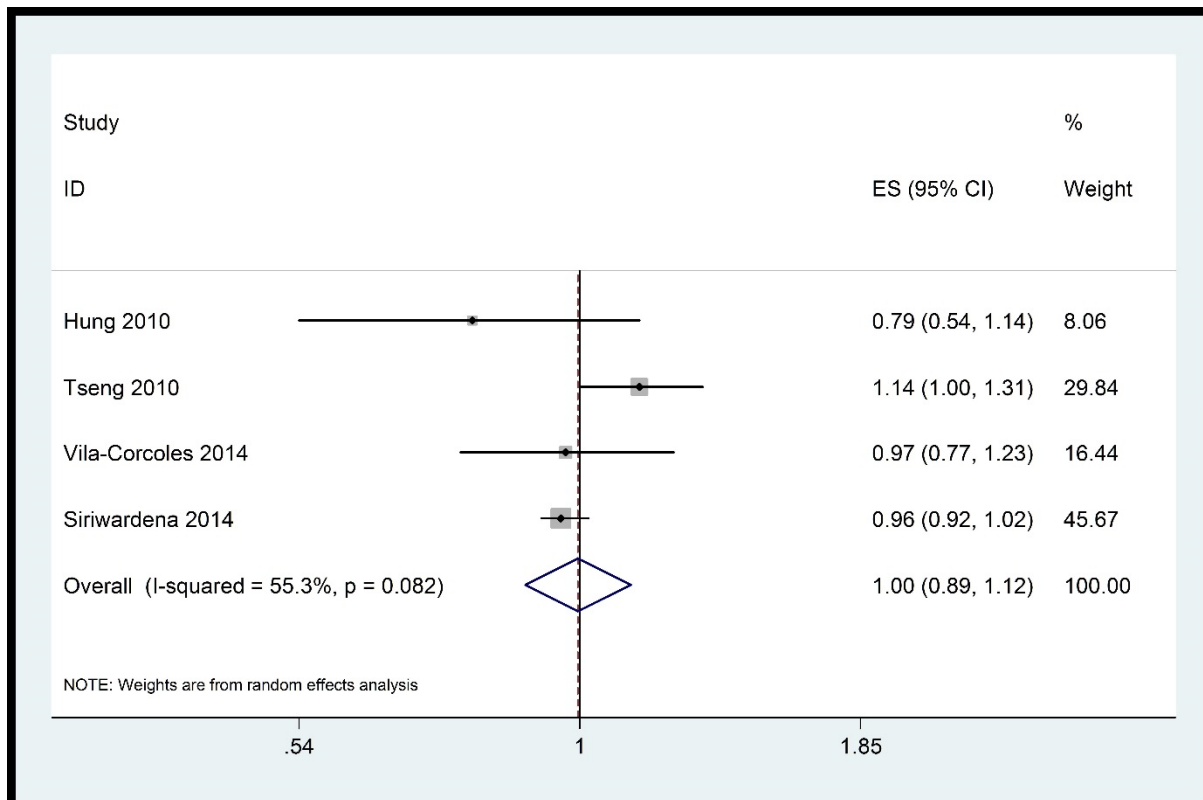
#68 MeSH descriptor: [Vaccination] explode all trees 1802

#69 vaccin* or immuni* 13841

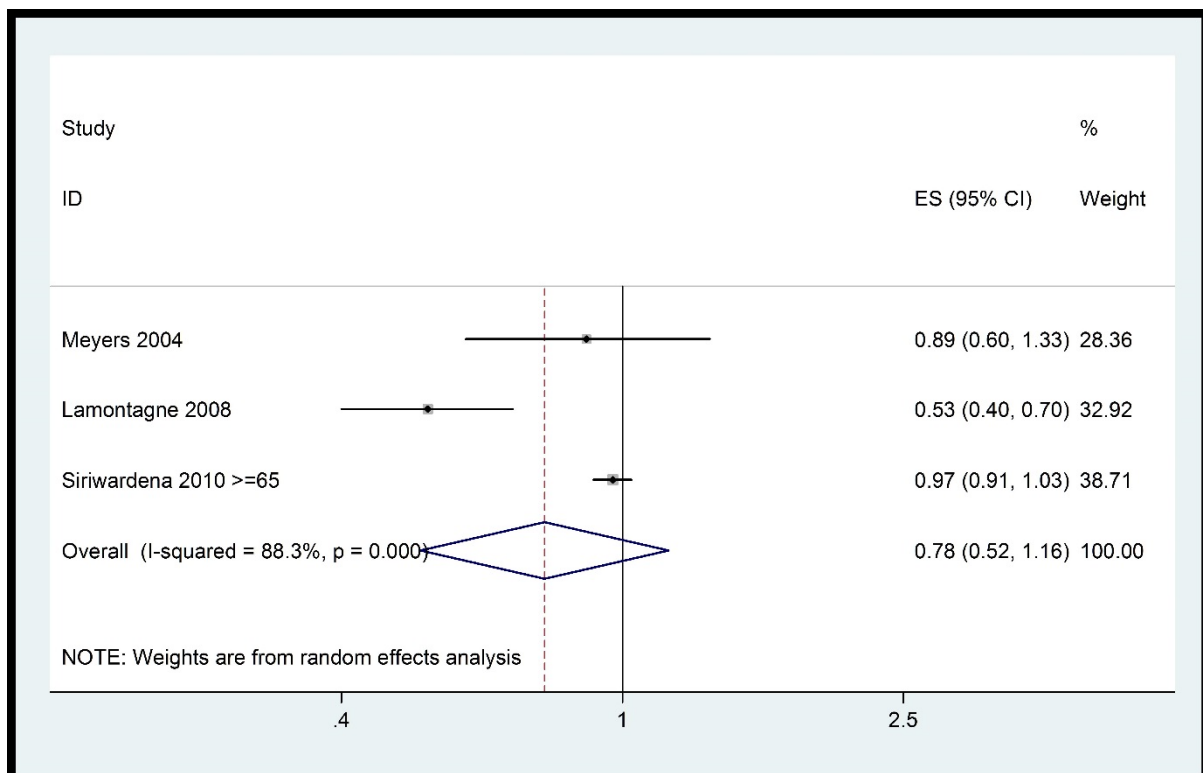
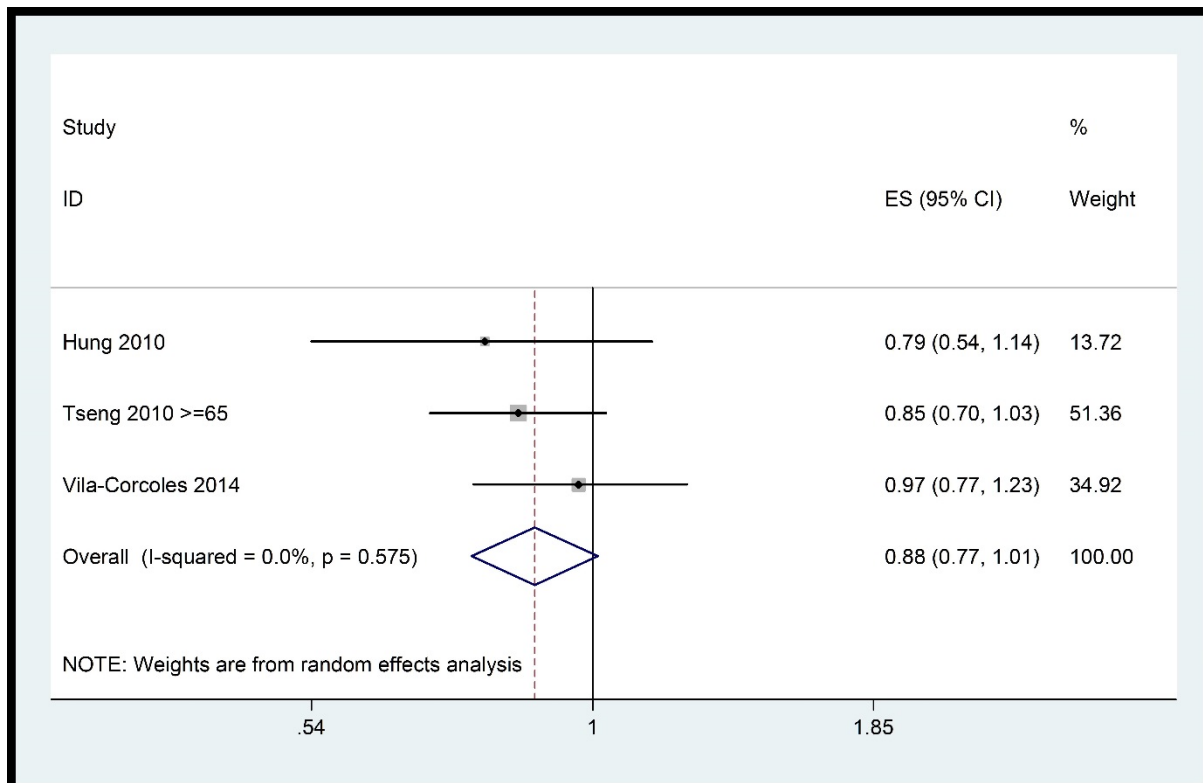
#70 (#66 or #67) and (#68 or #69) 315

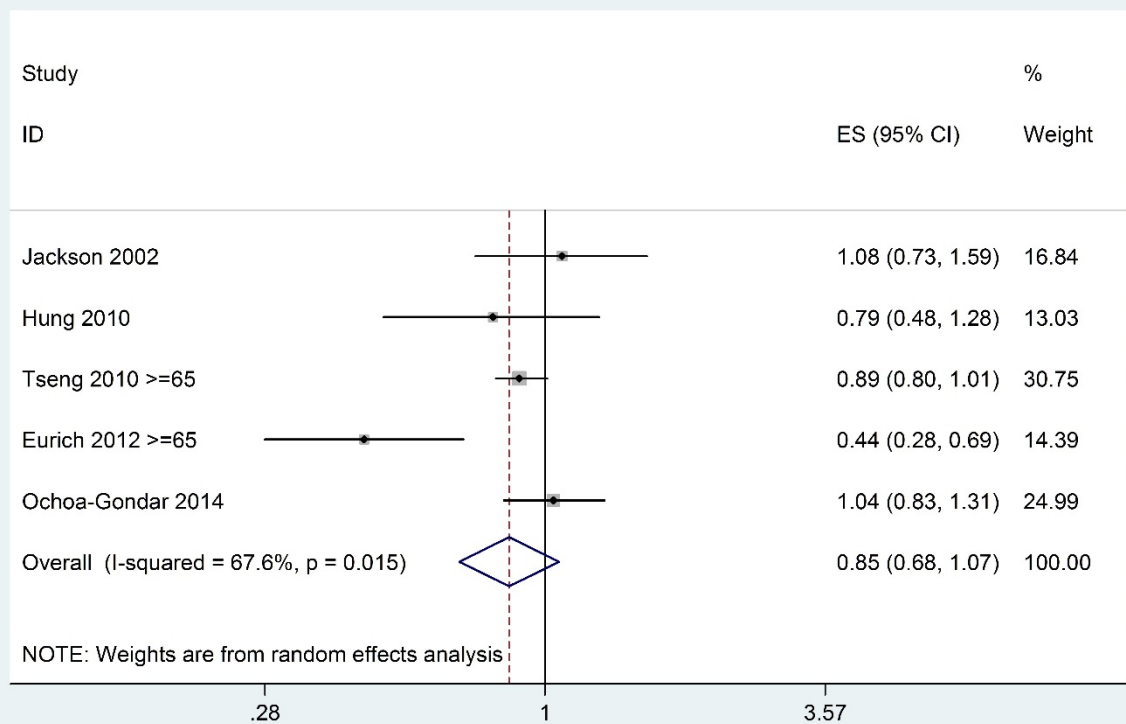
#71 (#63 or #64 or #65 or #70) 855
#72 (#54 or #62) and #71 75

Appendix 3: Forest plots of analysis of PPV and ACS events (upper), PPV and stroke (lower), without age restriction



Appendix 4: Forest plots of analysis of PPV and ACS events for cohort studies (upper), PPV and ACS events for case-control studies (middle), PPV and stroke for cohort studies (lower), age restricted to ≥ 65 years where possible





Appendix 5

STATA output for meta-regression

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. metareg ratio sex, wsse(selogr) eform graph
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Meta-regression

REML estimate of between-study variance

% residual variation due to heterogeneity

Proportion of between-study variance explained

With Knapp-Hartung modification

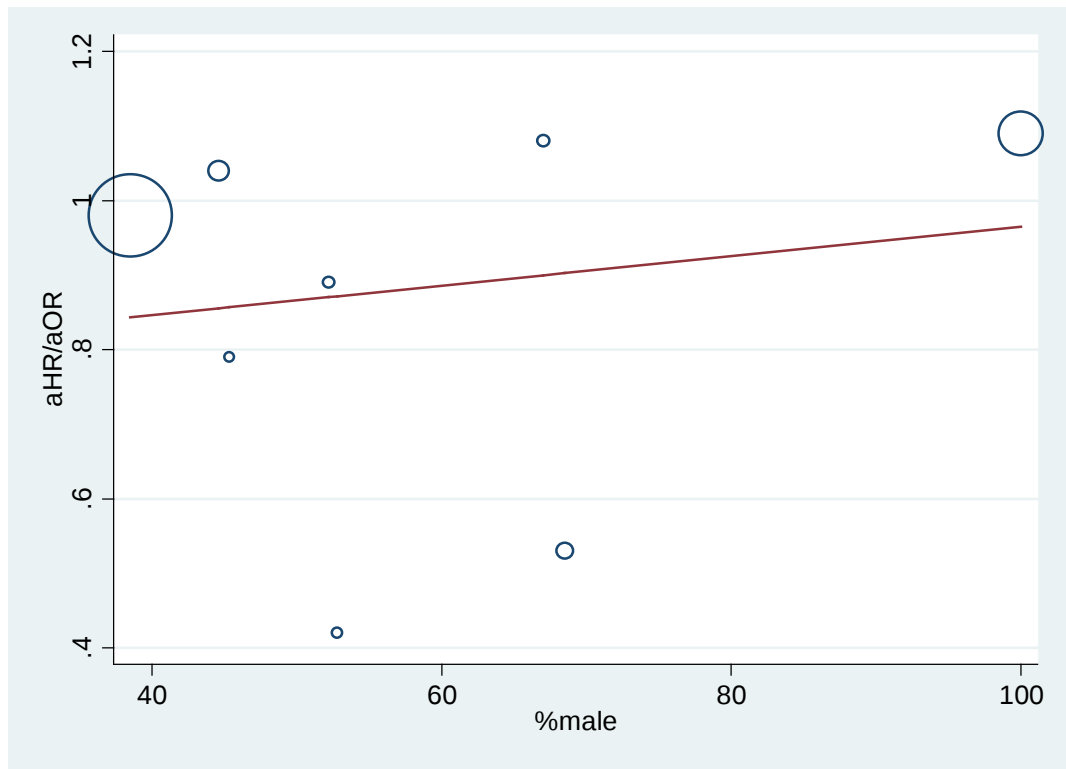
Number of obs = 8

tau2 = .04707

I-squared_res = 68.96%

Adj R-squared = -33.36%

ratio	exp(b)	Std. Err.	t	P> t	[95% Conf. Interval]	
sex	1.00197	.0044628	0.44	0.674	.9911093	1.01295



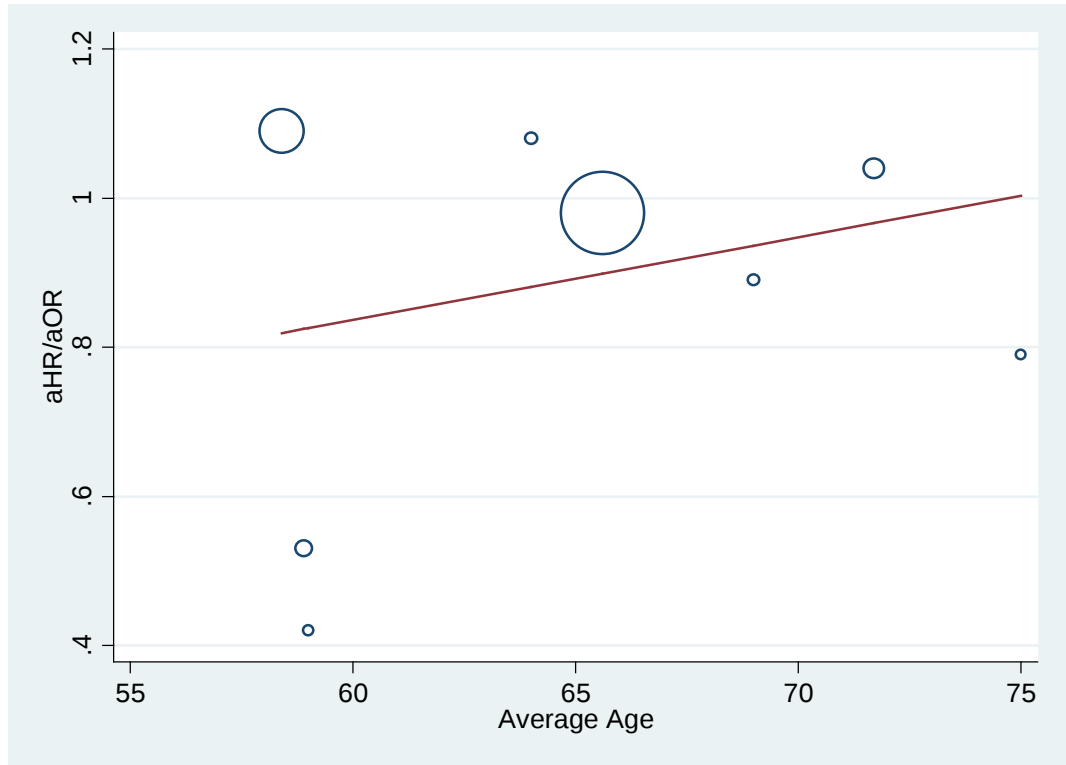
. metareg ratio age, wsse(selogr) eform graph

. . metareg ratio age, wsse(selogr) eform graph

Meta-regression
REML estimate of between-study variance
% residual variation due to heterogeneity
Proportion of between-study variance explained
With Knapp-Hartung modification

Number of obs = 8
tau2 = .04298
I-squared_res = 71.78%
Adj R-squared = -21.76%

ratio	exp(b)	Std. Err.	t	P> t	[95% Conf. Interval]	
age	1.011153	.0162883	0.69	0.517	.9720724	1.051805

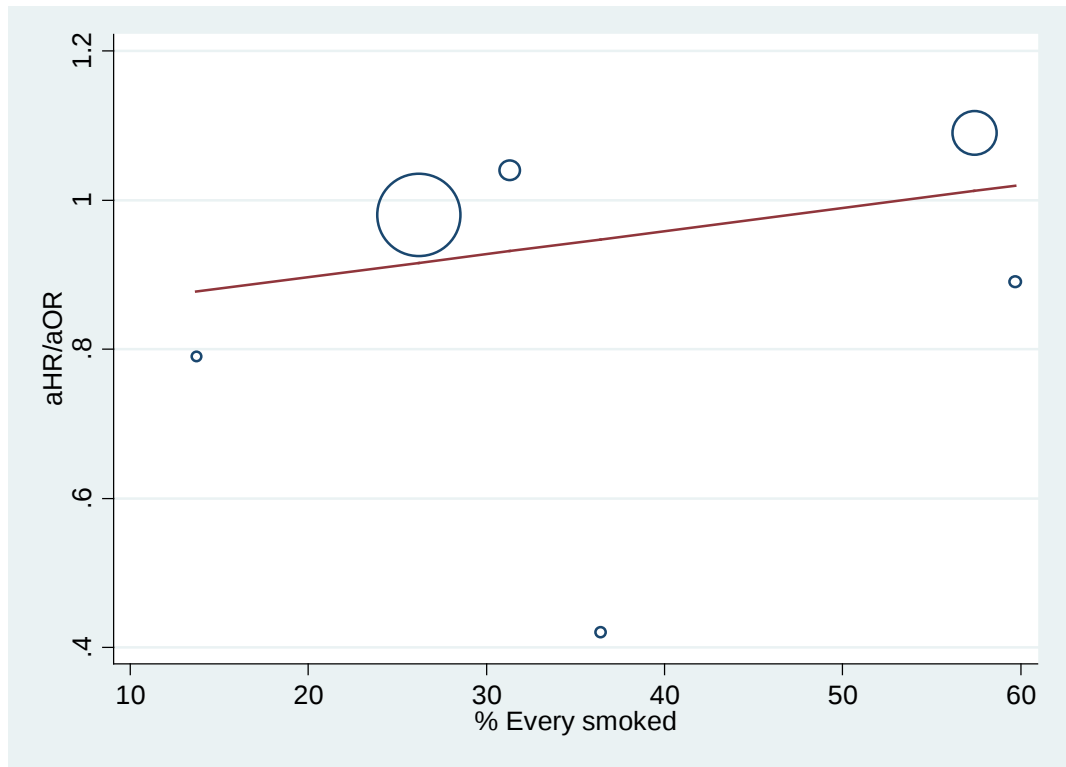


. metareg ratio smoke, wsse(selogr) eform graph

Meta-regression
REML estimate of between-study variance
% residual variation due to heterogeneity
Proportion of between-study variance explained
With Knapp-Hartung modification

Number of obs = 6
tau2 = .01719
I-squared_res = 50.90%
Adj R-squared = -186.65%

ratio	exp(b)	Std. Err.	t	P> t	[95% Conf. Interval]	
smoke	1.003098	.005554	0.56	0.606	.987795	1.018637



. metareg ratio dm, wsse(selogr) eform graph

Meta-regression
REML estimate of between-study variance
% residual variation due to heterogeneity
Proportion of between-study variance explained
With Knapp-Hartung modification

Number of obs = 6
tau2 = .05919
I-squared_res = 79.45%
Adj R-squared = -13.41%

ratio	exp(b)	Std. Err.	t	P> t	[95% Conf. Interval]	
dm	1.014908	.0200318	0.75	0.495	.9607874	1.072077

