Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis

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ABSTRACT
Animal models and clinical studies suggest a mechanism link between the pneumococcal polysaccharide vaccine (PPV) and a cardiovascular protective effect. However, conflicting results exist from several large observational studies in humans. We set out to systematically review current literature and conduct meta-analyses of studies on PPV and cardiovascular outcomes. Medline, Embase and CENTRAL were searched for randomised controlled trials (RCTs) and observational studies in adults, using PPV as the intervention, up to 30 April 2014. Studies that compared PPV with a control (another vaccine, no vaccine or placebo) and recorded ischaemic events were included in this review. Two investigators extracted data independently on study design, baseline characteristics and summary outcomes. Study quality was examined using the Newcastle-Ottawa Quality Assessment Scale. Pooled estimates using random effects models and their 95% CIs were calculated separately for the outcomes of acute coronary syndrome (ACS) events and stroke. No RCT data were available. A total of 230 426 patients were included in eight observational studies and recorded as ACS events. PPV was associated with significantly lower odds of ACS events in patients 65 years and older (pooled OR=0.83 (95% CI 0.71 to 0.97), I²=77.0%). However, there was no significant difference in ACS events when younger people were included (pooled OR=0.86 (95% CI 0.73 to 1.01), I²=81.4%). Pooling of four studies, covering a total of 192 210 patients, did not find a significantly reduced risk of stroke in all patients (pooled OR=1.00 (95% CI 0.89 to 1.12), I²=55.3%), or when restricted to those 65 years and older (pooled OR=0.96 (95% CI 0.87 to 1.05), I²=22.5%). In this meta-analysis of observational studies, the use of PPV was associated with a significantly lower risk of ACS events in the older population, but not stroke. An adequately powered and blinded RCT to confirm these findings is warranted.

INTRODUCTION
Coronary heart disease and stroke are the two leading causes of death worldwide in people aged 60 years and above, and are major contributors to the global burden of disease.1 Cholesterol, especially low-density lipoprotein (LDL), is widely believed to play a role in atherosclerotic plaque formation and subsequent cardiovascular diseases.2,3 Murine models have demonstrated that immunisation against oxidised LDL (oxLDL) reduces atherosclerosis.4,5 Interestingly, pneumococcal immunisation has been shown to elicit such anti-oxLDL antibodies in mice.5 It is therefore postulated that the pneumococcal polysaccharide vaccine (PPV), by inducing the production of anti-oxLDL antibodies, may have a protective effect on cardiovascular disease in humans. This mechanistic link is supported by a recent clinical study, which found a significant association between pneumococcal IgG and anti-oxLDL antibody titre.6

To date, there have been several observational studies published on the occurrence of ischaemic events post-PPV administration. Lamontagne et al7 conducted a case-control study of 4995 patients and found that PPV was associated with a greater than 50% reduction in myocardial infarction. Similarly, a cohort study of 6171 participants by Eurich et al9 reported that PPV exposure was associated with a 60% reduction in acute coronary syndrome (ACS) events. However, large observational studies by Siriwardena et al9 (N=78 706, case-control) and Tseng et al10 (N=84 170, cohort) did not detect such benefits of the PPV. Given the conflicting results from existing observational studies, a review is warranted to resolve inconsistencies, explore heterogeneity and provide a more precise pooled estimate. We therefore set out to systematically review and meta-analyse available randomised controlled trials (RCTs) and observational studies on the PPV in preventing ischaemic cardiac events and stroke.

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Meta-analysis

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METHODS
Inclusion/exclusion criteria
We included studies in human adults where PPV was the tested intervention, compared to placebo or no vaccination, and ischaemic myocardial events or ischaemic cerebrovascular events were the recorded outcomes. In contrast, studies were excluded if PPV was not the tested intervention, ischaemic events were not the recorded outcomes, did not have a comparator, or were conducted in children. Guidelines, reviews, editorial letters, conference abstracts without published data, case reports, surveys and incomplete trials were also excluded.

Randomised controlled trials
Medline, Embase and CENTRAL were searched for RCTs of PPV that either reported ischaemic events as a primary outcome or recorded these events as adverse events after vaccination, up to 30 April 2014. The search terms were adapted from the Cochrane systematic review on vaccines for preventing pneumococcal infection in adults for both study inclusion and data extraction were resolved by consensus. Only published results were considered for this review; study authors were not contacted for unpublished data.

Observational studies
Medline, Embase and CENTRAL were searched for observational studies on PPV and cardiovascular disease up to 30 April 2014, using search terms adapted from relevant Cochrane systematic reviews, the Cochrane Stroke Review Group and the Scottish Intercollegiate Guidelines Network (SIGN). The observational studies filter from SIGN was used. See online supplementary appendix 2 for a detailed search strategy.

The title and abstract were screened by two independent reviewers (SR and PM) and papers were excluded as per the exclusion criteria stated above. Shortlisted studies had their full text reviewed independently by the two reviewers (SR and PM) and discrepancies were resolved by consensus. Only published results were considered for this review; study authors were not contacted for unpublished data.

RESULTS
RCTs of PPV
A total of 1041 unique results were found after removing duplicates, of which only three studies reported cardiovascular or neurological causes of death for control and vaccine groups separately during follow-up. None of these were suitable for data extraction due to uncertainty over whether these events were ischaemic in nature. Causes of death were listed simply as ‘Cardiac’, ‘Neurologic’, ‘Cardiovascular’, ‘Cerebrovascular’ and ‘Central nervous’ in the three studies, and there were insufficient data to tell whether these deaths were due to haemorrhagic or chronic congestive causes. See figure 1 for a flow chart of the selection process.

Observational studies
A total of 263 unique results were found after removing duplicates (see figure 2 for a flow chart of the selection process). Thirteen papers describing nine studies were included for data extraction. Four studies were case-control designs examining exposure to PPV in those with myocardial infarction or stroke events. Five studies were cohort studies that reported on ACS events

Sensitivity analyses
Some studies reported effect sizes for subsets such as older population. Our primary analyses were restricted to people aged 65 years and above where data existed, since this population is considered to be at increased risk of morbidity and mortality from pneumococcal infection. Additional analyses were carried out using all available data to explore changes to the overall pooled ratio.

Statistical analyses
Data were analysed using STATA V.11 (StataCorp, 2009. Stata Statistical Software: Release 11. College Station, Texas, USA: StataCorp LP.). Random effects models were used for meta-analyses and studies were pooled according to the measured outcomes (ACS or stroke). The adjusted ORs (aOR) or HRs (aHR) from each study were weighted and combined to produce an overall pooled ratio for each outcome. Q statistics and I² were calculated to examine heterogeneity. Where between-study heterogeneity existed, meta-regression was carried out to determine the source of heterogeneity. Meta-regression only used individual predictors that were available consistently across published data. Where the average age of the entire cohort was not reported, it was calculated from the age category proportions published. For probability testing, α was set to 0.05. The Egger test was performed to detect study size effects (interpreted as potential publication bias) and a contour-enhanced funnel plot was used to demonstrate this graphically.
after PPV administration. Three of these cohort studies also reported incidence of stroke post-PPV exposure. A summary of the studies included in this review is presented in tables 1 and 2. In general, study quality was reasonable with all studies scoring at least 6/9 on the Newcastle-Ottawa Quality Assessment Scale (see online supplementary file for a detailed assessment). Lengths of follow-up for cohort studies varied from 90 days postvaccination for primary outcome in Eurich et al to a maximum of 6 years in other studies. It also appears that Jackson et al only included results of PPV association with ACS as a post hoc analysis.

ACS outcomes
In the primary meta-analysis of PPV and ACS events in people aged 65 years and above (age restriction was possible in three studies), contour-enhanced funnel plots of eight studies did not indicate the presence of publication bias (Egger test p value=0.165). $\chi^2$ (77.0%) demonstrated significant heterogeneity between studies. A pooled ratio of 0.83 (95% CI 0.71 to 0.97) was in favour of PPV (figures 3 and 4).

When age restriction was not applied (ie, younger population included from Tseng et al, Eurich et al and Siriwadena et al), the analysis produced a pooled ratio of 0.86 (95% CI 0.73 to 1.01). Publication bias was not detected (Egger test p value=0.202) while heterogeneity remained significant ($\chi^2$=81.4%) (see online supplementary appendix 3).

Additional analyses were performed with pooling of studies based on design (cohort or case–control). The five cohort studies produced a pooled HR of 0.85 (95% CI 0.68 to 1.07, $\chi^2$=67.6%), while the three case–control studies produced a pooled OR of 0.78 (95% CI 0.52 to 1.16, $\chi^2$=88.3%) for ACS events (age restriction applied where possible) (see online supplementary appendix 4).

Meta-regressions using average age, gender, smoking status or history of diabetes mellitus as individual
<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study type</th>
<th>Location</th>
<th>Study period</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Follow-up time (retrospective for case–control studies)</th>
<th>Case Control</th>
<th>Total participants</th>
<th>Average age (years)</th>
<th>% male</th>
<th>Previous ischaemic events (%)</th>
<th>MI</th>
<th>ACS</th>
<th>Ever smoked (%)</th>
<th>History of DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al (2002)</td>
<td>Cohort</td>
<td>Washington state, USA</td>
<td>August 1992—December 1996</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>Median 2.3 years</td>
<td>All AMI</td>
<td>36 636*</td>
<td>64</td>
<td>67</td>
<td>7.3</td>
<td>100</td>
<td>13.7</td>
<td>24.4</td>
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</tr>
<tr>
<td>Hung et al (2010)</td>
<td>Cohort</td>
<td>Hong Kong</td>
<td>03 December 2007—30 June 2008</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>Mean 4.7 years, Median 5.3 years</td>
<td>New AMI</td>
<td>84 170</td>
<td>75</td>
<td>67</td>
<td>3.4</td>
<td>1.2</td>
<td>57.4</td>
<td>12.4</td>
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<tr>
<td>Tseng et al (2010)</td>
<td>Cohort</td>
<td>California, USA</td>
<td>January 2002—December 2007</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>90 days</td>
<td>New bone fractures</td>
<td>6171</td>
<td>59</td>
<td>52.8</td>
<td>36.4</td>
<td>11.3</td>
<td>31.3</td>
<td>4.75</td>
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<tr>
<td>Eurich et al (2012)</td>
<td>Cohort</td>
<td>Alberta, Canada</td>
<td>2000–2002</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>3 years, 76 033 person-years</td>
<td>New AMI Surgical admissions</td>
<td>27 204</td>
<td>71.7</td>
<td>44.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vila-Corcoles et al (2014)</td>
<td>Case–control</td>
<td>Tarragona, Spain</td>
<td>December 2008—November 2011</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>Maximum 5 years</td>
<td>New AMI Random matched 1:4</td>
<td>534</td>
<td>69</td>
<td>52.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Ochoa-Gondar et al (2014)</td>
<td>Case–control</td>
<td>Kansas, USA</td>
<td>November 2001—March 2002</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>Maximum 10 years</td>
<td>New stroke/TIA Random matched 1:1</td>
<td>4995</td>
<td>69</td>
<td>68.5</td>
<td>6.25 (stroke or TIA)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Siriwardena et al (2010)</td>
<td>Case–control</td>
<td>England and Wales</td>
<td>September 2001—August 2009</td>
<td>PPV</td>
<td>Unvaccinated</td>
<td>Not specified</td>
<td>Stroke or TIA</td>
<td>78 706</td>
<td>58.9</td>
<td>65.3§</td>
<td>38.5</td>
<td>48.0</td>
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</table>

*27 268 participants from PPV alone and unvaccinated groups used in meta-analysis. Original study included influenza vaccine as well.
†53 568 participants from stroke only cases and matched controls used in meta-analysis, as adjusted ORs were reported separately for stroke and TIA.
‡Range or SD of average age were not presented in all original publications.
§Average age not published, calculated using data available for proportions of those 40–64 years old and ≥65 years old. Average life expectancy for 2001 estimated as 80 years old using UK National Statistics accessed via http://www.statistics.gov.uk

ACS, acute coronary syndrome; AMI, acute myocardial infarction; DM, diabetes mellitus; PPV, pneumococcal polysaccharide vaccine; TIA, transient ischaemic attack.
Table 2  Summary results of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Study type</th>
<th>Newcastle-Ottawa quality scale</th>
<th>Number of events or event rate</th>
<th>Most adjusted ratio</th>
<th>95% CI</th>
<th>2nd outcome/intervention recorded</th>
<th>Number of events or event rate</th>
<th>Most adjusted ratio</th>
<th>95% CI</th>
<th>3rd outcome recorded</th>
<th>Number of events or event rate</th>
<th>Most adjusted ratio</th>
<th>95% CI</th>
<th>4th outcome recorded</th>
<th>Number of events or event rate</th>
<th>Most adjusted ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al (2002)</td>
<td>Cohort</td>
<td>3/4</td>
<td>21/1000 p-y (PPV only), 21/1000 p-y (unvaccinated)</td>
<td>aHR=0.79</td>
<td>0.48–1.28</td>
<td>Ischaemic stroke</td>
<td>1724/36309 (PPV), 981/47861 (unvaccinated)</td>
<td>aHR=1.09</td>
<td>0.98–1.21</td>
<td>Stroke (all ages)</td>
<td>799/36309 (PPV), 335/47861 (unvaccinated)</td>
<td>aHR=1.14</td>
<td>1.00–1.31</td>
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<tr>
<td>Hung et al (2010)</td>
<td>Cohort</td>
<td>3/4</td>
<td>25/724 (PPV), 54/724 (unvaccinated)</td>
<td>aHR=0.89</td>
<td>0.80–1.01</td>
<td>Ischaemic stroke</td>
<td>25/725 (PPV), 150/5446 (unvaccinated)</td>
<td>aHR=0.85</td>
<td>0.70–1.03</td>
<td>AMI (all ages)</td>
<td>136/8981 (PPV), 223/18223 (unvaccinated)</td>
<td>aHR=0.42</td>
<td>0.27–0.66</td>
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<tr>
<td>Tseng et al (2010)</td>
<td>Cohort</td>
<td>2/2</td>
<td>136/8981 (PPV), 223/18223 (unvaccinated)</td>
<td>aHR=0.46</td>
<td>0.28–0.73</td>
<td>Composite ACS†</td>
<td>25/725 (PPV), 150/5446 (unvaccinated)</td>
<td>aHR=0.97</td>
<td>0.77–1.23</td>
<td>AMI (age ≥65)</td>
<td>133/8981 (PPV), 210/18223 (unvaccinated)</td>
<td>aHR=0.97</td>
<td>0.93–1.04</td>
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<td>Eurich et al (2012)</td>
<td>Cohort</td>
<td>2/2</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aHR=1.04</td>
<td>0.83–1.31</td>
<td>Ischaemic stroke</td>
<td>133/8981 (PPV), 210/18223 (unvaccinated)</td>
<td>aHR=0.97</td>
<td>0.91–1.03</td>
<td>PPV (all ages)</td>
<td>5531/10671 (cases), 41335/20522 (controls)</td>
<td>aOR=0.97</td>
<td>0.91–1.05</td>
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<tr>
<td>Vila-Corcoles et al (2014)</td>
<td>Cohort</td>
<td>3/3</td>
<td>71/199 (cases), 465/3996 (controls)</td>
<td>aHR=0.89</td>
<td>0.60–1.33</td>
<td>PPV only§</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aOR=0.83</td>
<td>0.40–0.70</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=1.00</td>
<td>0.94–1.05</td>
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<tr>
<td>Ochoa-Gondar et al (2014)</td>
<td>Cohort–control</td>
<td>2/3</td>
<td>5531/10671 (cases), 20134/41335 (controls)</td>
<td>aHR=0.97</td>
<td>0.83–1.13</td>
<td>PPV (age ≥65)</td>
<td>71/199 (cases), 20134/41335 (controls)</td>
<td>aOR=0.37</td>
<td>0.28–0.69</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=0.97</td>
<td>0.94–1.05</td>
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<tr>
<td>Meyers et al (2004)</td>
<td>Case–control</td>
<td>1/2</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aOR=0.89</td>
<td>0.83–1.13</td>
<td>PPV (age ≥65)</td>
<td>71/199 (cases), 465/3996 (controls)</td>
<td>aOR=0.83</td>
<td>0.40–0.70</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=1.00</td>
<td>0.94–1.05</td>
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<tr>
<td>Lamontagne et al (2008)</td>
<td>Case–control</td>
<td>2/2</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aHR=1.04</td>
<td>0.83–1.31</td>
<td>Ischaemic stroke</td>
<td>71/199 (cases), 465/3996 (controls)</td>
<td>aOR=0.83</td>
<td>0.40–0.70</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=1.00</td>
<td>0.94–1.05</td>
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<tr>
<td>Siriwardena et al (2010)</td>
<td>Case–control</td>
<td>3/3</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aHR=1.04</td>
<td>0.83–1.31</td>
<td>Ischaemic stroke</td>
<td>71/199 (cases), 465/3996 (controls)</td>
<td>aOR=0.83</td>
<td>0.40–0.70</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=1.00</td>
<td>0.94–1.05</td>
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<tr>
<td>Siriwardena et al (2014)</td>
<td>Case–control</td>
<td>3/3</td>
<td>107/335 (cases), 78/199 (controls)</td>
<td>aHR=1.04</td>
<td>0.83–1.31</td>
<td>Ischaemic stroke</td>
<td>71/199 (cases), 465/3996 (controls)</td>
<td>aOR=0.83</td>
<td>0.40–0.70</td>
<td>PPV (age ≥65)</td>
<td>14835/20522 (cases), 15394/20522 (controls)</td>
<td>aOR=1.00</td>
<td>0.94–1.05</td>
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</table>

*Composite of non-fatal MI and atherosclerotic cardiovascular disease death, including MI, IHD, CHF, hypertensive heart disease, cardiac arrest and AF.
†Including myocardial infarction or unstable angina or death attributed to ACS.
‡The propensity-matched analysis (c-statistic=0.86) permitted 724 of the 725 (99.9%) patients exposed to PPV to be matched to 724 controls. Propensity (to receive PPV) score analysis was based on variables present before pneumonia onset that could be associated with the decision to administer PPV.
§Original study also included influenza vaccination as another intervention.
ACS, acute coronary syndrome; AF, atrial fibrillation; aHR, adjusted HR; AMI, acute myocardial infarction; aOR, adjusted OR; CHF, congestive heart failure; IHD, ischaemic heart disease; MI, myocardial infarction; PPV, pneumococcal polysaccharide vaccine; p-y, person-years.
predictors of aOR or aHR did not identify any source of between-study heterogeneity (see online supplementary appendix 5).

Stroke outcomes
Separate analysis of the three cohort studies and the one case–control study on PPV and stroke risk, and restricting age to 65 years and above in two of the studies for primary meta-analysis, produced a pooled ratio of 0.96 (95% CI 0.87 to 1.05). I² (22.5%) did not indicate significant heterogeneity. A contour-enhanced funnel plot and Egger test p value=0.151 did not indicate any publication bias, although with so few studies such bias would be difficult to detect (figures 2 and 3).

Meta-analysis without age restriction in these four studies produced a similar pooled ratio of 1.00 (95% CI 0.89 to 1.12), with I² (55.3%) suggesting some degree of heterogeneity (see online supplementary appendix 3).

Additional analysis was performed with the pooling of cohort studies. The three cohort studies produced a pooled HR of 0.88 (95% CI 0.77 to 1.01, I²=0.0%) for stroke outcomes (age restriction applied where possible) (see online supplementary appendix 4).

Meta-regression was not carried out due to a lack of sufficient studies.

DISCUSSION
In this meta-analysis of 230 426 patients from eight observational studies, PPV was associated with significantly lower odds of ACS in the population aged 65 years and above. PPV was not associated with a lower risk of stroke from meta-analysis of four observational studies.
studies consisting of 192,210 patients. This is the first published systematic review on this topic, to the best of the authors’ knowledge, and provides further impetus for the need for a large RCT on this important topic.

To date, there have been no known RCTs examining cardiovascular protective effects of PPV. This systematic review did not identify any RCTs of the PPV that reported ischaemic events either as primary end points or as adverse events in sufficient detail to be included. Most of the recorded adverse events after PPV administration were local injection site reactions and systemic reactions such as fever and fatigue. The majority of these studies only had follow-up of hours to days post-PPV administration, which was too short to observe the development of ischaemic events. Several RCTs mentioned cardiovascular complications during follow-up, but failed to specify whether these were in control or vaccinated groups. The three studies considered for data extraction used broad terms such as ‘cardiovascular disease’, ‘cardiac’, ‘central nervous’, and ‘neurologic’ to describe the causes of death in their patients; hence, we could not be certain they were ischaemic in nature. The overall numbers of events were also low, totalling 178 across all three RCTs, 166 of which were from one study. They were therefore excluded from further data extraction and analysis.

Figure 4. Contour-enhanced funnel plots of studies included in the primary analysis of pneumococcal polysaccharide vaccine (PPV) and acute coronary syndrome events (upper), PPV and stroke (lower).
This review supports the postulated atherosclerotic protective effect of PPV in preventing ACS events, in the elderly population. We found that administration of PPV is associated with an approximately 17% relative reduction in the odds of ACS in people aged 65 years and above. Although the point estimate remained similar, this benefit lost statistical significance when a younger population was included, most likely due to the lower event rate and hence decreased power. An association between PPV and stroke risk was not observed regardless of age restriction; this may be due to the lower incidence of stroke compared with ACS and with the lower number of studies. In addition, stroke risk may be contaminated by haemorrhagic stroke instead of ischaemic stroke, or stroke mimics in some of the older studies without MRI confirmation. This would lead to a greater misclassification of stroke compared with ACS, which would reduce power.

Past research has consistently shown that vaccination with Streptococcus pneumonia leads to a reduction of atherosclerosis in mice.\(^4\)\(^5\) It appears that phosphorylcholine lipid antigens expressed on the cell wall polysaccharide of S. pneumonia induce the production of antibodies that cross-react with oxLDL, a component of atherosclerotic plaques. There are three possible mechanisms by which these antibodies may have a cardioprotective effect\(^28\):

1. The antibodies bind oxLDL and may prevent their uptake by macrophages, thereby blocking the formation of foam cells in plaques.
2. The antibodies may bind to oxLDL on apoptotic cells in the plaque and help clear them.
3. The antibodies may neutralise the proinflammatory cascade in plaques induced by oxLDL.

Similar mechanisms may also occur in humans, leading to the possibility that pneumococcal vaccination protects against atherosclerosis, which would be consistent with our findings.

A large proportion of the literature search results classified as ‘intervention irrelevant’ were studies of the pneumococcal protein conjugate vaccine (PCV), tested in children or immunocompromised adults. However, the PCV has altered structure and antigenicity compared with the PPV, and hence is not thought to trigger the formation of the protective antibodies against oxLDL.

A recent meta-analysis of six RCTs involving 6735 patients, with a mean follow-up time of 7.9 months, demonstrated that influenza vaccination was associated with a significantly lower risk of major adverse cardiovascular events (risk ratio=0.64, 95% CI 0.48 to 0.86).\(^{29}\) It has been suggested that the reduced short-term risk of cardiovascular events offered by this vaccination is due to a reduction in infection, which can be a trigger in the inflammatory cascade that leads to the progression of atherosclerosis.\(^7\) The protective effect of influenza vaccine seems to wane by 9–12 months. In contrast, most of the studies in this review demonstrated a protective association of PPV over several years, suggesting a different mechanism that takes longer to develop, consistent with the proposed anti-oxLDL pathway.

The absence of RCT data in the review means the meta-analysis was solely based on observational data and prone to many biases, confounders and design inconsistencies. We have used the most adjusted summary statistics from each study in the meta-analysis in an attempt to minimise their impact, but residual confounding may nevertheless still be present. Risk of a ‘healthy user effect’ in observational studies, that is, that those who obtain the vaccine are healthier than those who do not, could bias results away from the null. However, demographics of the immunised group across virtually all studies indicated more comorbidity than that of the non-immunised group, which would bias towards more cardiovascular events rather than less in the immunised group, that is, in this case, residual confounding would most likely bias towards the null.

Major limitations of this meta-analysis included significant heterogeneity between studies and varying quality of individual observational studies. The follow-up time varied from 90 days to several years among the studies. Baseline data varied widely not only in magnitude but also in quality for average age, gender distribution, history of ischaemic events and risk factors. Meta-regression was restricted by these poorly defined baseline data, some of which were missing in some studies, limiting its usefulness in the exploration of between-study heterogeneity. ORs from retrospective case–control studies were combined with HRs from prospective cohort studies to produce an estimate of true relative risk. Types of ischaemic events recorded ranged from broad spectrum cardiac events to specifically AMIs only. Tseng et al’s definition of stroke cases included “acute, but ill-defined cerebrovascular diseases (ICD-9 code 436.xx)” and “deaths caused by stroke, not specified as haemorrhage or infarction (ICD-10 code I64)”, and therefore may have miscategorised some non-ischaemic strokes as outcome. This ‘noise’ in classification of outcomes would be expected to reduce power but not cause bias, as long as it is not differential between vaccinated and unvaccinated groups.

It is also noted that the inclusion of young (less than 65 years old) participants removed any protective effect; we believe this is most likely due to the low event rate in this group and hence the ‘dilution’ of the pooled OR seen with older patients. Only Tseng et al, Eurich et al and Siriwardena et al reported outcomes for the subgroups aged 65 years and above, probably because a large proportion of their study participants were younger, healthier and would have been less likely to benefit from PPV. Other studies with an average age less than 65 (Jackson et al and Lamontagne et al) did not perform separate analyses for their older, more disease susceptible groups. This rendered their results less applicable to the clinical population, where the pneumococcal vaccine is recommended for the elderly and those more prone to pneumococcal infections.\(^14\)
From the trends observed in the age restricted analyses, the pooled estimate would probably favour PPV had all studies reported outcomes consistently across age groups.

We suggest that the results of this review on the cardiovascular protective effect of PPV be treated with cautious optimism. Despite many limitations in methodology due to the different qualities of individual studies, the pooled effect favours PPV intervention for the elderly, especially since there is a strong possibility of confounding that would bias against the vaccine because vaccinated groups consistently showed greater comorbidity than non-vaccinated groups. Given the prevalence of heart attack and stroke, even a small protective effect of PPV would offer significant health benefits. An RCT investigating the effects of PPV on ischaemic events as the primary outcome is needed to prove causality. Indeed, such an RCT has been funded and is in the planning stages; we estimate that recruitment will require 6000 participants aged 55–60 years with at least two risk factors for CVD, randomised 1:1 with active or placebo vaccine and followed for at least 5 years to detect this protective effect with 80% power at a significance level of p=0.05.

Contributors SR, DN, SCL and JA were involved in the study design. SR, EW and PM were involved in the study selection and data extraction. SR was responsible for the data analysis and writing of drafts. AH edited and rewrote subsequent versions of the manuscript. All authors proofread and contributed to the final version of the manuscript for submission. SR, DN and JA contributed to the revision of the manuscript after feedback from reviewers.

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REFERENCES


NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Jackson et al. 2002

Selection 3/4

1) Representativeness of the exposed cohort
   a) truly representative of the average _______________ (describe) in the community ✨
   b) somewhat representative of the average ______________ in the community ✨
   ✓ c) selected group of users eg nurses, volunteers – Those with first MI
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   ✓ a) drawn from the same community as the exposed cohort ✨
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   ✓ a) secure record (eg surgical records) ✨
   b) structured interview ✨
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   ✓ a) yes ✨
   b) no

Comparability 2/2

1) Comparability of cohorts on the basis of the design or analysis
   ✓ a) study controls for __ previous MI___ (select the most important factor) ✨
   ✓ b) study controls for any additional factor ✨ (This criteria could be modified to indicate specific control for a second important factor.) adjusts for smoking

Outcome 3/3

1) Assessment of outcome
   ✓ a) independent blind assessment ✨
   ✓ b) record linkage ✨
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   ✓ a) yes (select an adequate follow up period for outcome of interest) ✨
   b) no

3) Adequacy of follow up of cohorts
   ✓ a) complete follow up - all subjects accounted for ✨
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✨
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Hung et al. 2010

Selection 3/4

1) Representativeness of the exposed cohort
   a) truly representative of the average _______________ (describe) in the community ✨
   ✓ b) somewhat representative of the average vaccinated elderly in the community ✨
   Most
patients belonged to the lower socioeconomic strata of HK and had similar levels of education

c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   ✔ a) drawn from the same community as the exposed cohort ❗
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   ✔ a) secure record (eg surgical records) ❗
   b) structured interview ❗
   c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ❗
   b) no

Comparability 0/2 (did not adjust for previous ischaemia or smoking)

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for __ischemia___ (select the most important factor) ❗
   b) study controls for any additional factor ❗ (This criteria could be modified to indicate specific control for a second important factor.) smoking

Outcome 2/3

1) Assessment of outcome
   ✔ a) independent blind assessment ❗
   b) record linkage ❗
   c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ❗
   b) no

3) Adequacy of follow up of cohorts
   ✔ a) complete follow up - all subjects accounted for ❗
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ❗
   c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Tseng et al. 2010

Selection 3/4

1) Representativeness of the exposed cohort
   ✔ a) truly representative of the average __exposed men 45-69___ (describe) in the community ❗
   b) somewhat representative of the average ______________ in the community ❗
   c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   ✔ a) drawn from the same community as the exposed cohort ❗
   b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   ✔ a) secure record (eg surgical records) ❗
   b) structured interview ❗
   c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✗
   ✗b) no

Comparability 2/2

1) Comparability of cohorts on the basis of the design or analysis
   ✓a) study controls for ischemia in propensity adjusted (select the most important factor) ✗
   ✓b) study controls for any additional factor ✗ (This criteria could be modified to indicate specific
      control for a second important factor.) smoking in propensity score adjusted

Outcome 2/3

1) Assessment of outcome
   ✓a) independent blind assessment ✗
   b) record linkage ✗
   c) self report
d) no description

2) Was follow-up long enough for outcomes to occur
   ✓a) yes (select an adequate follow up period for outcome of interest) ✗
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✗
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an
      adequate %) follow up, or description provided of those lost) ✗
   ✓c) follow up rate < _84_% (select an adequate %) and no description of those lost
d) no statement

Eurich et al. 2012

Selection 2/4

1) Representativeness of the exposed cohort
   a) truly representative of the average __________ (describe) in the community ✗
   b) somewhat representative of the average ________ in the community ✗
   ✓c) selected group of users eg nurses, volunteers – CAP patients who present to hospital
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   ✓a) drawn from the same community as the exposed cohort ✗
   b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   ✓a) secure record (eg surgical records) ✗
   ✓b) structured interview ✗
   c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✗
   ✗b) no

Comparability 2/2

1) Comparability of cohorts on the basis of the design or analysis
   ✓a) study controls for __IHD___ (select the most important factor) ✗
   ✓b) study controls for any additional factor ✗ (This criteria could be modified to indicate specific
      control for a second important factor.) smoking

Outcome 3/3
1) **Assessment of outcome**
   a) independent blind assessment ✫
   b) record linkage ✫
   c) self report
   d) no description

2) **Was follow-up long enough for outcomes to occur**
   a) yes (select an adequate follow up period for outcome of interest) ✫
   b) no

3) **Adequacy of follow up of cohorts**
   a) complete follow up - all subjects accounted for ✫
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost ✫
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

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**Vila-Corcoles et al. 2014 & Ochoa-Gondar et al. 2014**

**Selection 3/4**

1) **Representativeness of the exposed cohort**
   a) truly representative of the average exposed elderly (describe) in the community ✫
   b) somewhat representative of the average in the community ✫
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) **Selection of the non exposed cohort**
   a) drawn from the same community as the exposed cohort ✫
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) **Ascertainment of exposure**
   a) secure record (eg surgical records) ✫
   b) structured interview ✫
   c) written self report
   d) no description

4) **Demonstration that outcome of interest was not present at start of study**
   a) yes ✫
   b) no

**Comparability 2/2**

1) **Comparability of cohorts on the basis of the design or analysis**
   a) study controls for ischemia (select the most important factor) ✫
   b) study controls for any additional factor ✫ (This criteria could be modified to indicate specific control for a second important factor.) smoking

**Outcome 3/3**

1) **Assessment of outcome**
   a) independent blind assessment ✫
   b) record linkage ✫
   c) self report
   d) no description

2) **Was follow-up long enough for outcomes to occur**
   a) yes (select an adequate follow up period for outcome of interest) ✫
   b) no

3) **Adequacy of follow up of cohorts**
   a) complete follow up - all subjects accounted for ✫
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an
adequate %) follow up, or description provided of those lost) ⭐
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Meyers et al. 2004

Selection 3/4

1) Is the case definition adequate?
   ✓ a) yes, with independent validation ⭐
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   ✓ a) consecutive or obviously representative series of cases ⭐
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ⭐
   ✓ b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ⭐
   ✓ b) no description of source

Comparability 1/2

1) Comparability of cases and controls on the basis of the design or analysis
   ✓ a) study controls for smoking only (Select the most important factor.) ⭐
   b) study controls for any additional factor ⭐ (This criteria could be modified to indicate specific control for a second important factor.) Unsure if ischaemic history captured or adjusted for

Exposure 2/3

1) Ascertainment of exposure
   a) secure record (eg surgical records) ⭐
   b) structured interview where blind to case/control status ⭐
   ✓ c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   ✓ a) yes ⭐
   b) no

3) Non-Response rate
   ✓ a) same rate for both groups ⭐
   b) non respondents described
   c) rate different and no designation

Lamontagne et al. 2008

Selection 2/4
1) Is the case definition adequate?
   a) yes, with independent validation
   √b) yes, eg record linkage or based on self reports – ICD9 code in medical record
   c) no description

2) Representativeness of the cases
   √a) consecutive or obviously representative series of cases
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls
   √b) hospital controls
   c) no description

4) Definition of Controls
   √a) no history of disease (endpoint)
   b) no description of source

**Comparability 1/2**

1) Comparability of cases and controls on the basis of the design or analysis
   √a) study controls for _nil ischemic history_ (Select the most important factor.)
   b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.) smoking not captured

**Exposure 3/3**

1) Ascertainment of exposure
   √a) secure record (eg surgical records)
   b) structured interview where blind to case/control status
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes
   √b) no

3) Non-Response rate
   √a) same rate for both groups
   b) non respondents described
   c) rate different and no designation

**Selection 2/4**

1) Is the case definition adequate?
   a) yes, with independent validation
   √b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   √a) consecutive or obviously representative series of cases
   b) potential for selection biases or not stated

3) Selection of Controls
   √a) community controls
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint)
Comparability 2/2
1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for ___ischaemic history____ (Select the most important factor.) ★
   b) study controls for any additional factor ★ (This criteria could be modified to indicate specific
      control for a second important factor.) smoking

Exposure 3/3
1) Ascertainment of exposure
   a) secure record (eg surgical records) ★
      b) structured interview where blind to case/control status ★
      c) interview not blinded to case/control status
      d) written self report or medical record only
      e) no description

   2) Same method of ascertainment for cases and controls
      a) yes ★
      b) no

   3) Non-Response rate
      a) same rate for both groups ★
      b) non respondents described
      c) rate different and no designation

Siriwardena et al. 2014

Selection 3/4
1) Is the case definition adequate?
   a) yes, with independent validation ★
      b) yes, eg record linkage or based on self reports
      c) no description

   2) Representativeness of the cases
      a) consecutive or obviously representative series of cases ★
      b) potential for selection biases or not stated

   3) Selection of Controls
      a) community controls ★
      b) hospital controls
      c) no description

   4) Definition of Controls
      a) no history of disease (endpoint) ★
      b) no description of source

Comparability 2/2
1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for ___Stroke or TIA_______ (Select the most important factor.) ★
   b) study controls for any additional factor ★ (This criteria could be modified to indicate specific
      control for a second important factor.) smoking

Exposure 3/3
1) Ascertainment of exposure
   a) secure record (eg surgical records) ★
      b) structured interview where blind to case/control status ★
      c) interview not blinded to case/control status
d) written self report or medical record only
  e) no description

2) Same method of ascertainment for cases and controls
   ✓ a) yes ✧
   b) no

3) Non-Response rate
   ✓ a) same rate for both groups ✧
   b) non respondents described
   c) rate different and no designation
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$).tw.
4. exp streptococcus pneumoniae/
5. (streptococc$ 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 vasc$ or cerebral vasc$ 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$)).tw.
57. ((venous or arteriovenous or brain vasc$) 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) adj5 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 parietic 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.
PPV and ischaemic events observational studies search strategy on Medline

1. exp pneumococcal vaccines/
2. (pneumococc$ adj3 vaccin$).tw.
4. exp streptococcus pneumoniae/
5. (streptococc$ 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 gangl$ or subarachnoid or putaminal or putamen or posterior or 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 insult or attack$))).tw.
48. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).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) adj5 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 anomii$ 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/
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 eca* or apoplex* or "ischemi* attack*" or "ischaemi* attack*" or TIA or TIAs or "neurologic* deficit*" or SAH or AVM 30771
(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

(lacunar or cortical) near/5 infarct* 140

(brain* or cerebr* or cerebell* 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

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

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

(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

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

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

CVDST or CVT 40

(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

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

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

carotid* 3613

patent foramen ovale 93

PFO 68

asymptomatic cervical bruit 12

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

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

(#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

MeSH descriptor: [Cardiovascular Diseases] explode all trees 67103

heart (Word variations have been searched) 62011

coronary (Word variations have been searched) 26651

(cardiac (Word variations have been searched) 28319

myocardial 21229

cardiovascular 31785

angina 8388

{or #55–#61} 122772

MeSH descriptor: [Pneumococcal Vaccines] explode all trees 460

pneumococc* near vaccin* 800

pneumococc* near immuni* 207

MeSH descriptor: [Streptococcus pneumoniae] explode all trees 442

streptococc* near pneumon* 1111

MeSH descriptor: [Vaccination] explode all trees 1802

vaccin* or immuni* 13841

(#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

<table>
<thead>
<tr>
<th>Study</th>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung 2010</td>
<td></td>
<td>0.79 (0.54, 1.14)</td>
<td>8.06</td>
</tr>
<tr>
<td>Tseng 2010</td>
<td></td>
<td>1.14 (1.00, 1.31)</td>
<td>29.84</td>
</tr>
<tr>
<td>Vila-Corcoles 2014</td>
<td></td>
<td>0.97 (0.77, 1.23)</td>
<td>16.44</td>
</tr>
<tr>
<td>Siriwardena 2014</td>
<td></td>
<td>0.96 (0.92, 1.02)</td>
<td>45.67</td>
</tr>
<tr>
<td>Overall (I-squared = 55.3%, p = 0.082)</td>
<td></td>
<td>1.00 (0.89, 1.12)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson 2002</td>
<td></td>
<td>1.08 (0.73, 1.59)</td>
<td>9.55</td>
</tr>
<tr>
<td>Hung 2010</td>
<td></td>
<td>0.79 (0.46, 1.28)</td>
<td>7.29</td>
</tr>
<tr>
<td>Tseng 2010</td>
<td></td>
<td>1.09 (0.98, 1.21)</td>
<td>18.61</td>
</tr>
<tr>
<td>Eriuch 2012</td>
<td></td>
<td>0.42 (0.27, 0.66)</td>
<td>8.18</td>
</tr>
<tr>
<td>Ochoa-Gondar 2014</td>
<td></td>
<td>1.04 (0.83, 1.31)</td>
<td>14.57</td>
</tr>
<tr>
<td>Meyers 2004</td>
<td></td>
<td>0.89 (0.60, 1.33)</td>
<td>9.32</td>
</tr>
<tr>
<td>Lamontagne 2008</td>
<td></td>
<td>0.53 (0.40, 0.70)</td>
<td>12.80</td>
</tr>
<tr>
<td>Siriwardena 2010</td>
<td></td>
<td>0.98 (0.93, 1.04)</td>
<td>19.68</td>
</tr>
<tr>
<td>Overall (I-squared = 81.4%, p = 0.000)</td>
<td></td>
<td>0.86 (0.73, 1.01)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
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

**Forest plots of analysis of PPV and ACS events for cohort studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung 2010</td>
<td>0.79 (0.54, 1.14)</td>
<td>13.72</td>
</tr>
<tr>
<td>Tseng 2010 &gt;=65</td>
<td>0.85 (0.70, 1.03)</td>
<td>51.36</td>
</tr>
<tr>
<td>Vila-Corcoles 2014</td>
<td>0.97 (0.77, 1.23)</td>
<td>34.92</td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.77, 1.01)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

**Forest plots of analysis of PPV and ACS events for case-control studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyers 2004</td>
<td>0.89 (0.60, 1.33)</td>
<td>28.36</td>
</tr>
<tr>
<td>Lamontagne 2008</td>
<td>0.53 (0.40, 0.70)</td>
<td>32.92</td>
</tr>
<tr>
<td>Sinwardena 2010 &gt;=65</td>
<td>0.97 (0.91, 1.03)</td>
<td>38.71</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.52, 1.16)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
<table>
<thead>
<tr>
<th>Study</th>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson 2002</td>
<td></td>
<td>1.08 (0.73, 1.59)</td>
<td>16.84</td>
</tr>
<tr>
<td>Hung 2010</td>
<td></td>
<td>0.79 (0.48, 1.28)</td>
<td>13.03</td>
</tr>
<tr>
<td>Tseng 2010 &gt;=65</td>
<td></td>
<td>0.89 (0.80, 1.01)</td>
<td>30.75</td>
</tr>
<tr>
<td>Eurich 2012 &gt;=65</td>
<td></td>
<td>0.44 (0.28, 0.69)</td>
<td>14.39</td>
</tr>
<tr>
<td>Ochoa-Gondar 2014</td>
<td></td>
<td>1.04 (0.83, 1.31)</td>
<td>24.99</td>
</tr>
<tr>
<td>Overall (I-squared = 67.6%, p = 0.015)</td>
<td></td>
<td>0.85 (0.68, 1.07)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis.
### STATA output for meta-regression

```
. metareg ratio sex, wsse(selogr) eform graph
```

**Meta-regression**
- Number of obs = 8
- tau2 = 0.04707
- I-squared_res = 68.96%
- Adj R-squared = -33.36%

**Proportion of between-study variance explained**

| ratio | exp(b)    | Std. Err. | t     | P>|t| | [95% Conf. Interval] |
|-------|-----------|-----------|-------|-----|---------------------|
| sex   | 1.00197   | 0.0044628 | 0.44  | 0.674 | .9911093 - 1.01295  |

**Graph**

The graph shows the relationship between the natural logarithm of the ratio (aHR/aOR) and the percentage of male participants (%male). The data points are plotted with a trend line indicating a positive correlation.
```
. metareg ratio age, wsse(selogr) eform graph

. metareg ratio age, wsse(selogr) eform graph

Meta-regression
Number of obs = 8
REML estimate of between-study variance = .04298
% residual variation due to heterogeneity = 71.78%
Proportion of between-study variance explained = -21.76%
With Knapp-Hartung modification

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

![Graph showing the relationship between average age and adjusted hazard ratio or odds ratio (aHR/aOR) with data points and a line of best fit.](Image)
Meta-regression

REML estimate of between-study variance

% residual variation due to heterogeneity

Proportion of between-study variance explained

With Knapp-Hartung modification

| ratio  | exp(b)   | Std. Err. | t    | P>|t|  | [95% Conf. Interval] |
|--------|----------|-----------|------|------|----------------------|
| smoke  | 1.003098 | 0.005554  | 0.56 | 0.606 | 0.987795 - 1.018637  |
Meta-regression

REML estimate of between-study variance: $\tau^2 = 0.05919$

% residual variation due to heterogeneity: $I^2_{\text{res}} = 79.45\%$

Proportion of between-study variance explained: $\text{Adj R-squared} = -13.41\%$

With Knapp-Hartung modification

| ratio | exp(b)    | Std. Err. | t    | P>|t|   | [95% Conf. Interval] |
|-------|-----------|-----------|------|-------|----------------------|
| dm    | 1.014908  | 0.0200318 | 0.75 | 0.495 | 0.9607874 - 1.072077 |

Percentage Diabetes Mellitus vs. $aHR/aOR$