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Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies

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Abstract

Aims: *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia (CAP) and CAP-related mortality in adults. Pneumococcal vaccination (PV) could protect subjects from cardiovascular events by reducing pneumonia severity or even preventing it. We sought to determine the ability of PV to protect from the risk of cardiovascular events.

Methods and results: A comprehensive search of electronic databases was conducted up to March 2014. Cohort studies that reported relative risk (RR) estimates with 95% confidence intervals (CI) were included. Eleven studies were included (332,267 participants, mean follow-up 20.1 months). The pooled RRs for cardiovascular events and cardiovascular mortality were 0.86 (95% CI: 0.76–0.97) and 0.92 (95% CI: 0.86–0.98; fixed-effects), respectively, for subjects with PV versus without PV. Protective ability was more prominent in high cardiovascular risk populations and with older age. The protective role of PV was attenuated after 1 year (RR: 0.72; 95% CI: 0.59–0.88 vs RR: 1.03; 95% CI: 0.93–1.14; $p = 0.002$, for follow-up >1 year vs ≤ 1 year, respectively). It also increased as the presence of cardiovascular and pulmonary disease increased. Regarding myocardial infarction (MI) and cerebrovascular events, the protective role of PV was statistically significant only in the elderly (RR: 0.90; 95% CI: 0.817–0.999; fixed-effects and RR: 0.86; 95% CI: 0.75–0.99, respectively).

Conclusion: PV is associated with decreased risk of cardiovascular events and mortality. This protective effect increases at older age and in high cardiovascular risk subjects and decreases as the time elapses from PV. PV decreases the risk of MI and cerebrovascular events in the elderly.

Keywords

Pneumococcal vaccination, cardiovascular disease, cardiovascular mortality, myocardial infarction, stroke, meta-analysis

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Introduction

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide.[1] Streptococcus pneumoniae is the most common cause of CAP in adults, accounting for more than 40% of cases.[2,3] In people aged ≥65, CAP infections may result in hospital admission in more than 25–40% of episodes and in 10% the infection may be fatal.[4]

It is estimated that more than half the elderly patients with CAP have a chronic cardiac condition.[5]

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Hospitalization for CAP is associated with an up to eight-fold increase in the risk of acute myocardial infarction (MI) and many 'pneumonia-related deaths' are related to non-infectious complications including acute coronary syndrome (ACS) events.[6,7] Many proposed pathophysiological mechanisms contribute to cardiovascular (CV) complications including endothelial dysfunction, plaque instability, inflammation, sympathetic activation, hypercoagulability, tissue hypoxaemia, depression of ventricular function, arterial stiffness, volume overload and arrhythmias.[8,9]

Pneumococcal vaccine (PV) has been studied for more than a century.[10] Recent developments with the use of conjugate vaccines show great promise. However, the 23-polyvalent polysaccharide PV with its limitations and controversies is the most widely used and has been investigated in adults in the last three decades.[10] Since PV can reduce pneumonia severity or even prevent it, it has been suggested that the vaccine could protect patients from CV events, especially the more fragile ones such as elderly and patients with chronic diseases. A number of non-randomized studies examined the ability of PV to protect from future CV events with conflicting results.[11–35] Despite the extensive meta-analyses[36,37] of adult PV on all-cause mortality and pneumonia-related events, the overall quantitative estimate of the effect of PV on CV outcomes has never been investigated. We conducted the present systematic review and meta-analysis with the primary aim of providing an overview of relevant cohort studies and to calculate robust quantitative estimates of the possible protective role of PV for different CV outcomes. Secondly, we investigated whether publication bias could have affected our results. Thirdly, we evaluated the effect of several factors such as age and history of chronic disease on the possible protective role of PV.

Methods

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[38,39] The outcomes of interest were: (1) total CV events (CV death, MI, coronary artery disease, revascularization, cerebrovascular events, peripheral vascular disease, unstable angina, heart failure (HF) and CV hospitalizations); (2) CV mortality; (3) MI; and (4) cerebrovascular events (stroke, transient ischaemic attacks, intracranial haemorrhage).

Data sources and searches

Studies evaluating relationships of PV in adults with the risk of future clinical events were drawn from a systematic review of the English literature in the Medline, Cochrane and Embase databases up to March 2014. The search terms are cited in the online Supplementary Material. Data sources were also identified through manually searching the references of articles, reviews and meta-analyses. We subsequently searched online resources such as major CV and infectious disease conventions abstracts from 2000 to 2013 and clinicaltrials.gov to ensure identification of all published and unpublished studies.

Study selection

Studies were deemed eligible if they: (1) were full-length publications in peer-reviewed journals or abstracts in major conventions; (2) included adult patients that received the 23-polyvalent pneumococcal vaccine and were compared to unvaccinated patients; (3) reported a combined CV outcome or CV mortality or MI (for details see online Supplementary Material and Table S1) or cerebrovascular event; (4) the follow-up period was at least 1 month and did not include exclusively in-hospital CV events; (5) were either retrospective or prospective cohort studies. For details of exclusion criteria see online Supplementary Material.

Data extraction and quality assessment

The literature search, selection of studies, quality assessment (for details see online Supplementary Material) and extraction of data were done independently by two reviewers (CV, DT), as previously reported.[40–42] We used the Newcastle-Ottawa scale to assess the risk of bias in observational studies.[43] We evaluated the quality of evidence using criteria selected from the grading of recommendations assessment, development and evaluation (GRADE) framework.[44]

Data synthesis and analysis

The risk estimates of each study were reported as a hazard ratio, relative risk (RR), odds ratio or dichotomous frequency data. We treated hazard ratios as RRs, as we have previously reported.[40–42] When available, we used the adjusted risk estimates from propensity score or multivariate models. We performed meta-analyses of studies investigating PV to obtain the pooled RRs with 95% confidence intervals (CI) separately for: (1) total CV events; (2) CV mortality; (3) MI; and (4) cerebrovascular events. The proportion of inconsistency across studies not explained by chance was quantified with the I^2 statistic. Heterogeneity between subgroups was calculated with Cochran's Q test.[45] When significant heterogeneity (p-value ≤ 0.10) existed among studies, the random effects model was used to obtain the pooled

RRs. In cases of non-significant heterogeneity both fixed and random-effects analysis were used and presented. We also calculated adjusted RRs of PV vs no PV groups in each study. The effectiveness of PV in reducing CV events is thought to be influenced by proximity of vaccine receipt because antibody titres induced by PV decrease with time. We performed a sensitivity analysis to evaluate whether the strength of risk estimates differs between studies with follow-up up to 1 year and more than 1 year. Risk estimates between subgroups were compared with a test of interaction.[46] Moreover, to further evaluate the robustness of our study results, we conducted several additional sensitivity analyses (for details see online Supplementary Material). The RRs and CIs of individual studies were illustrated with forest plots. To estimate the contribution of continuous study moderators to the overall heterogeneity, we ran a meta-regression analysis with fixed-effects estimates. The presence of publication bias was investigated graphically by funnel plots of precision, and its implications for our results were assessed by the trim-and-fill method[47] and the classic fail-safe N method. Begg and Egger tests were also performed and $p > 0.05$ was considered to be no significant publication bias. All analyses were performed with Comprehensive Meta Analysis Version 2 (Biostat, Englewood, New Jersey).[48]

Results

Literature search

The results of the literature search are shown in Figure 1. We retrieved 1662 articles from our preliminary search. Of these, 25 articles were identified for full review. For details of exclusion of studies[23–34] after full review see online Supplementary Material.

Study characteristics

Our meta-analysis included 13 original articles assessing relationships of PV with clinical events. In total, the included studies analysed 332,267 subjects (88,054 with PV). Several populations such as patients with MI, renal disease and pneumonia and subjects from the general population are included. Details of the individual studies are shown in Table 1. Of the 11 studies included (332,267 participants, mean follow-up 20.1 months, 13 full-text articles),[11–22] 11 reported results on total CV events (332,267 individuals),[11–22] four reported on CV mortality (152,365 individuals),[14,15,19,22,35] four reported on MI (140,078 individuals)[12,13,17,21] and four reported on cerebrovascular events (156,152 individuals).[12,13,20,21] All studies were published after 2002,[12] and the mean/median follow-up ranged from

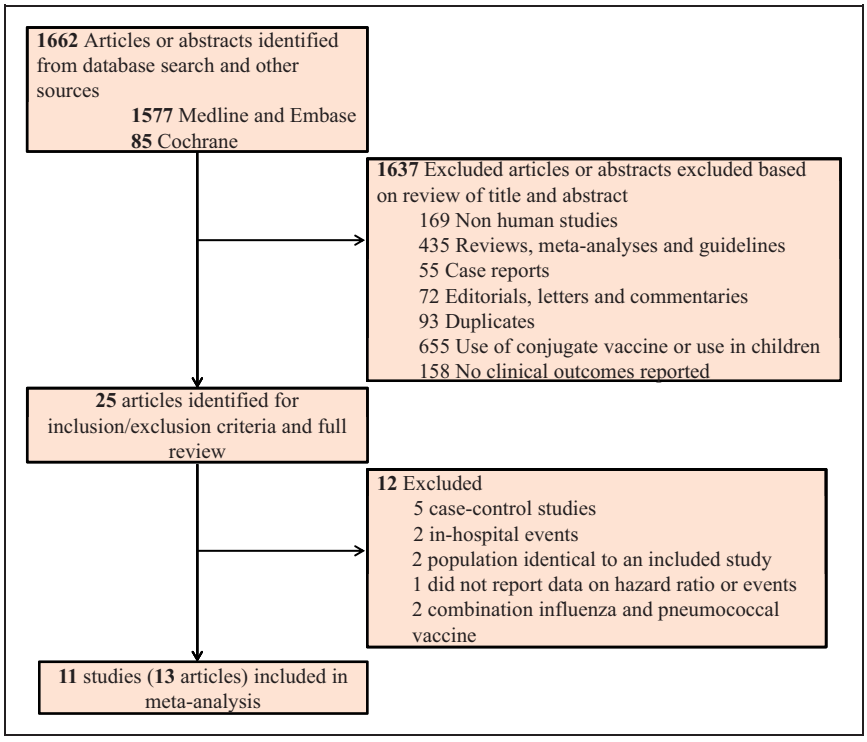

Figure 1. Flow chart of selection of studies for inclusion in meta-analysis.

Table 1. Overview of studies on the association between 23-valent pneumococcal vaccine and clinical end points.

First author, country, year (ref[a])	Population (sample size)	Mean age ± SD, median age or age range (years)	Mean/median follow-up duration (months)	Men (%)	Vaccinated population (%)	Events	Patients vaccinated for influenza (%)	Patients with CVD, n (%)	Adjusted for (variables)/propensity score matching (yes/no)	Study quality (up to 9 points)
Jackson et al., United States 2002[11]	1378 patients with MI	64	27.6	924 (67)	661 (48)	89 non-fatal MI, 23 fatal MI, 15 CVD deaths	1016 (74)	1378 (100)	Age, gender, influenza vaccination, shock or severe HF during the incident MI hospitalization, smoking status, DM, hypertension, chronic HF, COPD/asthma, use of CCBs and statins (no)	9
Tseng et al., United States 2010[12b]	84,170 middle-aged men	58.4 ± 7.1	56.4	84,170 (100)	36,309 (43)	2705 MI and 1134 strokes	NR	6020 (7)	Age, region, race/ethnicity, smoking, BMI, physical inactivity, income, education, history of MI, history of stroke, history of PAD, high cholesterol, high BP, DM, other HD, nutrition, alcohol consumption, outpatient visits, sedentary status, influenza vaccinations (yes)	9
Hung et al., China 2010[13c]	27,268 patients aged ≥65 years	75	15	12,779 (47)	1875 (7)	Ischaemic HD, ischaemic stroke, acute MI, HF, CCU admissions	0 (0)	2118 (8)	Sex and COPD (no)	7
Gilbertson et al., United States 2011[14]	118,533 haemodialysis patients	Over 18 years	6 (influenza season)	62,779 (53)	25,091 (21)	Cardiac death	88,775 (75)	60,441 (51)	Patient characteristics, comorbidity and influenza vaccinations (no)	8
Chan et al., China 2012[15]	457 nursing home older adults	86	12	171 (37)	246 (54)	99 CV deaths	457 (100)	182 (39)	Age, gender, smoking status, number of medications and feeding status, CCI, BI (20), nursing home of	9

(continued)

Table 1. Continued.

First author, country, year (ref[a])	Population (sample size)	Mean age ± SD, median age or age range (years)	Mean/median follow-up duration (months)	Men (%)	Vaccinated population (%)	Events	Patients vaccinated for influenza (%)	Patients with CVD, n (%)	Adjusted for (variables)/propensity score matching (yes/no)	Study quality (up to 9 points)
									origin, hospitalization in preceding year and vaccination status for pneumococcus and seasonal influenza (no)	
Chang et al., Taiwan 2012[16]	16,284 elderly aged ≥75 years	80	4 (influenza season)	7466 (46)	8142 (50)	224 hospitalizations for HF	16,284 (100)	7279 (45)	Age, gender, baseline comorbid conditions, and health care use during the preceding 12 months prior to October 2008 (yes)	8
Zahid et al., United States 2012[17]	1436 patients hospitalized with suspected ACS/non-ST elevation MI	67	6	1403 (94)	937 (65)	70 MI	571 (40)	1436 (100)	Influenza vaccination only, pneumococcal and influenza vaccinations, age (per year), systolic BP < 90 mmHg, pulmonary oedema on admission, haemoglobin <11.5 gm/dl, left ventricular ejection fraction <35%, current or past smoker, troponin elevated, DM, statin use and missing data (yes)	8
Johnstone et al., worldwide 2012[18d]	31,546 high CV risk patients in four separate time cohorts (2003–2004, 2004–2005, 2005–2006, 2006–2007)	66	6 (in 4 influenza seasons)	15,853 (71) 18,790 (70) 18,413 (70) 18,278 (70)	3303 (15) 3855 (14) 3756 (14) 3726 (14)	1382 with a composite of major adverse vascular events (CV death, non-fatal MI and non-fatal stroke)	8566 (38) 11,624 (43) 18,876 (28) 12,441 (47)	16,685 (75) 20,059 (75) 19,685 (75) 19,584 (75)	CAD, DM, hypertension, stroke, admission to a nursing home; use of aspirin, beta-blockers, lipid-lowering drugs, ACE inhibitors, or	8

(continued)

Table 1. Continued.

First author, country, year (ref[a])	Population (sample size)	Mean age ± SD, median age or age range (years)	Mean/median follow-up duration (months)	Men (%)	Vaccinated population (%)	Events	Patients vaccinated for influenza (%)	Patients with CVD, n (%)	Adjusted for (variables)/propensity score matching (yes/no)	Study quality (up to 9 points)
									ARB and propensity score for age, sex, BMI, ethnicity, education, vitamin use, smoking, alcohol use and history of influenza vaccination (yes)	
Eurich et al., Canada 2012[19e]	6481 adults with CAP (310 vaccinated in hospital, 2nd analysis)	59	1.5 and 60 months	3261 (53)	725 (12) and 310 (5)	162 non-fatal ACS and 23 fatal ACS in 90 days	837 (14)	1105 (18)	Pneumonia severity based on the PSI; comorbidities including COPD, DM, CAD, functional status, smoking status and CV and other medications (yes)	7
Chen et al., Taiwan 2012[20]	17,510 elderly	Over 75 years	12 months	NR	361 (2)	924 strokes	0 (0)	NR	Age, gender, OPD amount, DM, chronic lung disease, chronic kidney disease, chronic HD, immunodeficiency, cancer, geographical area and urbanization of residence, socioeconomic status (no)	7
Vila-Corcoles et al. 2013,[21] Ochoa-Gondar et al. 2014,[22]	27,204 individuals 60 years or older	72	36 months	12,137 (45)	8981 (33)	359 MI, 55 deaths from MI, 343 strokes and 45 deaths from stroke	14,368 (53)	1733 (6)	Age, sex, number of outpatient visits to family physician, nursing-home residence,	9

(continued)

Table 1. Continued.

First author, country, year (ref[a])	Population (sample size)	Mean age ± SD, median age or age range (years)	Mean/median follow-up duration (months)	Men (%)	Vaccinated population (%)	Events	Patients vaccinated for influenza (%)	Patients with CVD, n (%)	Adjusted for (variables)/propensity score matching (yes/no)	Study quality (up to 9 points)
Vila-Corcoles et al. 2014,[35] Spain[b,f]									history of hospitalization for pneumonia in previous 5 years, history of CAD, history of cerebrovascular disease, presence of chronic pulmonary disease, chronic HD, hypertension, hypercholesterolaemia, obesity, DM, smoking status, alcoholism, chronic severe liver disease, chronic severe nephropathy, cancer, dementia, immunosuppressive medication and influenza vaccine status at study start (yes)	

[a]When studies reported individuals with atherosclerotic disease in distinct vascular territories (coronary, cerebrovascular, peripheral), the vascular territory with the largest number of subjects was chosen to represent cardiovascular disease percentage.
[b]Estimation of the relative risk for total CV events was the combination of relative risk for myocardial infarction and stroke.
[c]Estimation of the relative risk for total CV events was the combination of relative risk for ischaemic heart disease, acute MI, acute ischaemic stroke and heart failure.
[d]Estimation of the relative risk for total CV events was the combination of risks for the four influenza seasons.
[e]Estimation of the relative risk for total CV events was the combination of relative risk from the primary analysis and the sensitivity analysis.
[f]Studies have the same population but different clinical endpoints; the Vila-Corcoles et al. 2013 study was used for estimation of total CV events, MI and stroke, the Ochoa-Gondar et al. 2014 study was used for estimation of CV mortality (death from MI) and in the estimation of total CV events and MI of high CV risk (patients with CAD) subjects and the Vila-Corcoles et al. 2014 study was used for estimation of CV mortality (death from stroke) and in the estimation of total CV events of high CV risk (stroke patients) subjects. Estimation of the relative risk for CV mortality was the combination of relative risk for death from MI and death from stroke.
CV, cardiovascular; HD, heart disease; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; ACE, angiotensin-converting enzyme; MI, myocardial infarction; CVD, cardiovascular disease; CAD, coronary artery disease; CCU, coronary care unit; HF, heart failure; BMI, body-mass index; BP, blood pressure; CAP, community-acquired pneumonia; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; ACS, acute coronary syndrome; CCI, Charlson Comorbidity Index; BI, Barthel Index; PSI, pneumonia severity index; OPD, outpatient department; NR, not reported.

1.5 to 60 months.[19] The sample sizes ranged from 457[15] to 118,533[14] individuals. Age, influenza vaccination and other risk factors for CV events were controlled for in most of the studies.

Meta-analysis

PV and total CV events

The magnitude of risk in individuals who had PV was significantly lower compared with the risk of individuals without PV. The pooled RR for PV was 0.86 (95% CI: 0.76–0.97; $p=0.016$) for total CV events (Figure 2A).

Since we observed significant heterogeneity ($I^2=76.1\%$, $p<0.001$) between the included studies, we conducted between-study subgroup analyses to investigate its sources. Specifically, as regards the duration of follow-up, the RR for studies[14–20] with follow-up of 1 year or less was lower compared to studies[11–13,21] with follow-up of more than 1 year (RR: 0.72; 95% CI: 0.59–0.88 vs RR: 1.03; 95% CI: 0.93–1.14; $p=0.002$).

To further investigate the protective role of PV in high-risk populations we performed a sensitivity analysis in which we included studies that investigated the role of PV on elderly and high CV risk individuals. The protective role of PV in studies with elderly[12,13,15–21] (RR: 0.80; 95% CI: 0.70–0.92; $p=0.001$) and patients with high CV risk (RR: 0.92; 95% CI: 0.87–0.98; $p=0.010$)[11,12,14,17,18,22,35] was similar to or even better than the overall combined estimated risk.

The results remained similar and statistically significant when each endpoint was entered separately in the overall analysis as well as in the sensitivity analyses (eFigure 1, for details see online Supplementary Material).

PV and CV mortality

The magnitude of risk for CV mortality in individuals with PV was significantly lower compared with the risk of individuals without PV. The pooled RR for PV for CV mortality with fixed effects was 0.92 (95% CI: 0.86–0.98; $p=0.008$) and with random effects was 0.95 (95% CI: 0.77–1.18; $p=0.651$) (Figure 2B).

PV and MI

The magnitude of risk in individuals with PV was similar compared with the risk of individuals without PV. The pooled RR for PV for MI with fixed effects was 1.05 (95% CI: 0.96–1.16) and with random effects was 1.00 (95% CI: 0.84–1.18) (Figure 2C).

To further investigate the possible protective role of PV in high-risk populations we performed a sensitivity analysis in which we included studies that investigated the role of PV on elderly and high CV risk individuals. The protective role of PV in studies of the elderly[12,13,17,21] was statistically significant and different to the overall combined estimated risk with fixed effects (RR: 0.90; 95% CI: 0.817–0.999; $p=0.047$) but this protective effect was attenuated with random effects (RR: 0.90; 95% CI: 0.80–1.03; $p=0.123$). On the other hand, the RR of PV in studies with patients with high CV risk[12,17,22] was lower compared to the overall combined estimated risk but not statistically significant with both fixed (RR: 0.96; 95% CI: 0.82–1.12; $p=0.57$) and random effects (RR: 0.87; 95% CI: 0.64–1.16; $p=0.34$).

PV and cerebrovascular events

The magnitude of risk in individuals with PV was similar compared with the risk of individuals without PV. The pooled RR for PV was 0.93 (95% CI: 0.74–1.17) for cerebrovascular events (Figure 2D).

To further investigate the possible protective role of PV in high-risk populations we performed a sensitivity analysis in which we included studies that investigated the role of PV on the elderly. In contrast to the overall combined estimated risk, the protective role of PV in studies with elderly subjects[12,13,20,21] was statistically significant (RR: 0.86; 95% CI: 0.75–0.99; $p=0.032$).

Risk of bias and quality of evidence assessment

The Newcastle-Ottawa scale scores for risk of bias ranged from 7 to 9 out of a maximum of 9, with a median of 8 across studies (Table 1). Based on an adaptation of the GRADE approach to assess the quality of evidence, our confidence in risk estimates was very low for all endpoints.

Publication bias

The funnel plot was asymmetrical at the bottom for total CV events, suggesting a low likelihood of small studies with small or positive risk estimates in our meta-analysis (Figure S2 in online Supplementary Material). None of the statistical tests for funnel plot asymmetry showed significant publication bias (for details see online Supplementary Material). These findings suggest that the apparent publication bias is insufficient to affect our results or interpretations in a meaningful way for total CV events.

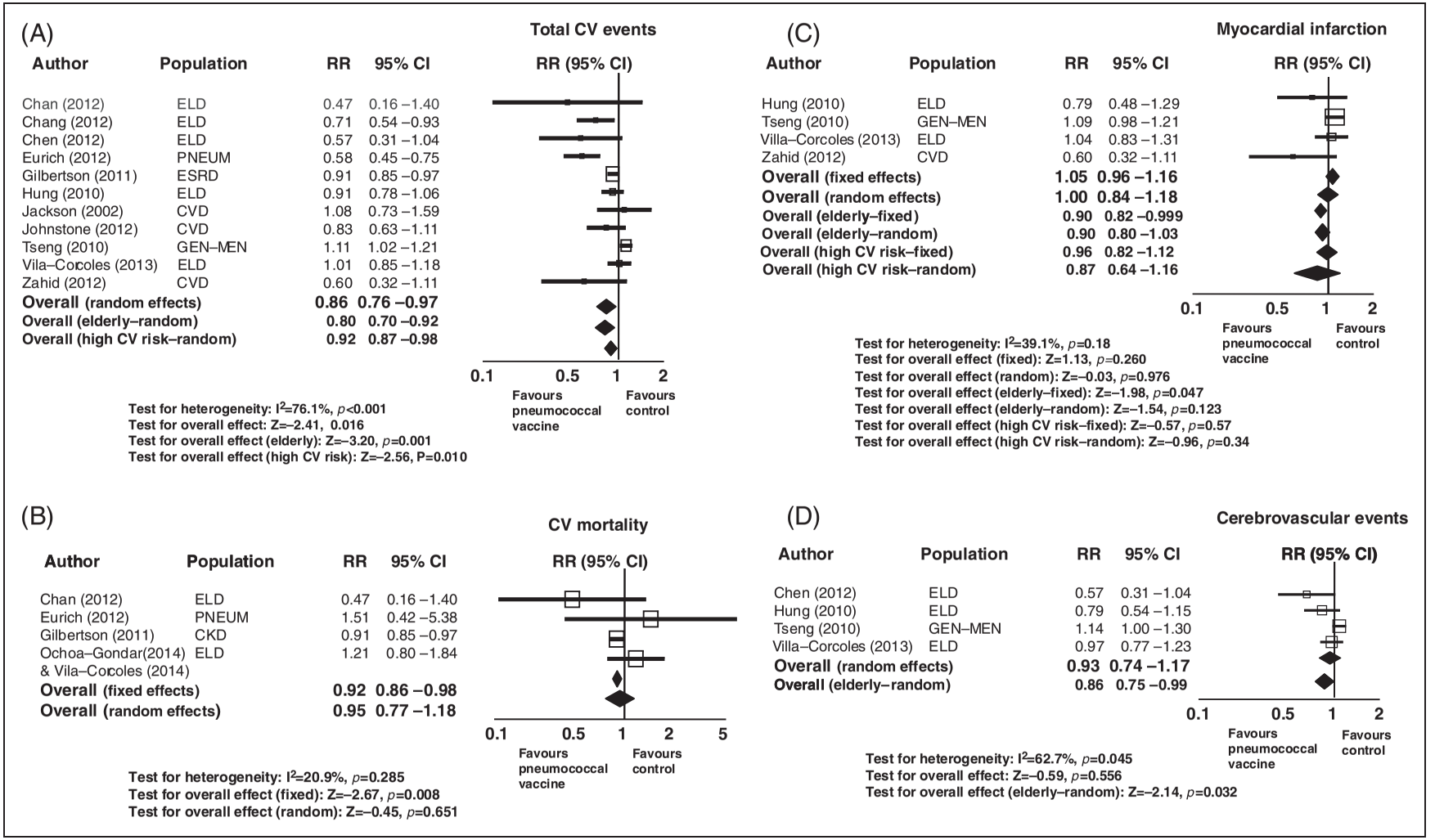

Figure 2. Relative risk (RR) and 95% CI for PV and clinical events. RR and 95% CI for PV and total cardiovascular (CV) events (A), CV mortality (B), myocardial infarction (C), cerebrovascular events (D). Studies are listed alphabetically. Boxes represent the RR and lines represent the 95% CI for individual studies. The diamonds and their widths represent the pooled RRs and the 95% CI, respectively.

CVD, cardiovascular disease; PNEUM, pneumonia; ESRD, end-stage renal disease; GEN-MEN, general population–men; ELD, elderly.

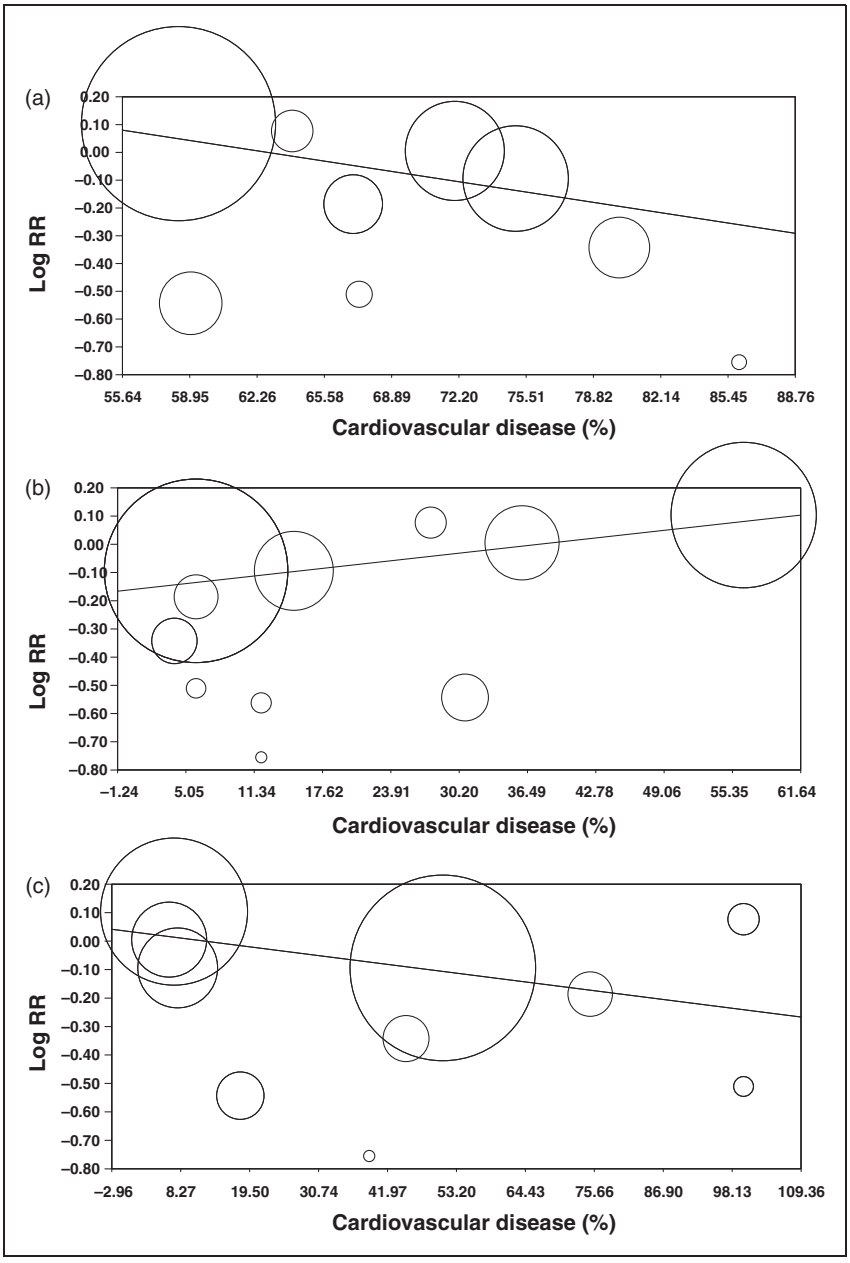

Figure 3. Relative risk (RR) of total CV events in patients with PV as a function of the following: (A) age (data from nine studies[11–13,15–19,21]); (B) follow-up (data from 11 studies[11–21]); (C) cardiovascular disease (CVD) percentage in study population (data from 10 studies[11–19,21]). Each study is represented by a circle that shows the actual coordinates (observed effect size by each one of the above-mentioned variables) for that study. The size of each circle is proportional to the weight of the respective study in the analysis, i.e. the inverse of the within-study variance for each study. The centre line shows the predicted values by fixed-effects meta-regression. The vertical axis is on a log scale.

Meta-regression analysis

Age at enrolment was a strong predictor of the magnitude of the log RR in patients with PV and related to the protective role of PV for total CV events (Figure 3A, $p = 0.005$).[11–13,15–19,21] Duration of follow-up was also a predictor of the magnitude of the log RR in patients with PV (Figure 3B, $p < 0.001$).[11–21] The percentage of patients with CV disease[11–19,21] (Figure 3C), with HF[11–15,17,18,21] and with chronic obstructive pulmonary disease (COPD)[11–16,19,21] in each study showed positive associations with the protective role of PV ($p = 0.004$, $p = 0.005$ and $p < 0.001$, respectively) and the quality of studies showed inverse association with the protective role of PV ($p < 0.001$).[11–21] The percentage of patients

vaccinated with influenza in each study[11,13–21] and the socioeconomic status for each country[11–17,19–21] in the meta-analysis were not predictors of the magnitude of the log RR ($p = 0.34$ and $p = 0.153$, respectively).

Discussion

In this systematic review and meta-analysis, we pooled the data for 332,267 participants investigated for PV from 13 available published articles, which were followed up for a mean of 20.1 months. Our study is the first meta-analysis to investigate the protective role of PV on CV endpoints and to assess factors influencing this ability. Our principal finding is that subjects with PV compared to patients without PV have a significantly lower risk by 14% for total CV events and 8% for CV mortality. Importantly, the protective role of PV for total CV events is more prominent in older patients and in patients with high CV risk. Furthermore, shorter follow-up period is associated with a higher protective value of PV for CV events in comparison to longer follow-up, indicating an attenuation of the beneficial effect of PV with time. The protective ability of PV increases with increased percentage of CV disease and COPD in included studies. Furthermore, concomitant administration of influenza vaccination does not seem to influence the protective role of PV. Finally, the protective role of PV for MI and cerebrovascular events is evident only in the elderly.

PV, prevention of pneumonia and mortality

The literature shows that although PV seems to protect (even modestly) against invasive pneumococcal disease, its effect on all-cause pneumonia and mortality is small and studies have yielded conflicting results.[36,37] However, this could be ascribed either to methodological problems, such as inclusion of non-representative high-risk populations, or to inadequate population size.[49] Indeed, the incidence of invasive pneumococcal disease and pneumococcal pneumonia has been dramatically reduced by the introduction of conjugate pneumococcal vaccines for infants since 2000 in United States possibly due to the resultant herd immunity.[50–52]

Pneumococcal disease, PV and CV events

However, the situation may be different in the reduction of CV events with PV. Many observational studies support a possible link between an acute respiratory infection and an increased risk of acute CV events.[7,8] Moreover, *Streptococcus pneumoniae* is responsible for more than 50% of CAP, it is the most common cause of severe CAP and it is the agent associated with the highest number of deaths[2] and in-hospital CV events.[29] On the contrary, all viral causes (including influenza) are identified in less than 15% of CAP and have a low mortality rate.[2] Pneumococcal infection produces higher inflammatory expression than other pathogens, implying a more severe inflammatory response.[53] Data have pointed out that hospitalized patients with a severe form of CAP have an increased risk of CV events.[6] In patients hospitalized with pneumococcal pneumonia, 7% have concurrent acute MI at the time of admission, suggesting events may even precede hospital admission.[54] In a recent study, more than 1 of 10 patients with *S. pneumoniae* or *Haemophilus influenzae* pneumonia developed ACS during their first 15 days of hospitalization.[55] Even after hospital discharge, patients infected with pneumococcal pneumonia have an increased risk of CV events for as long as 14 years.[20,54,56] Interestingly, these patients have the highest risk of ACS in the first 3 months, which was approximately four-fold higher than patients without pneumococcal pneumonia.[56] There are several plausible pathophysiological mechanisms that can support the possible protective effects of PV including reduction in inflammation and atherogenesis.[50,57] However, it appears that PV has less effect on plaque rupture and type 1 MI; rather, its possible protective effect may be mediated through protection against type 2 MI, that is secondary to ischaemia from a supply-and-demand mismatch,[58] by preventing the continuum of pneumococcal infection, pneumonia, decompensation of HF, pulmonary oedema and MI, especially in frail elderly patients. The latter explanation fits with the fact that PV shows a clear protective effect on total CV events in elderly but there is only a trend for protective effect on MI.

Further dissection of our principal finding provided interesting information. According to our analysis, the protective ability of PV for CV events is higher in studies with follow-up of one year. In adults, antibody titres induced by a first PV tend to decline significantly in the year after vaccination and approximate pre-vaccination levels within 4–7 years.[10] The clinical significance of this decline is not well defined. It seems plausible that the protective effect of PV on CV outcomes attenuates as the years pass since inoculation. This notion is supported by individual studies as well. Specifically, Eurich et al.[19] showed that there was a gradual reduction of the protective effect of PV on ACS from inoculation to 5 years after PV, while in the Community-Acquired Pneumonia, Acute Myocardial Infarction and Stroke (CAPAMIS) study, a well-conducted prospective study, interim 1-year analysis[30] showed a modest but statistically significant reduction of the composite endpoint of stroke and MI that disappeared after 3 years.[21]

Further important findings relate effectiveness of PV with age, baseline CV risk and COPD. On the other hand, despite the synergistic effect of PV and influenza vaccination on CV events implied by several studies,[13,20,32,33] we found no association of influenza vaccination percentage with the effect of PV.

Clinical implications

Our findings are potentially applicable to clinical practice. First, they support suggestion of PV by the United States Advisory Committee on Immunization Practices for all persons 65 years of age and older and for adults 19–64 years who are at increased risk of invasive pneumococcal disease.[59] However, in contrast to the vaccination for influenza no CV guidelines clearly recommend the use of PV for primary or secondary CV prevention.[60] Only in HF patients is there a general recommendation to receive PV.[61] Given the profound underuse of PV among high-risk subjects[62] and the potential impact this preventive strategy may have on high-risk patients, relevant recommendations in CV guidelines should be revisited. Another important issue is revaccination; indeed health policies could be revisited in light of our earlier data[10] to deal with the possible attenuation of the effect of PV with time. Furthermore, our data point to specific patient groups that could benefit from PV such as the elderly,[63] patients with high baseline CV risk and subjects with COPD. In this way a targeted approach would maximize effectiveness and avoid unnecessary vaccinations, as with influenza vaccination during the summer, which lacks significant CV protection. Finally, the administration of conjugate vaccines that contain highly immunogenic protein-conjugated polysaccharides of *S.pneumoniae* in immunocompetent adults poses an appealing alternative for reduction of CV events that needs to be further investigated.

Strengths and limitations

An important strength of our study is the exhaustive search strategy that probably enabled us to capture most, if not all, relevant studies. Moreover, our study for the first time includes data from published studies for meta-regression analysis thus integrating our approach to examine the possible protective role of PV in CV disease. Furthermore, as a meta-analysis, the present study overcomes the potentially biased inclusion and weighing of results that may appear in reviews when interpreting the available evidence. Finally, we dealt with potential publication bias.

For the large and growing population of elderly patients with high CV risk, it is important to identify clinically relevant measures of biological age and their contribution to risk. Frailty is an important concept in medicine denoting decreased physiological reserves and increased vulnerability. In many of the included studies, vaccinated patients were in most cases more frail, i.e. older and with more co-morbidities, however no study has addressed this vital issue. Thus, it is reasonable to assume that patients with PV were a priori at higher baseline risk than non-vaccinated patients, suggesting a possible underestimation of the effect of PV. However, this inherent limitation of most prospective studies was dealt with mainly by adjusting for the potential confounders with propensity or multivariable analysis between vaccinated and non-vaccinated patients. Thus, it appears that the decreased risk with PV is unlikely to be a consequence of the different baseline CV risk of patients with PV.

Most of the studies included patients who had been vaccinated as many as 5 years prior to initiation of the study. Therefore, it is plausible that many of the subjects with PV had little or even no immunity for *S.pneumoniae*, suggesting an underestimation of the real effect of PV on CV endpoints. A factor that could also induce a dilution effect is revaccination status on which data are limited.[12] All these aforementioned issues underline the need for controlled randomized studies as well as for the investigation of the role of conjugate PV on CV endpoints.

Observational studies have many inherent limitations and should be interpreted with caution. The main issues are the strong likelihood of bias and confounding, the heterogeneity between studies, the lower quality of data and validation of outcomes, as well as the fact that the conclusions may not be easily applicable across a generalized population. Due to the non-randomized design of the included studies the overall quality of evidence was low (evaluation was conflicting: very low according to GRADE, better according to the Ottawa-Newcastle score) and this is a limitation of our study. However, our study could provide a well-established setting for the conduction of a large randomized study on PV and CV outcomes. According to our analysis the best population to investigate the effect of pneumococcal vaccination on CV outcomes is subjects over 65 years with known cardiovascular disease. Based on power sample size calculation it was estimated that a sample size of 3468 to 4241 per group in two equal groups (one for placebo and the other for PV) with 10% lost in follow-up would yield 80% power with two-sided alpha = 0.05 to see a 14% reduction (RR = 0.86) in incidence of a combined CV endpoint over a 3-year period (for details see online Supplementary Material).

In this analysis, we used aggregate data as reported in published articles (or calculated from other data provided in the articles) rather than data for individual

patients. Also, due to the use of data reported in articles, we could not perform our analysis using the bayesian method and this is a limitation of our study. However, our results encourage the future presentation of an individual patient meta-analysis that could overcome this limitation. Accordingly, we did not deal with potential methodological problems of the original studies.

There is an apparent discrepancy between our findings and the results of the Tseng et al.[12] study, which included a large number of participants and a meticulous analysis of results. However, there are explanations that could reconcile the results of Tseng et al.[12] and our findings. Firstly, the study[12] was conducted in relatively young men that have a decreased risk of pneumococcal infection. Secondly, most of the men in the study were of low or medium CV risk, which means that their event rate for a CV endpoint was even lower. This is confirmed by the low incidence of the primary outcomes (incidence for both MI and stroke was <5% in the cohort of median 5.3 years' follow-up). Therefore, it would be extremely difficult even for this large study to have adequate power for conclusive results in this population. For further corroboration, in the elderly subanalysis of the same study, the results were similar to the other studies showing a possible protective role of pneumococcal vaccination.

Conclusions

PV is associated with a decreased risk of CV events and CV mortality, while the protective value of PV for total CV events increases at older ages and in high CV risk subjects and decreases as time elapses from the PV. PV is associated with a decreased risk of MI and cerebrovascular events in the elderly.

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Conflicts of interest

None reported by the authors.

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