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Smoking cessation for secondary prevention of cardiovascular disease (Review)

Wu AD, Lindson N, Hartmann-Boyce J, Wahedi A, Hajizadeh A, Theodoulou A, Thomas ET, Lee C, Aveyard P

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[Intervention Review]

Smoking cessation for secondary prevention of cardiovascular disease

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ABSTRACT

Background

Smoking is a leading cause of cardiovascular disease (CVD), particularly coronary heart disease (CHD). However, quitting smoking may prevent secondary CVD events in people already diagnosed with CHD.

Objectives

To examine the impact of smoking cessation on death from CVD and major adverse cardiovascular events (MACE), in people with incident CHD.

Search methods

We searched the Cochrane Tobacco Addiction Group's Specialised Register, CENTRAL, MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature, and the trials registries clinicaltrials.gov and the International Clinical Trials Registry Platform. We ran all searches from database inception to 15 April 2021.

Selection criteria

We included cohort studies, and both cluster- and individually randomised controlled trials of at least six months' duration. We treated all included studies as cohort studies and analysed them by smoking status at follow-up. Eligible studies had to recruit adults (> 18 years) with diagnosed CHD and who smoked tobacco at diagnosis, and assess whether they quit or continued smoking during the study. Studies had to measure at least one of our included outcomes with at least six months' follow-up. Our primary outcomes were death from CVD and MACE. Secondary outcomes included all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, new-onset angina and change in quality of life.

Data collection and analysis

We followed standard Cochrane methods for screening and data extraction.

We assessed the risk of bias for the primary outcomes using the ROBINS-I tool. We compared the incidence of death from CVD and of MACE (primary outcomes) between participants who quit smoking versus those who continued to smoke for each included study that reported these outcomes. We also assessed differences in all-cause mortality, incidence of non-fatal myocardial infarction, incidence of non-fatal stroke and new onset angina. We calculated hazard ratios (HRs) and 95% confidence intervals (95% CI). For our outcome, change in quality of life, we calculated the pooled standardised mean difference (SMD) and 95% CI for the difference in change in quality of life from baseline to follow-up between those who had quit smoking and those who had continued to smoke. For all meta-analyses we used a generic inverse variance random-effects model and quantified statistical heterogeneity using the I^2statistic.

We assessed the certainty of evidence for our primary outcomes using the eight GRADE considerations relevant to non-randomised studies.

Main results

We included 68 studies, consisting of 80,702 participants.

For both primary outcomes, smoking cessation was associated with a decreased risk compared with continuous smoking: CVD death (HR 0.61, 95% CI 0.49 to 0.75; I^2 = 62%; 18 studies, 17,982 participants; moderate-certainty evidence) and MACE (HR 0.57, 95% CI 0.45 to 0.71; I^2 = 84%; 15 studies, 20,290 participants; low-certainty evidence). These findings were robust to our planned sensitivity analyses. Through subgroup analysis, for example comparing adjusted versus non-adjusted estimates, we found no evidence of differences in the effect size. While there was substantial heterogeneity, this was primarily in magnitude rather than the direction of the effect estimates. Overall, we judged 11 (16%) studies to be at moderate risk of bias and 18 (26%) at serious risk, primarily due to possible confounding. There was also some evidence of funnel plot asymmetry for MACE outcomes. For these reasons, we rated our certainty in the estimates for CVD death as moderate and MACE as low.

For our secondary outcomes, smoking cessation was associated with a decreased risk in all-cause mortality (HR 0.60, 95% CI 0.55 to 0.66; I^2 = 58%; 48 studies, 59,354 participants), non-fatal myocardial infarction (HR 0.64, 95% CI 0.58 to 0.72; I^2 = 2%; 24 studies, 23,264 participants) and non-fatal stroke (HR 0.70, 95% CI 0.53 to 0.90; I^2 = 0%; 9 studies, 11,352 participants). As only one study reported new onset of angina, we did not conduct meta-analysis, but this study reported a lower risk in people who stopped smoking. Quitting smoking was not associated with a worsening of quality of life and suggested improvement in quality of life, with the lower bound of the CI also consistent with no difference (SMD 0.12, 95% CI 0.01 to 0.24; I^2 = 48%; 8 studies, 3182 participants).

Authors' conclusions

There is moderate-certainty evidence that smoking cessation is associated with a reduction of approximately one-third in the risk of recurrent cardiovascular disease in people who stop smoking at diagnosis. This association may be causal, based on the link between smoking cessation and restoration of endothelial and platelet function, where dysfunction of both can result in increased likelihood of CVD events.

Our results provide evidence that there is a decreased risk of secondary CVD events in those who quit smoking compared with those who continue, and that there is a suggested improvement in quality of life as a result of quitting smoking. Additional studies that account for confounding, such as use of secondary CVD prevention medication, would strengthen the evidence in this area.

PLAIN LANGUAGE SUMMARY

Does stopping smoking make people with heart disease less likely to have another heart attack?

Key messages

• People with heart disease who stop smoking are likely to experience a decreased risk in future heart attacks or other events linked to the heart or blood vessels, such as stroke.

• People with heart disease who stop smoking are unlikely to have worse quality of life.

Smoking and heart disease

Smoking increases the chances that a person will have a heart attack, however there is less information on whether stopping smoking can reduce the risk of having a second heart attack.

Why we did this Cochrane Review

We wanted to find out whether stopping smoking after a heart attack can reduce the chances of having further heart attacks or other types of disease linked to the heart or blood vessels. If stopping smoking does prevent further illness this could motivate more people to quit smoking and encourage doctors and nurses to provide more active support to help people to stop.

What did we do?

We searched for studies that lasted at least 6 months, and that included people diagnosed with heart disease who were smoking when the study started. Studies also had to measure whether people did or did not stop smoking and whether or not they had another event linked to their heart or blood vessels, such as another heart attack or a stroke.

Search date: we included studies published up to 15 April 2021.

What we found

We found 68 studies with 80,702 people. Most studies included adult men and women from the general population, however, 11 studies included only men. We looked at the combined results of 60 studies that measured events linked to heart disease and of 8 studies that measured people's quality of life over a period of 6 months or more.

What are the results of our review?

Compared with people who continued to smoke, people who stopped smoking were a third less likely to die from heart disease or stroke (evidence from 17,982 people in 18 studies) and a third less likely to have another heart attack or stroke (evidence from 20,290 people in 15 studies). Our confidence in these results was moderate (death from heart disease or stroke) and low (death from heart disease or stroke, another heart attack or another stroke) respectively. Our confidence in the strength of our results was reduced because of issues with how some of the studies were designed and carried out. However, when we only examined studies of a higher standard, we continued to find that people who stopped smoking were less likely to die from heart disease or stroke. This suggests that while we may be uncertain about how big the reduction in the chance of dying is, people who stop smoking are likely to reduce their chances of dying from heart disease or stroke to some degree. We found similar results for a decreased likelihood of dying from any cause, having another heart attack that does not lead to death and having a stroke that does not lead to death.

We also found that people who stopped smoking had a suggested improvement in quality of life compared with those who continued smoking after being diagnosed with heart disease.

Summary of findings 1. Smoking cessation compared to continuous smoking for prevention of secondary cardiovascular disease events

Smoking cessation compared to continuous smoking for prevention of secondary cardiovascular disease events

Patient or population: people with coronary heart diease

Setting: hospital and community
Intervention: smoking cessation
Comparison: continuous smoking

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with continuous smoking	Risk with smoking cessation			
Death from cardiovascular disease at 19 months to 126 months	Study population		HR 0.61 (0.49 to 0.75)	17,982 (18 observational studies)	⊕⊕⊕⊖ Moderate[a,b]
	210 per 1000	134 per 1000 (109 to 162)			
Major adverse cardiovascular events (MACE) at 19 months to 110 months	Study population		HR 0.57 (0.45 to 0.71)	20,521 (15 observational studies)	⊕⊕⊖⊖ Low[c,d,e]
	323 per 1000	227 per 1000 (196 to 262)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to risk of bias. No studies were assessed as low risk of bias, however when we removed 11 studies at high risk this did not change the result, therefore we only downgraded by one level.
[b]Did not downgrade due to inconsistency. I^2 = 62% and was not explained by subgroup and sensitivity analyses, however, heterogeneity was primarily due to magnitude rather than direction of effect.

[c]Downgraded one level due to risk of bias. No studies were assessed as low risk of bias, however when we removed five studies at high risk, it did not change the result, therefore we only downgraded by one level.
[d]Downgraded one level due to publication bias. Funnel plot suggested that smaller studies are of lower methodological quality and therefore produce exaggerated intervention effect estimates.
[e]Did not downgrade due to inconsistency. I^2 = 70% and was not explained by subgroup and sensitivity analyses, however heterogeneity was primarily due to magnitude rather than direction of effect.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is responsible for approximately 31% of all global mortality (Kendir 2018). The Global Burden of Disease study reported that 18.6 million deaths per year are attributed to CVD globally (Roth 2020). In the USA, CVD accounts for more deaths since 1919 than any other single major cause of death, with the majority caused by coronary heart disease (CHD; 43.2%), followed by stroke (16.9%; Benjamin 2019). According to a 2017 review, approximately 17% of the population of Europe are living with CVD (Wilkins 2017). It is well-established that tobacco smoking is a risk factor for incident CVD (Banks 2019; Carter 2015; Gakidou 2017). A retrospective cohort study conducted in the UK noted that out of a sample of 12,393 people diagnosed with incident CHD between 1999 and 2013, 18.2% of people with incident disease identified as a person who smokes. One year later, around half of those people were still smoking (Farley 2017). Similar rates of persistent smoking after a CVD event have been reported in South Korea (Choi 2013; Lim 2017), and Greece (Rallidis 2005).

Description of the intervention

As tobacco smoking is a risk factor for CHD, it follows that stopping smoking may improve cardiovascular health and help prevent recurrent CVD events in people diagnosed with CHD. Although many people who quit do so without support (Hummel 2018), quit attempts are more likely to be successful when supported by evidence-based behavioural (Hartmann-Boyce 2021), and pharmacological interventions (Cahill 2013; Thomas 2021). This review will focus on the effects of successfully quitting smoking, and not on any particular intervention to aid cessation.

How the intervention might work

There are several mechanisms by which smoking cessation could reduce recurrent CVD incidence in people with CHD. The primary underlying pathophysiological mechanism that leads to CVD is atherosclerosis, with endothelial dysfunction suggested as an early marker (Davignon 2004). Stopping smoking improves endothelial function (Celermajer 1993; Delgado 2020). Atherosclerosis is the build-up of lipids (fats) in the inner layers of arteries, which leads to the hardening and narrowing of these arteries, and the thickening of the arterial wall. This can result in thrombosis (blood clots), which can lead to myocardial infarction (heart attacks), or Ischaemic stroke (Nagareddy 2013). Smoking impairs platelet function, making their coagulation, the first stage in clot formation, more likely (Pamukcu 2011). Cessation restores normal platelet function within days, as the half-life of platelets is only a matter of days (Morita 2005). Smoking may also affect the formation of fatty deposits in arteries and blood clots, oxidative stress, haemostatic factors (platelet function, fibrinogen, and d-dimer), fibrinolysis, inflammation, lipid modification, and vasomotor function (IARC 2007). The 2010 US Surgeon General's report concluded that following smoking cessation, the risk for endothelial dysfunction, thrombosis, and reduced oxygen delivery can lessen within a short period (USDHHS 2010). Therefore, while reducing the incidence of recurrent CVD through cholesterol-lowering therapies, such as statins, is an option for risk reduction, smoking cessation may also play a substantial role in reducing the risk of further CVD events in people diagnosed with CHD (Wilt 2004).

Why it is important to do this review

The 2020 US Surgeon General's report concluded that for people who currently smoke and are diagnosed with CHD, there is sufficient evidence to infer a causal relationship between smoking cessation and reduced risk of new and recurrent cardiac events, all-cause mortality, deaths due to cardiac causes, and sudden death (USDHHS 2020). While they noted the trends in risk ratios across the different studies, predominantly suggesting that smoking cessation decreased risk, they did not calculate an overall risk ratio from the evidence they gathered. A Cochrane Review published in 2003 compared the risk of mortality in people who stopped smoking versus those who continued, and synthesised the data in a meta-analysis (Critchley 2003a; Critchley 2003b). This review supersedes the 2003 paper. They included 20 studies that followed participants with CHD for at least two years, and found the pooled risk ratio for death was 0.64 (95% confidence interval 0.58 to 0.71) when comparing people who had quit smoking with those who had not.

Many health guidelines, such as the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for secondary prevention in people with coronary artery disease now include smoking cessation as a secondary prevention intervention for CVD events in people with CHD (Smith 2011). However, as previously discussed, there is still a large proportion of people diagnosed with CHD who continue to smoke (Choi 2013; Farley 2017; Lim 2017; Rallidis 2005). Despite the evidence that smoking cessation interventions prevent CVD events, there appears to be a gap between this knowledge, and translating it into providing active smoking cessation treatment to people diagnosed with CHD, which we know can increase quit rates (Cahill 2013; Hartmann-Boyce 2021). An update of the evidence to understand the magnitude and speed of this risk reduction due to smoking cessation could motivate clinicians to provide cessation treatment, as well as statins and aspirin for people with CHD, who are under their care. Therefore, this review aims to establish the certainty of the evidence that smoking cessation changes the prognosis of CHD, the strength of the effect, and how this effect changes in the time following diagnosis.

This review builds upon the previously published Cochrane Review (Critchley 2003a; Critchley 2003b). The previous review focused solely on studies with a minimum two-year follow-up. We decided to shorten the required follow-up period, to establish whether beneficial effects of smoking cessation occur more quickly following cessation. This review will also investigate new outcomes, such as the risk for major adverse cardiac endpoints, which have been informed by patient and public involvement (PPI), and attempt to understand the role of potential mediating factors on smoking cessation effects in CHD.

OBJECTIVES

To examine the impact of smoking cessation on death from CVD and major adverse cardiovascular events (MACE), in people with incident CHD.

METHODS

Criteria for considering studies for this review

Types of studies

Cohort studies, and both cluster- and individually randomised controlled trials (RCTs) of at least six months' duration. We treated all included studies as cohort studies in order to compare people who quit smoking with those who did not (rather than differences between randomised groups in RCTs).

Types of participants

We included adults (> 18 years) diagnosed with CHD (including myocardial infarction, stable or unstable angina, heart failure due to atherosclerosis), who smoked tobacco at study baseline. To maximise our review's sensitivity, we included any definition of CHD used by the included studies, as explicit definitions may have excluded studies that failed to report their diagnostic criteria. We included any participants who were defined as smoking at baseline, based on the criteria of the individual studies.

Types of interventions

Conceptually, the intervention in this review is smoking cessation, and not interventions (for example behavioural interventions) offered to support smoking cessation. The comparator is continued smoking. In order to identify people who had stopped smoking in contrast to those who had continued, smoking status had to be measured on at least two occasions during the study: at baseline, and at some point after that. We accepted the definition of smoking cessation described by each included study. If multiple definitions were provided, we favoured the most stringent (i.e. continuous over point prevalence abstinence, and biochemically validated abstinence over self-report).

Types of outcome measures

Primary outcomes

- Death from cardiovascular disease
- Major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Secondary outcomes

- All-cause mortality
- Non-fatal myocardial infarction (STEMI (ST-elevation myocardial infarction)), NSTEMI (non-STEMI), or both)
- Non-fatal stroke
- New-onset angina
- Quality of life

To be included in the review, studies had to measure at least one of the outcomes above, with at least a six-month follow-up from baseline. In the studies that measured these outcomes, we also investigated the following secondary manifestations of arterial disease (SMART) risk score laboratory results as potential mediators of the effect of smoking cessation on death from cardiovascular disease and major cardiac endpoints (Dorresteijn 2013).

- HDL-cholesterol (high-density lipoprotein cholesterol)
- Total cholesterol
- Estimated glomerular filtration rate (eGFR)
- High-sensitivity C-reactive protein (CRP)

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to date of search.

- Cochrane Tobacco Addiction Group's Specialised Register (CRS-Web)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 3) via CRS Web
- MEDLINE, Ovid (1946 to 15 April 2021)
- Embase, Ovid (1974 to 15 April 2021)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL), EBSCOhost (1961 to 15 April 2021)

We searched all databases from inception through to 15 April 2021. At the time of the search, the Register included the results of searches of MEDLINE (via Ovid) to update 20210407; Embase (via Ovid) to week 202114; PsycINFO (via Ovid) to update 20210329. For details of how the Register is populated see the Cochrane Tobacco Addiction Group's website. By searching CENTRAL, we were able to identify studies registered in the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch) and U.S. National Library of Medicine's ClinicalTrials.gov. See Appendix 1 for our search strategies.

Searching other resources

We contacted experts in the field to identify existing reviews and studies, or research underway.

Data collection and analysis

Selection of studies

Two review authors (of ADW, AH, AT, AW, CL, ET) independently screened titles and abstracts of records returned by the searches. When disagreements arose, they were resolved through discussion or referral to a third review author (JHB, NL). We aimed to maximise sensitivity in this initial screening by including studies that might not have information directly relevant to our research question presented in the title and abstract. We translated non-English language studies, where required. We acquired the full text of potentially relevant articles identified at the title and abstract screening stage. Two review authors (of ADW, AH, AT, AW, ET) independently screened these texts for final inclusion. Disagreements were resolved through discussion or referral to a third review author (JHB, NL). We recorded reasons for exclusion at the full-text screening stage. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021).

Data extraction and management

We first piloted the data extraction form, and subsequently made the appropriate and necessary changes. Two review authors (of ADW, AH, AW, ET) independently extracted study data. We compared extractions and resolved any disagreements through

discussion or referral to a third review author (JHB, NL). We extracted the following data from each study.

- Authors
- Date and country of publication
- Study design
- Study dates
- Inclusion and exclusion criteria
- Analysis method
- Outcome measure(s)
- Length of follow-up
- Coronary heart disease definition
- Smoking cessation intervention(s) used (if relevant)
- Author declarations of interest
- Study funding source
- Additional comments
- Number (n) at baseline and follow-up
- Percentage (%) female
- Mean age (standard deviation (SD))
- Smoking cessation definition
- Type of biochemical validation (if any)
- Covariates adjusted for
- Potential mediators
- Risk of bias information for making assessments using ROBINS-I (Sterne 2016)
- Unadjusted and adjusted estimates to calculate the hazard ratios (HR) of CVD mortality outcome, MACE outcomes, all-cause mortality, non-fatal myocardial infarction, non-fatal stroke and new-onset angina for smokers and non-smokers
- Unadjusted and adjusted estimates to calculate the SMD in quality-of-life outcomes: for each group – mean at baseline and follow-up, mean change from baseline to follow-up, and the difference in mean change from baseline to follow-up, and variance
- Details of any analyses investigating the difference in effects moderated by sex

Assessment of risk of bias in included studies

We assessed the risk of bias for all primary outcomes reported in our included studies using ROBINS-I (Sterne 2016). This tool determines the risk of bias in non-randomised studies based on the following domains: bias due to confounding; bias in selection of participants into the study; bias in classification of interventions; bias due to deviations from intended interventions; bias due to missing data; bias in measurement of outcomes; and bias in selection of the reported result. Two review authors (of ADW, AH, AW) independently assessed bias. Where disagreements arose, we resolved them through discussion or referral to a third review author (JHB, NL). We categorised the risk of bias as low, moderate, serious, or critical for each domain, and for each study overall, using the signalling questions built into the tool.

As part of our assessment, we investigated whether each study had controlled for the following potential confounders.

- Socioeconomic status
- Age
- The severity of the initial event, risk of future events
- Lipids
- Hypertension
- Medications for secondary prevention of CHD (aspirin, statins, and beta-blockers)
- Diabetes status

Measures of treatment effect

We compared the CVD mortality rates and MACE outcomes (primary outcomes), between participants who quit smoking versus those who continued to smoke for each included study that reported these outcomes. We also compared the all-cause mortality rate, changes in quality of life, non-fatal stroke rates, non-fatal myocardial infarction, and new-onset angina (secondary outcomes) between participants who quit smoking versus those who continued smoking for each included study, where these were measured.

We extracted data to calculate the HR and 95% confidence interval (CI) for CHD-related mortality, MACE outcomes, all-cause mortality rate, and rates of non-fatal stroke, non-fatal myocardial infarction, and new-onset angina for people who continued to smoke and those who stopped smoking. Where studies provided both unadjusted and adjusted estimates, we extracted both.

For continuous measures of quality of life, we first calculated mean differences (MD) from baseline to follow-up, so we could subsequently calculate SMD and 95% CI for each study. We extracted data in the following order of preference for meta-analyses: 1) adjusted or unadjusted MD and measure of variation between exposure groups (preference for adjusted estimates); 2) mean change in quality-of-life scores from baseline to follow-up and measure of variance, by exposure group; 3) mean quality-of-life scores and measures of variance at baseline and follow-up, by exposure group. We then used a standard formula to calculate the mean change and variance by exposure group (Follmann 1992). From there, we calculated the SMD using standard formulae outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We classified the effect size according to Cohen's D, where we deemed an effect size of 0.2 to be small (Cohen 2013).

Unit of analysis issues

We did not encounter any unit of analysis issues because people, not clusters, continue smoking or stop smoking, and we did not analyse participants according to their randomised groups.

Dealing with missing data

We wrote to study authors if additional data were necessary to calculate effect estimates for any included studies. When we could not obtain outcome data, we reported studies narratively.

Assessment of heterogeneity

We assessed whether, and which studies we could pool, based on the similarity of participants and their diagnoses at baseline, and the methodological characteristics of studies. As between-study variance was within appropriate levels, we carried out meta-analyses. We investigated statistical heterogeneity using the I^2 statistic for our meta-analyses, which quantifies the percentage of between-study variability explained by genuine heterogeneity

rather than chance (Higgins 2003). An I^2 value above 75% indicates substantial heterogeneity (Deeks 2021). Therefore, where we detected an I^2 statistic of 75% or higher, we assessed whether presenting a pooled analysis was appropriate. We conducted the subgroup and sensitivity analyses for both our primary outcomes, described below, to investigate any causes of observed heterogeneity regardless of level of heterogeneity.

Assessment of reporting biases

We examined funnel plots for evidence of asymmetry where 10 or more studies contributed to a meta-analysis. Funnel plots are used to illustrate the relationship between the effect estimates of individual studies and the study's size or precision – the greater the asymmetry, the greater the potential risk of reporting bias.

Data synthesis

We used random-effects generic inverse variance methods to pool eligible studies reporting on our dichotomous outcomes and present the resulting HRs and 95% CIs. A HR of less than 1 indicated that quitting smoking was associated with better CVD outcomes at follow-up.

For our quality-of-life outcome, we pooled SMDs and 95% CIs for individual studies using random-effects generic inverse variance methods, to generate a pooled SMD and 95% CIs. An SMD greater than zero indicated that quitting smoking was associated with better quality of life at follow-up.

When individual studies reported both adjusted and unadjusted outcomes, we first pooled the adjusted estimates in our analyses and only pooled unadjusted for subsequent sensitivity analyses.

We planned to account for the impact of our prespecified mediators by running a meta-regression, and adjusting for the mediators measured at the 'per study' level, however this was not possible due to lack of data. We had also planned to identify any studies that carried out in-study mediation analyses, and summarise these results narratively but this was also not feasible as no study presented such data. In addition, we tried to identify studies that carried out in-study analyses to investigate any potential differences in effect by sex and report them narratively, however no study reported this.

We ran all meta-analyses using Review Manager Web (RevMan Web 2022).

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses for our primary outcomes, when appropriate:

- comparing the effect estimates from studies that presented adjusted estimates versus unadjusted estimates;
- comparing the effect estimates from studies that presented HRs as effect estimates versus risk ratio (RR);
- comparing studies that used bio-chemical validation for classifying people's smoking status with those that did not use bio-chemical validation;
- comparing the effect estimates from studies that adjusted for secondary coronary event medication use versus those that did not report medication use or did not adjust for medication use;
- comparing effect estimates based on the sex of the studies' populations (men only versus women only versus mixed population of men and women);
- comparing the effect estimates from studies that presented MACE outcomes with the same definition as our review versus those with a variation of coronary composite events.

Sensitivity analysis

We conducted the following sensitivity analyses for both of our primary outcomes:

- testing the impact of excluding studies that were deemed to be at higher risk of bias from analyses of our primary outcomes, i.e. assessed at critical and serious risk, or at critical risk (if all other studies are classed at serious risk), in one of the ROBINS-I domains;
- testing the difference between using adjusted or unadjusted estimates for studies that provided both.

Summary of findings and assessment of the certainty of the evidence

We used GRADEpro GDT software to create a summary of findings table that reports the pooled effect estimates for our primary outcomes.

- Death from cardiovascular disease
- Major adverse cardiovascular events (MACE)

Two review authors (ADW, NL) judged the certainty of this evidence according to GRADE's eight considerations for non-randomised studies (risk of bias, inconsistency, imprecision, indirectness, publication bias, size of the effect, plausible confounding, dose response gradient (Schünemann 2013)). We categorised the certainty of the evidence for each primary outcome as high, moderate, low, or very low, and we took this into account when drawing our conclusions.

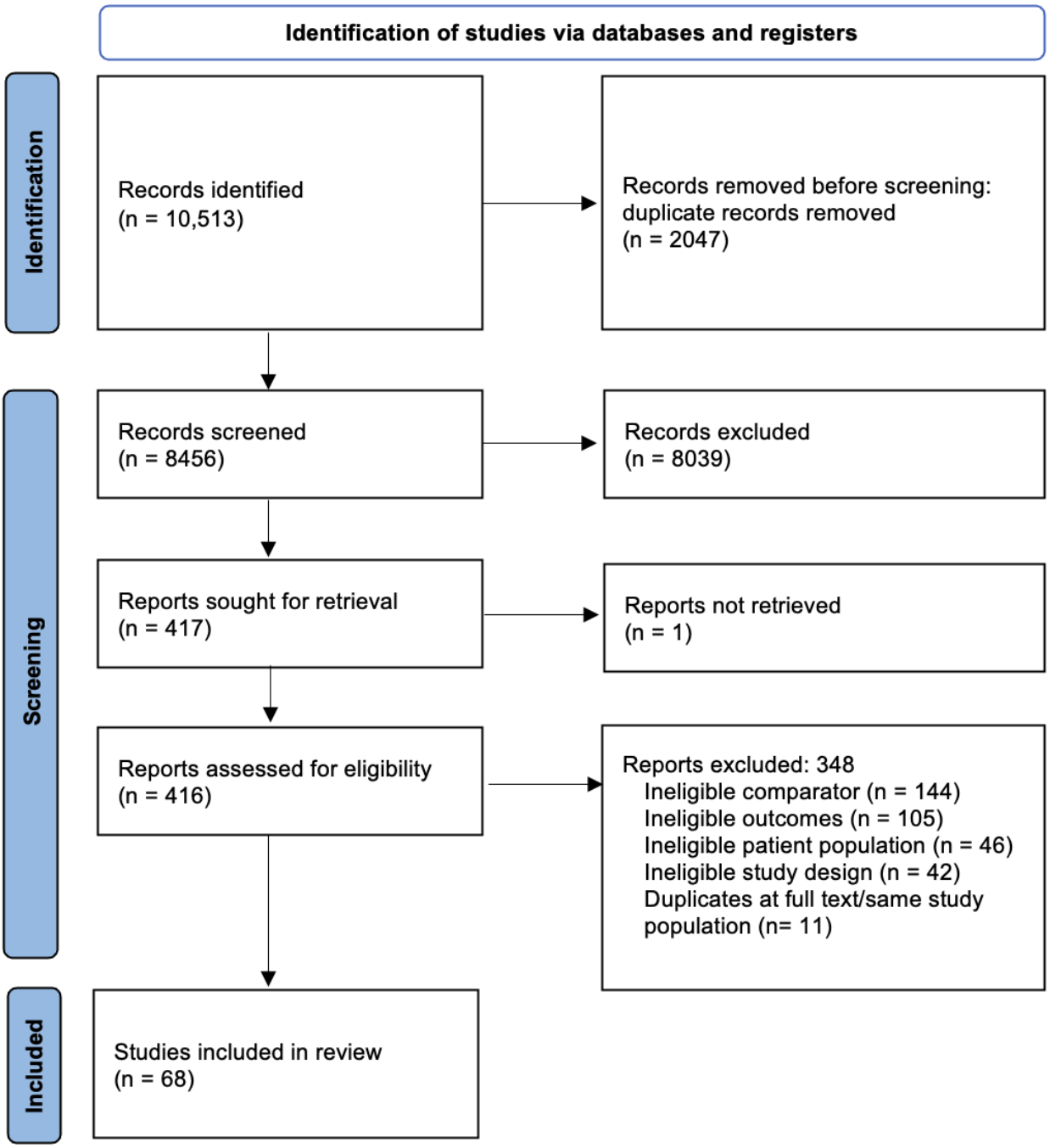
RESULTS

Description of studies

Results of the search

Our searches identified 10,513 records. After removing duplicates, we screened 8456 records at the titles and abstracts stage, of which 8039 we deemed irrelevant. We retrieved and assessed the full-text of 416 studies for inclusion, of which we excluded 349. Examples of excluded studies can be found in Characteristics of excluded studies with reasons for exclusion. See Figure 1 for flow diagram.

Figure 1. PRISMA flow diagram of studies



Included studies

In total, 68 studies were eligible for inclusion in this systematic review. We included all 20 studies that were included in the 2003 review (Critchley 2003a; Critchley 2003b), and 48 new studies. We were unable to access the unpublished data from one study in the original review despite attempting to contact the authors, therefore we used the data that were published in the original review for our meta-analysis (Toefler 1993).

Forty-seven of the studies were longitudinal cohort studies and six were retrospective cohort studies. We included 15 studies that were either secondary analyses of RCTs analysed as observational cohorts or RCTs that reported the necessary outcomes by smoking status, and therefore were analysed as cohort studies.

Participants

The 68 included studies had 80,702 participants. Two studies were conducted in Australia, two in Canada, six in China, four in Finland, one in Germany, three in Greece, one in India, one in Iran, three in Ireland, two in Israel, two in Italy, two in Japan, two in Norway,

one in Poland, one in South Korea, two in Spain, seven in Sweden, seven in the Netherlands, four in the UK and nine in the USA. Three studies were conducted in the USA and Canada together, one study was based in the USA, Canada, Germany, Spain, Italy, Turkey, Brazil and Argentina, and one study in the USA, Canada, Pakistan, Iran, Tunisia and India. Chow 2010 reported that data came from 41 countries as part of the OASIS 5 trial; however, we could not find the list of the 41 included countries. All studies were conducted in an adult population; however, several included specific age requirements. Rallidis 2008 and Rallidis 2015 only recruited individuals under the age of 35 when they had their diagnosis of CHD. Boggon 2014 recruited only participants above the age of 30. Three studies also only included individuals under the age of 60 (Daly 1985; Grand 1992; Mulcahy 1982). Of the studies that reported a mean age for their population, these ranged from 44 to 65 years, and the mean was 56.5. Eleven studies included only men, and one study was limited to women (Johansson 1985). Of the studies that included a mixed-gender population, the average percentage of women was 18.4% (ranging from 7.7% to 28.4%). The included studies categorised their population either through a clinical diagnosis of CHD (49 studies) or through a surgical procedure, such as coronary artery bypass grafting or percutaneous coronary intervention (18 studies). The severity of initial CHD diagnosis was not well recorded and reported in the included studies and therefore we could not synthesise these data.

Intervention/exposure

The studies used a variety of methods to measure smoking cessation. The primary definition was point prevalence abstinence, where participants were asked whether they were smoking or not at a follow-up point. Twenty-five studies measured smoking status change at one point after diagnosis of CHD, with a mean follow-up time of 10 months (ranging from 1 month to 36 months after diagnosis). The time when smoking status was reported was unclear in 18 studies. Twenty-four studies reported smoking status at multiple follow-up time points. Studies that assessed smoking status multiple times most commonly followed up during months 1, 6 and 12. When multiple time points were given, we used the longest follow-up time point for smoking status. We assumed smoking status to be consistent until the relevant follow-up point. This is common practice in the field; although individuals' smoking status may change during follow-up, the likelihood of this should be consistent across studies and so this choice should not introduce spurious variation to the meta-analysis.

Seven studies biochemically verified smoking status, or biochemically verified a subgroup of the population; usually through measuring participants' exhaled carbon monoxide or urine (Quist-Paulsen 2006), or blood cotinine concentration (Breitling 2011).

Twenty studies reported some form of behavioural support for smoking cessation; this was typically offered as smoking cessation counselling and participants were advised on the relationship between heart disease and smoking. Five studies offered some form of pharmacological support as part of their study to either some or the entire study population; three of these studies were RCTs (Qi 2014; Wiggers 2006; Zhang 2013). Qi 2014 and Zhang 2013 offered bupropion to approximately half of their sample and a placebo to the other half, whereas Wiggers 2006 offered nicotine replacement therapy to those in the experimental group. Boggon 2014 reported that approximately 15% of the study population were offered some form of pharmacological smoking cessation support after the diagnosis from their routine care, similarly Cordero 2012 noted that 30% received pharmacological support. As this review focuses on whether or not individuals who stopped versus those who continued smoking had different CVD outcomes, we did not analyse data based on whether or not smoking cessation interventions were offered.

Outcomes

Of the 68 included studies:

- 18 reported on death due to cardiovascular disease
- 15 reported on MACE
- 51 reported on all-cause mortality
- 24 reported on non-fatal myocardial infarction
- 9 reported on non-fatal stroke
- 1 reported on new onset angina
- 8 reported on quality of life

As only one study reported new onset angina, we report results narratively. Additionally, we were unable to include three further studies in meta-analyses as we could not calculate estimates from reported results, and we were unable to obtain the data needed from the study authors (Lotan 2017; Murphy 2020 all-cause mortality; Kievit 2009 non-fatal myocardial infarction. Results from these are also summarised narratively. The eight studies that reported quality of life used six different quality-of-life scales.

Full details for each included study can be found in Characteristics of included studies.

Excluded studies

The primary reasons for excluding studies were that:

- they did not analyse outcomes by smoking status as the comparator;
- they did not collect relevant outcomes; or
- the study design was not eligible (e.g. qualitative study or cross-sectional design).

Full exclusion reasons are available in the PRISMA flow chart (Figure 1), and we list a sample of 10 excluded studies in Characteristics of excluded studies that were randomly selected, as many potentially relevant studies were excluded for common reasons.

Risk of bias in included studies

We assessed risks of bias for each study that included at least one of the two primary outcomes using ROBINS-I (Sterne 2016). Therefore, we assessed 29 studies, 16 for CVD death and 13 for MACE. Where studies reported both primary outcomes, we used only one outcome for assessment; this was the case for three studies (Sun 2011; Zhu 2009 CVD death; Boggon 2014 MACE). We selected based on which analysis was reported first. Overall, we judged 11 studies to be at moderate risk and 18 at serious risk. The full breakdown for each study and domain is illustrated in Figure 2 and Figure 3 (figures generated using robvis: McGuinness 2021).

Figure 2. Risk-of-bias: 'traffic light' plot of the domain-level judgements for each individual result according to the ROBINS-I tool

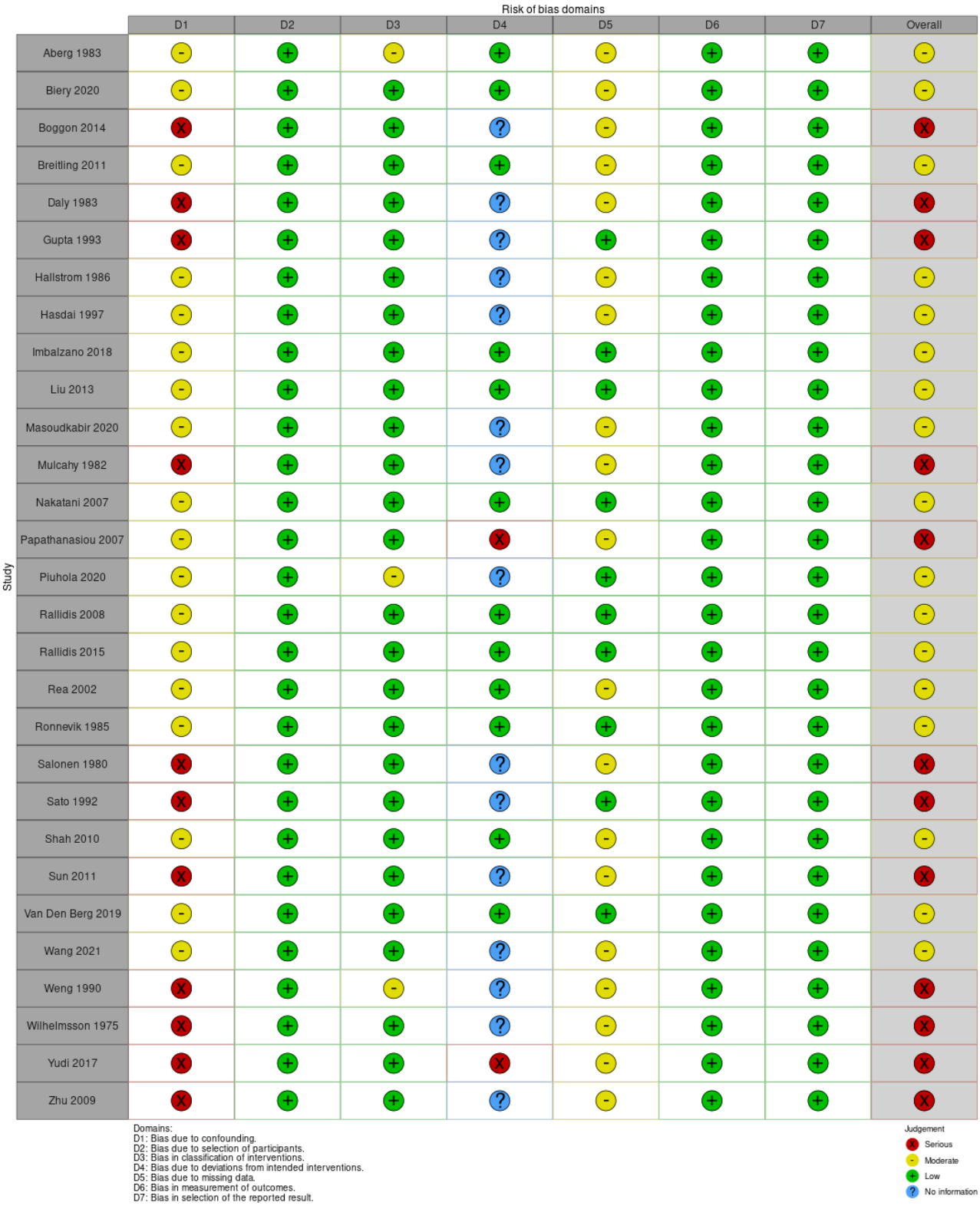
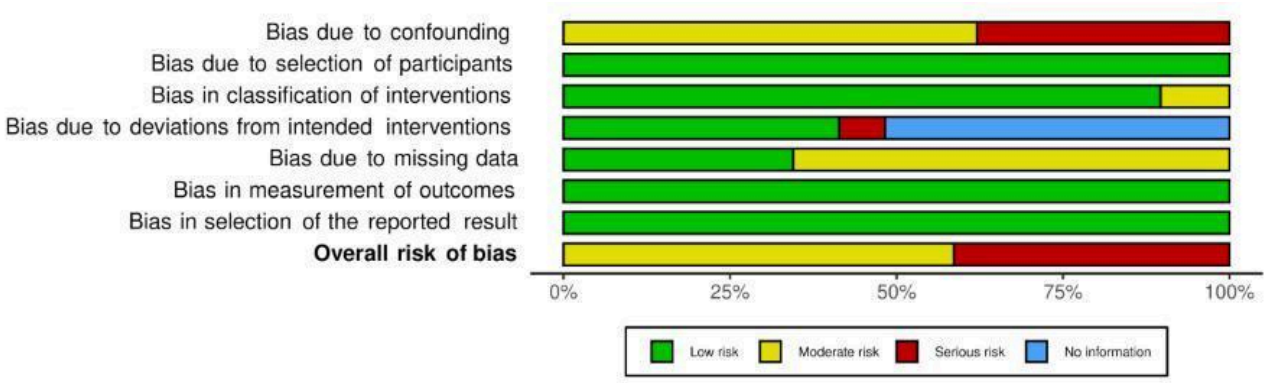


Figure 3. Risk-of-bias: weighted bar plot of the distribution of risk-of-bias judgements within each bias domain according to the ROBINS-I tool



Bias due to confounding

We judged 18 studies at moderate risk and 11 at serious risk for this domain. We judged studies that reported estimates based off unadjusted analysis to be at serious risk. While several studies did not control for confounding in their outcome analysis, baseline measurements were not significantly different. However, they did not include all potential confounders that we had listed as part of study, therefore, we assessed bias due to confounding to be at moderate risk.

Bias in selection of participants into the study

The selection of participants into each study (or analysis) was not based on participant characteristics observed after participants attempted to quit smoking or any characteristics associated with quitting smoking, but based on participants having CHD and smoking; therefore, we judged all studies to be at low risk of bias for this domain.

Bias in the classification of follow-up smoking status

We judged all studies to be at low risk of bias in terms of smoking cessation definition, apart from three studies that we rated at moderate risk, as they did not clearly define abstinence (Aberg 1983; Piuhola 2019; Weng 1990). In all other cases, the differentiation between continued smoking and smoking cessation was clearly defined using a definition commonly used in the field.

Bias due to deviations from quitting smoking (i.e. relapsing) or through access to secondary prevention medications

We rated 12 studies as at low risk for this domain, two serious and 15 as 'no information'. A study was given 'no information' for risk of bias when there was a lack of reporting of whether secondary prevention medications such as aspirin and beta-blockers were used. The two studies that were at serious risk noted a difference in the rate of secondary prevention medication between the smoking cessation group and those who continued, which they did not adjust for in their analyses (Papathanasiou 2007; Yudi 2017).

Bias due to missing data

We judged all studies as either low (10) or moderate (19) risk for bias due to missing data. Studies assessed as low had outcome data available for more than 70% of recruited participants, and participants were not excluded from the analysis due to missing smoking status or outcome data. Those judged to be at moderate risk excluded participants from their analyses due to a lack of smoking cessation data.

Bias in measurement of outcomes

We judged all studies to be at low risk of bias for this domain as CVD death and MACE outcomes involve negligible subjective assessor judgment.

Bias in selection of the reported result

There was no evidence that studies carried out multiple analyses and selectively reported outcomes. We judged all studies to be at low risk of bias for this domain. As outcomes are measured in a binary format, it is impossible to generate multiple effect estimates for an individual measurement. However, we included seven studies that reported composite coronary outcomes that were defined slightly differently to our definition of MACE (Masoudkabir 2020; Nakatani 2007; Rallidis 2015; Rea 2002; Shah 2010; Yudi 2017; Zhu 2009). For example, Zhu 2009 included total mortality as part of their MACE outcome, and Shah 2010 included hospitalisation due to heart failure. While these studies reported MACE definitions that deviated from the definition our review used, we considered this to not represent a risk of bias and subsequently we ran a sensitivity analysis removing these seven studies.

Effects of interventions

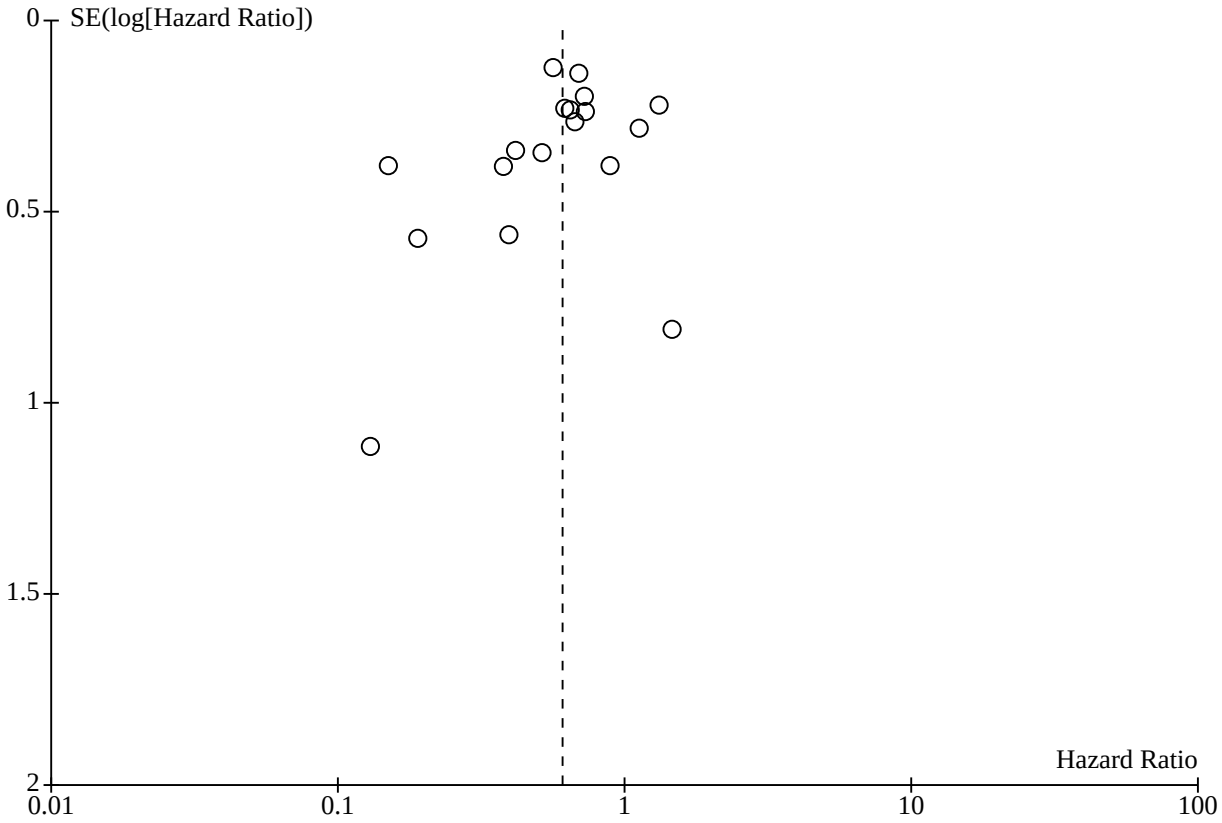
See: **Summary of findings 1** Smoking cessation compared to continuous smoking for prevention of secondary cardiovascular disease events

Death from cardiovascular disease (CVD)

Eighteen studies reported data used to calculate the pooled HR for CVD death. Data from 9341 people who quit smoking and 8641 people who continued smoking provided evidence that quitting smoking is associated with a lower risk of CVD death (HR 0.61, 95% CI 0.49 to 0.75; moderate-certainty evidence; Analysis 1.1). However, there was notable heterogeneity between studies (I^2 = 62%).

Figure 4

Figure 4. Funnel plot of comparison 1. Main analysis: difference in change (from baseline to longest follow-up) between people who quit and people who continued smoking, outcome: 1.1 primary outcome: death from cardiovascular disease



Sensitivity and subgroup analyses

We carried out a sensitivity analysis removing 11 studies assessed at critical or serious risk of bias; however, this did not account for the statistical heterogeneity or meaningfully change the effect estimate (Analysis 1.2). Our original plan was to use a sensitivity analysis to test the difference between adjusted or unadjusted estimates for studies that provided both; however, only one study provided both unadjusted and adjusted estimates. Biery 2020 reported an unadjusted HR of 0.29 (95% CI 0.11 to 0.79) versus an adjusted HR of 0.19 (95% CI 0.06 to 0.56). When we substituted the adjusted HR for the unadjusted HR this did not change the outcome of our analysis (HR 0.61, 95% CI 0.50 to 0.75; I^2 = 60%; Analysis 1.3).

We also tested the impact of adjustment for confounding by comparing three studies that adjusted their estimates and 15 that did not in subgroup analysis (Analysis 1.4). There was no evidence that effect estimates differed between studies that had and had not adjusted for confounders (P = 0.11; I^2 = 60.2%), and both subgroup results indicated that quitting smoking was associated with lower risk of CVD death. We also conducted a subgroup analysis exploring the reporting of HRs versus risk ratio (RR) as the effect estimate. Three studies reported HRs, and for the other 15 studies, we used RR as approximate HRs; we found no meaningful subgroup differences (P = 0.19, I^2 = 40.5%, Analysis 1.5). Another subgroup analysis comparing studies that used biochemical validation of smoking cessation (two studies) versus those that did not (16 studies) found no evidence of subgroup differences (P = 0.92, I^2 = 0%; Analysis 1.6), and neither did an analysis splitting studies according to whether they reported the use of secondary prevention medications such as statins and beta-blockers (P = 0.56, I^2 = 0%, Analysis 1.7). Four studies reported balanced medication use or adjusted for medication, one presented unbalanced and unadjusted effect estimates, and 13 had no record of secondary medication. Finally, we compared seven studies that only included men versus 11 studies with a mixed-sex population and again found no evidence of subgroup differences (P = 0.68, I^2 = 0%, Analysis 1.8).

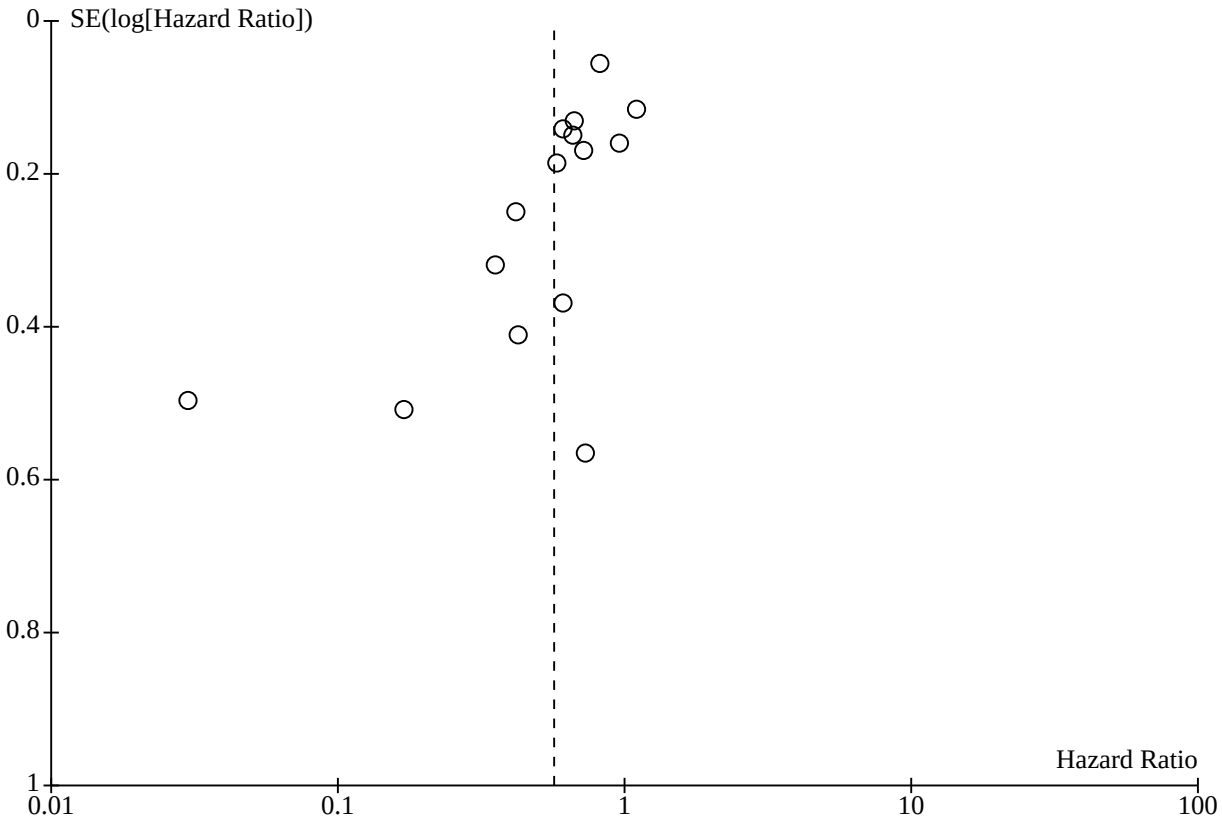
We could not run a planned subgroup analysis comparing studies shorter than two years versus studies of two years and longer, as only one study had a follow-up of less than two years (Zhu 2009). Therefore, we ran a sensitivity analysis removing Zhu 2009 and found no notable difference in the effect estimate (Analysis 1.9). Additionally, included studies did not report whether they considered nicotine replacement therapy and e-cigarette users as individuals who had stopped smoking or individuals who were still smoking, therefore, we could not conduct an analysis comparing whether there was a difference in effect due to classification of nicotine replacement therapy and e-cigarette use. Finally, we planned to run meta-regressions to assess the impact of our prespecified mediators (SMART risk score laboratory results); however, as only two studies reported total cholesterol concentration this was not possible. Biery 2020 HDL, total

cholesterol and eGFR, and Gupta 1993 reported total cholesterol. No study reported high-sensitivity CRP. A summary of the results can be found in Table 1. Additionally had any studies not clinically validated CHD diagnosis, we would have removed those studies in a sensitivity analysis. We did not run this analysis as all included studies were clinically validated.

Major adverse cardiovascular events (MACE)

Fifteen studies reported data that could be used to calculate the pooled HR for MACE. Data from 11,952 people who quit smoking and 8569 people who continued smoking provided evidence that quitting smoking was associated with a lower risk of MACE (HR 0.57, 95% CI 0.45 to 0.71; 20,521 participants; low-certainty evidence; Analysis 2.1; Figure 5). However, there was substantial heterogeneity between studies (I^2 = 84%).

Figure 5. Funnel plot of comparison 2. Main analysis: difference in change (from baseline to longest follow-up) between people who quit and people who continued smoking, outcome: 2.1 primary outcome: major adverse cardiovascular events



Sensitivity and subgroup analyses

We performed a sensitivity analysis, excluding five studies assessed at critical or serious risk of bias; this analysis did not account for the heterogeneity or change the interpretation of the effect estimate (Analysis 2.2). Two studies reported both adjusted and unadjusted estimates for MACE. When we substituted unadjusted estimates for Masoudkabir 2020 and Rallidis 2015, this did not change the outcome of our analysis (HR 0.57, 95% CI 0.45 to 0.72; I^2 = 85%; Analysis 2.3). We conducted a subgroup analysis comparing eight studies that used unadjusted estimates with six studies that reported adjusted estimates (Analysis 2.4). There was no clear evidence that effect estimates differed between studies that had and had not adjusted for confounders, and both subgroup results indicated that quitting smoking resulted in lower risk for MACE (P = 0.94; I^2 = 0%). Seven studies reported HRs, and for the other six studies, we used RR as approximate HRs. We did not find meaningful subgroup differences based on this differentiation (P = 0.63; I^2 = 0%, Analysis 2.5).

Only one study (Breitling 2011), carried out biochemical validation of smoking cessation for MACE compared with 13 that relied on self-report only, therefore, we removed Breitling 2011 and ran a sensitivity analysis rather than the planned subgroup analysis. This did not make any clinically or statistically significant difference to the overall estimate (HR 0.60, 95% CI 0.48 to 0.74; I^2 = 83%; 20,322 participants; Analysis 2.6).

Eight studies reported balanced medication use or adjusted for medication use, one presented unbalanced and unadjusted effect estimates, and five had no record of secondary medication and there was evidence of subgroup differences (P < 0.001; I^2 = 89.3%, Analysis 2.7). The unbalanced and unadjusted subgroup resulted in an HR that favoured an increased risk of MACE after quitting but confidence intervals were wide and incorporated

both benefit and harm of quitting. Both the balanced or adjusted subgroup (I^2 = 86%) and no-information subgroup (I^2 = 29%) were associated with benefits of quitting. However, this subgroup analysis should be interpreted cautiously as the unadjusted group only included one of the 14 studies.

We removed one study that only included men to run a sensitivity analysis on the 13 studies with a mixed-sex population and again found no evidence of a change in heterogeneity or in the interpretation of the pooled result (HR 0.59, 95% CI 0.47 to 0.74; I^2 = 84%; 20,091 participants; Analysis 2.8). Finally, we ran a subgroup analysis to compare studies that followed our definition of MACE compared to studies that incorporated a slightly different composite of coronary outcomes (P < 0.01; I^2 = 89.7%, Analysis 2.9). While there was evidence of subgroup differences, the results were clinically similar, both showing a reduced risk after stopping smoking.

Only one study followed participants for less than 2 years (Zhu 2009) so it was not possible to conduct the planned subgroup analysis comparing studies with less than and more than 2 year follow-up. Therefore, we ran a sensitivity analysis removing Zhu 2009 and found no notable difference in heterogeneity or effect estimate (17,662 participants; I^2 = 72% compared to I^2 = 70%); Analysis 2.10). Zhu 2009 reported an effect estimate of RR 0.61 (CI 0.30 to 1.26) with a 19-month follow-up mean, which is consistent with the studies with longer follow-up times.

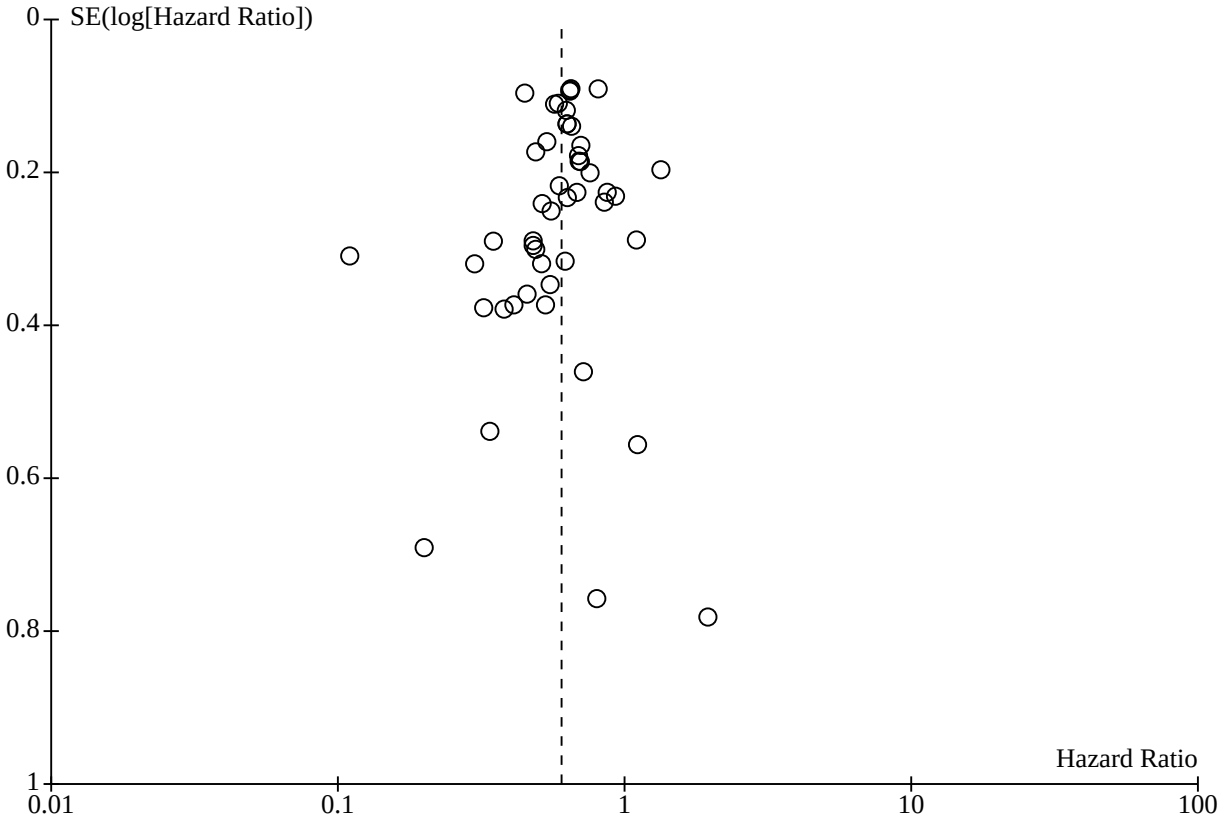
Finally, we ran a post-hoc sensitivity analysis removing Imbalzano 2018 as it was a clear outlier, demonstrating a substantially higher benefit of quitting smoking on MACE than the other studies in our analysis (Analysis 2.11). In addition to studying the impact of smoking cessation, this study also investigated the impact of having type D personality type (the tendency to experience negative emotions and to stop oneself from expressing said emotions). They noted that both type D and smoking cessation independently predicted MACE. However, as the study received a low weighting in our analysis (3.5%) there was no evidence of substantial change in heterogeneity or in the interpretation of the pooled result (HR 0.66% CI 0.56 to 0.78; I^2 = 70%; 20,290 participants).

We could not run meta-regressions using SMART risk score lab results as only Van Den Berg 2019 reported eGFR and CRP Table 1.

All-cause mortality

We included 48 studies in our meta-analysis investigating the risk of all-cause mortality, with data from 32,338 people who quit smoking and 27,016 people who continued smoking. We found that stopping smoking was associated with a lower risk of all-cause mortality (HR 0.60 95% CI 0.55 to 0.66; I^2 = 58%; 59,354 participants; Analysis 3.1; Figure 6). Three studies reported all-cause mortality outcomes in ways that meant we could not include them in the meta-analysis. Two studies (Lotan 2017; Murphy 2020), reported HR data using participants who had never smoked as the reference group; therefore, while we could extract a HR for each study, we could not calculate a 95% CI. Lotan 2017 found a decreased risk in all-cause mortality for individuals who had stopped smoking after their diagnosis (HR 0.73), and Murphy 2020 found a similar result (HR 0.68). Kievit 2009 reported that five-year survival in individuals who had quit smoking did not differ from individuals who continued to smoke; however, they did not provide the data, and we were unable to obtain them. Additionally, as we could not access the unpublished data from Toefler 1993, we used the data presented by New Reference in our meta-analysis.

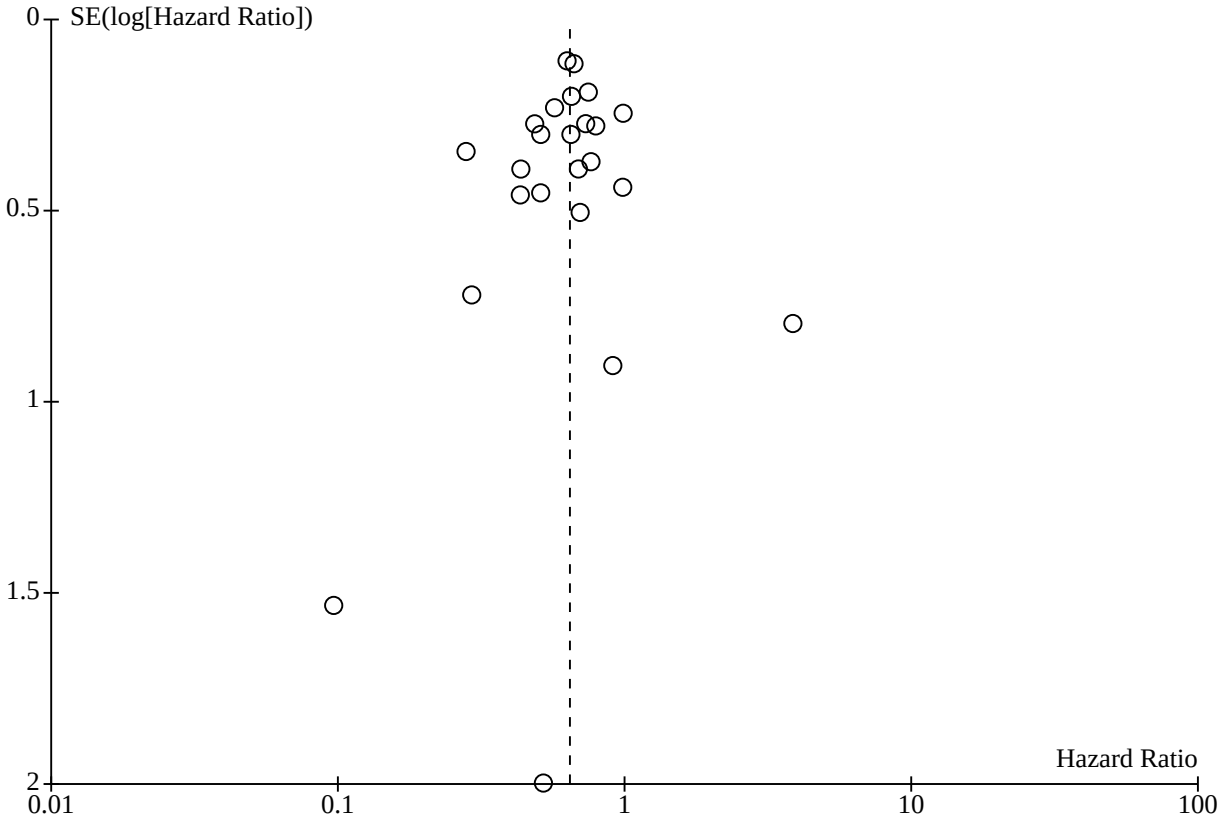
Figure 6. Funnel plot of outcome 3.1 all-cause mortality



Non-fatal myocardial infarction

Twenty-four studies included 12,192 people who stopped smoking and 11,072 people who continued smoking and reported on non-fatal myocardial infarction. Individuals who quit smoking had a lower risk of developing a second non-fatal myocardial infarction (HR 0.64 95% CI 0.58 to 0.72; I^2 = 2%; 23,264 participants; Analysis 4.1; Figure 7).

Figure 7. Funnel plot of outcome 4.1 non-fatal myocardial infarction



Non-fatal stroke

We included nine studies in our meta-analysis investigating the impact of stopping smoking on non-fatal stroke. In total, we analysed data from 6457 people who quit smoking and 4895 people who continued smoking and found that stopping smoking was associated with a lower risk of non-fatal stroke (HR 0.70 95% CI 0.53 to 0.90; I^2 = 0%; 11,352 participants; Analysis 5.1).

New-onset angina

Daly 1985 was the only included study that investigated new-onset angina. This study included 183 people who stopped smoking and 104 who continued and reported a RR of 0.52 (95% CI 0.31 to 0.87), indicating a lower risk of developing new-onset angina in individuals who stopped smoking.

Quality of life

Eight studies reported on the association between quitting and quality of life, comparing 1386 people who stopped smoking with 1796 people who continued smoking. Quitting smoking appeared to be associated with a slight increase in quality of life compared with continuing to smoke (SMD 0.12, 95% CI 0.01 to 0.24, I^2 = 48%; 3182 participants; Analysis 6.1). However, the lower boundary of the confidence interval includes the possibility of no meaningful association between quitting smoking and quality of life.

DISCUSSION

Summary of main results

We compared the change in risk for secondary CVD outcomes in people who stopped smoking with people who continued to smoke after incident CHD. Results uniformly showed decreased risk in those who quit smoking. For both of our primary outcomes, the evidence suggested that quitting smoking was associated with a third lower risk of CVD outcomes (cardiovascular death and MACE) than continuing to smoke for people with incident CHD (moderate- and low-certainty evidence respectively). Sensitivity analyses removing studies at the highest risk of bias left the results largely unchanged. Where there was evidence of subgroup differences, effect estimates differed in magnitude rather than the direction of effect. For all-cause mortality, non-fatal myocardial infarction and non-fatal stroke, we again found evidence suggesting that quitting was associated with a third lower risk compared to continued smoking. Only one study assessed the impact of smoking cessation on new-onset angina, indicating a lower risk in people who had stopped smoking. Although the pooled effect size for quality of life was deemed to be small, it suggests no harm to quality of life after stopping smoking and a possible improvement.

Overall completeness and applicability of evidence

The searches conducted in this study were broad and identified any study examining the association between smoking status and CHD. Our searches also covered trial registers to identify any ongoing or completed but unpublished registered studies comparing CVD

outcomes by smoking status. We translated all documents into English to screen them for inclusion or data extraction; therefore, we did not omit any study due to language differences.

We believe that we have investigated all essential outcomes. We included additional outcomes compared with the 2003 Cochrane Review (New Reference), including quality of life, as suggested by our public engagement work. However, despite the volume of data reviewed, it is crucial to assess whether the results from these studies apply worldwide to everyone diagnosed with CHD who smokes. Like most medical research, the great majority of studies were conducted in high-income countries, and many were conducted in Western settings. Additionally, specific population characteristics (e.g. socioeconomic status) were poorly reported. To our knowledge, there is no plausible reason why the biological reactions to smoking that lead to heart disease vary across the world. Nevertheless, cultural differences in how much people who smoke typically inhale could mean that risk estimates vary slightly from those we observed.

Quality of the evidence

All of the included studies were observational (or RCTs that we treated as observational studies), and there is potential for bias. None of our studies were assessed at a low risk of bias for all of our quality assessment domains. To investigate the potential impact of studies that we judged to be at higher risk of bias, we carried out sensitivity analyses, removing studies judged to be at higher risk from our analyses and observing the effects on results (where this was possible). In all cases, this did not affect the clinical interpretation of our results. While there remains uncertainty in the magnitude and speed of risk reduction, the evidence in this review suggests that stopping smoking reduces risk of secondary CVD events.

We used GRADE to assess the certainty of the evidence for our primary outcomes and created a summary of findings table (Summary of findings 1). We did not assess any of the included studies that contributed data to our primary outcomes (death from CVD and MACE) as low risk of bias using the ROBINS-I tool, primarily due to difficulties in controlling for the confounding factors discussed above; therefore, we downgraded our results by one level for risk of bias for both outcomes. While there was substantial statistical heterogeneity, this was primarily due to magnitude of effect estimates rather than direction of effect, therefore we did not downgrade our certainty in the evidence. Almost all studies favoured lower risk of the outcome for those who stopped smoking than those who continued. For MACE, we also downgraded the evidence because publication bias may have influenced the result. The funnel plot (Figure 5) suggested that smaller studies of lower methodological quality may be exaggerating the benefits of cessation.

In addition to the clinical significance of the effects observed, and the consistency in direction of our findings across studies and outcomes, there are plausible causal mechanisms by which smoking cessation can improve CVD outcomes. As previously mentioned, smoking cessation improves endothelial function (Johnson 2010). Endothelial dysfunction is considered an early marker for atherosclerosis (Davignon 2004), the primary underlying pathophysiological mechanism that leads to CVD. Therefore, the improvement of endothelial function can play an important secondary prevention strategy for CVD (Matsuzawa 2015). Additionally, smoking can impair platelet function, which can lead towards the first stage of clot formation (Pamukcu 2011), however, platelet function can be restored to normal levels within days of smoking cessation (Morita 2005). Despite the nature of the observational data included in this review, these arguments suggest that smoking cessation does lower the risk of CVD when compared to continuing smoking.

Potential biases in the review process

We followed the standard methods used by Cochrane Tobacco Addiction and developed our search strategy with an information specialist to maximise the sensitivity of our search. However, in some cases, included studies provided evidence on the association of change in smoking status and secondary CVD outcomes despite not being the main focus of the paper; therefore, it is possible we missed some studies with relevant data.

Potential biases may have been introduced into the analyses due to limitations of the data. As our original plan was to assess HRs, we approximated HRs by including RRs. RRs do not account for censoring or the timing of the event, unlike HRs, which may result in different effect estimates; although subgroup analyses found no evidence of such.

Additionally, as many of our pre-planned subgroup analyses only resulted in two or three studies being included in each subgroup, these were likely to be underpowered to detect a significant difference. Finally, some of our included studies presented a variety of quality-of-life measures, such as physical quality of life, mental health, and bodily pain. We had not considered this when drafting our protocol (Wu 2021), but made the post hoc decision to always use the scale that measured physical quality of life where this was the case.

Agreements and disagreements with other studies or reviews

An earlier version of this review, conducted in 2003, only investigated all-cause mortality and non-fatal myocardial infarction outcomes (Critchley 2003a; Critchley 2003b). We included more than three times as many studies in this review. However, we found similar effect estimates for the outcomes, with increased precision in our results. Our results found a 40% risk reduction (95% CI 0.55 to 0.66) compared to 36% risk reduction of all-cause mortality (CI 0.58 to 0.71) in the 2003 review. The increased precision with the inclusion of additional studies strengthens the evidence that smoking cessation improves secondary CVD outcomes. A similar reduction in incident CVD risk was found in people who stopped smoking compared to those who continued, with a greater decrease in risk the longer you stop smoking (Mons 2015). This result suggests that smoking cessation may decrease the risk for incident and secondary CVD events.

Despite the evidence that smoking cessation is an effective secondary prevention intervention, translation into medical practice is patchy. This is demonstrated by a 2016 study of nearly 8000 people in Europe who had experienced a coronary event, 26% of whom were smoking at diagnosis. Six months later, 61% of those people were still smoking. While the large majority of individuals were prescribed medications that can help reduce the risk of secondary events, such as statins, beta-blockers and ACE inhibitors, only 19% of people were advised to attend a smoking

cessation service. Of those who attended a cessation clinic, only one-fifth were offered cessation medication, such as bupropion or varenicline (Kotseva 2016). The apparent marked reduction in risk that accrues from cessation suggests that clinicians could actively assist cessation to improve the outcomes for people who smoke. However, it is essential to also recognise that clinicians may face numerous barriers when it comes to offering cessation, whether that be service structures, lack of availability or willingness of patients to take up help with smoking cessation. Therefore, this should be considered within healthcare structure, policy and funding, as well as clinician training and behaviour, to work towards providing good quality, evidence-based smoking cessation treatment as an active secondary prevention technique.

Brugts 2009 combined analysis from three large RCTs to compare the use of ACE inhibitors versus placebo on secondary CVD events. For all included outcomes risk was reduced by between approximately 11% and 20% for individuals prescribed ACE inhibitors rather than placebo. Gottlieb 1998 compared the use of different beta-blockers as secondary prevention medication and found an overall association of 40% reduction in risk for all-cause mortality. This is similar to the reduction observed in our review for all-cause mortality. Given the evidence that use of secondary prevention medications may be lower in people who currently smoke compared to those who stop smoking (Yusuf 2011), it is both essential to consider smoking cessation as an active intervention, as well as to conduct research that investigates the impact of combined interventions (smoking cessation and secondary prevention medication).

AUTHORS' CONCLUSIONS

Implications for practice

- People with heart disease who smoke, and their clinicians, can be reassured that stopping smoking is associated with a decreased risk of secondary cardiovascular disease (CVD) outcomes, including CVD, major adverse cardiovascular events (MACE), all-cause mortality, non-fatal myocardial infarction, non-fatal stroke and new-onset angina.
- People with heart disease who smoke, and their clinicians, can be reassured that smoking cessation will not worsen, and may improve quality of life.

Implications for research

- Further studies that examine the impact of smoking cessation while controlling for secondary CVD prevention medication and severity of initial coronary heart disease (CHD) event, as well as other listed confounding factors, would strengthen the evidence on the impact of smoking cessation.
- Research investigating the severity of the initial CHD event, as well as intensity of smoking prior to cessation, may strengthen the evidence on magnitude and speed of smoking cessation impact.
- Studies should also consider investigating the impact of combined benefit of smoking cessation and secondary prevention medication.
- Future studies should also stratify results by sex, where feasible, as the majority of studies in this review were predominately focused on men.
- Additional, larger studies that examine the impact of smoking cessation on CVD would also strengthen the evidence as the smaller studies included in the review may be exaggerating the benefits of cessation.
- A systematic review of intervention studies supporting smoking cessation in people with established cardiac disease would strengthen the evidence of causality. Individual trials are likely to be too small to show benefits, but pooling can improve statistical power to reveal the health impact.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aberg 1983

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Sweden
Participants	**Number of participants:** 1306; number analysed: 983
	Specific population category: men only
	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): not reported (SD not reported); sex (% female): 0 (0)
Interventions	**Definition of smoking cessation used:** “stopped smoking” unclear definition
	Time point of smoking cessation categorisation: 3 months after MI

Aberg 1983 *(Continued)*

	Smoking cessation intervention(s) used (if any): information brochures given outlining harm of smoking on CVD
	Measure of biovalidation (if any): carboxyhaemoglobin was tested in subset of population
Outcomes	**Outcome category:** CVD death, all-cause mortality and non-fatal MI
	Follow-up time: 126 months (mean)
Notes	Funding source: supported by grants from the Swedish Medical Research Council and the Swedish Tobacco Company
	Author COI: none reported

Alvarez 2011

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Spain
Participants	**Number of participants:** 1182; number analysed: 475
	Specific population category: none
	Definition of CHD: diagnosis of ACS
	Sample characteristics (at baseline): age (mean): 60.1 years (SD 1.1); sex (% female): 101 (8.5)
Interventions	**Definition of smoking cessation used:** self-report of current smoking status
	Time point of smoking cessation categorisation: 4 months
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** non-fatal stroke and non-fatal MI
	Follow-up time: 14 months (mean)
Notes	Funding source: no specific grant
	Author COI: none reported
	Study/trial registry: FRENA Registry

Baughman 1982

Study characteristics	
Methods	**Study design:** secondary analysis of RCT
	Country: USA
Participants	**Number of participants:** 138; number analysed: 77

Baughman 1982 *(Continued)*

	Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 65.6 years (SD not reported); sex (% female): 34 (38.2)
Interventions	**Definition of smoking cessation used:** "stopped smoking" unclear definition **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 99 months (mean)
Notes	Funding source: Public Health Service grant HL17665 Author COI: none reported

Bednarzewski 1984

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Poland
Participants	**Number of participants:** 1187; number analysed: 1010 Specific population category: men only Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age range: 22-84 years; sex (% female): 0 (0)
Interventions	**Definition of smoking cessation used:** self-report of current smoking status **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 42 months (mean)
Notes	Funding source: none reported Author COI: none reported

Biery 2020

Study characteristics	
Methods	**Study design:** retrospective cohort **Country:** USA
Participants	**Number of participants:** 618; number analysed: 618 Specific population category: none Definition of CHD: clinical validation of MI caused by atherothrombotic coronary artery disease **Sample characteristics** (at baseline): age (mean): 44 years (SD 5); sex (% female): 115 (18.6)
Interventions	**Definition of smoking cessation used:** sustained abstinence from inhaled tobacco for at least 3 months **Time point of smoking cessation categorisation:** 3 months before 1-year follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death and all-cause mortality **Follow-up time:** 122 months (median)
Notes	Funding source: none reported Author COI: none disclosed Study/trial registry: Partners YOUNG-MI

Boggon 2014

Study characteristics	
Methods	**Study design:** retrospective cohort **Country:** USA
Participants	**Number of participants:** 965; number analysed: 965 Specific population category: none Definition of CHD: hospitalisation for troponin-positive ACS **Sample characteristics** (at baseline): age ≥ 30 years; sex (% female): 275 (29.5)
Interventions	**Definition of smoking cessation used:** smoking status recorded in GPs' database **Time point of smoking cessation categorisation:** 3 months after diagnosis **Smoking cessation intervention(s) used (if any):** behavioural and pharmacological support was recorded if provided to patient (76.7% did not receive either support 3 months after diagnosis) **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death, MACE, all-cause mortality, non-fatal stroke and non-fatal MI

Boggon 2014 *(Continued)*

	Follow-up time: from date of hospital discharge to death, transfer out of the general practice, or the last data collection date
Notes	Funding source: Pfizer Author COI: none reported

Breitling 2011

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Germany
Participants	**Number of participants:** 1206; number analysed: 199 Specific population category: none Definition of CHD: clinical validation of MI or presence of coronary artery intervention **Sample characteristics** (at baseline): age (mean): 59 (SD 8); sex (% female): 185 (15.3)
Interventions	**Definition of smoking cessation used:** self-reported **Time point of smoking cessation categorisation:** blood samples for smoking status validation were taken at rehabilitation discharge and 1 and 3 years later by the participants' GP **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** cotinine measurements
Outcomes	**Outcome category:** MACE **Follow-up time:** 8.1 years (median)
Notes	Funding source: grant provided by Federal Ministry of Education and Research, the Pitzer Foundation and from the German Research Foundation's priority programme Author COI: the funding agencies had no role in study design, conduct, analysis, or publication Study/trial registry: KAROLA Notes: study included individuals who had never smoked and stopped smoking before the CVD event, therefore were excluded from analysis.

Buchanan 2015

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** USA
Participants	**Number of participants:** 1481; number analysed: 1481 Specific population category: none

Buchanan 2015 *(Continued)*

	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): 54.6 (SD 9.8); sex (% female): 470 (31.7)
Interventions	**Definition of smoking cessation used:** self-report of stopped smoking in past year
	Time point of smoking cessation categorisation: 1 year after baseline
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** QoL - Seattle Angina Questionnaire
	Follow-up time: 12 months (mean)
Notes	Funding source: National Heart Lung and Blood Institute
	Author COI: Dr Spertus owns the copyright for the Seattle Angina Questionnaire
	Study/trial registry: Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER)

Burr 1992

Study characteristics	
Methods	**Study design:** secondary analysis of RCT
	Country: UK
Participants	**Number of participants:** 1186; number analysed: 1186
	Specific population category: non-diabetic men
	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): 55.2 (SD not reported); sex (% female): 0 (0)
Interventions	**Definition of smoking cessation used:** unclear definition, reported current smoking habits
	Time point of smoking cessation categorisation: 6 months after MI diagnosis
	Smoking cessation intervention(s) used (if any): participants were “advised to stop smoking”
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: 24 months (mean)
Notes	Funding source: Welsh Scheme for the Development of Health and Social Research and the Health Promotion Research Trust
	Author COI: none reported
	Study/trial registry: Diet and reinfarction trial

Cavender 1992

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** USA and Canada
Participants	**Number of participants:** 312; number analysed: 284 Specific population category: none Definition of CHD: angiographically proved coronary artery disease **Sample characteristics** (at baseline): age (mean): 49 (SD not reported); sex (% female): 31 (9.9)
Interventions	**Definition of smoking cessation used: "**stopped smoking" at follow-up **Time point of smoking cessation categorisation:** 1-month follow-up evaluation **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 10 years (mean)
Notes	Funding source: National Heart, Lung, and Blood Institute Author COI: none reported Study/trial registry: Coronary Artery Surgery Study (CASS)

Cha 2018

Study characteristics	
Methods	**Study design:** retrospective cohort **Country:** South Korea
Participants	**Number of participants:** 4180; number analysed: 4180 Specific population category: patients who participated in a regular health check-up before and after AMI and aged between 40-80, includes non-smokers Definition of CHD: defined using ICD-10-CM codes or surgical procedures for MI **Sample characteristics** (at baseline): age (mean): 62.8 (SE 9); sex (% female): 3729 (entire study population = 13,452) (27.7)
Interventions	**Definition of smoking cessation used:** asked if currently smoking **Time point of smoking cessation categorisation:** 1.5 years after MI **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality

Cha 2018 *(Continued)*

	Follow-up time: 54 months (mean)
Notes	Funding source: Seoul National University Bundany Hospital Research Fund Author COI: none reported

Chow 2010

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** 41 countries – view study for details
Participants	**Number of participants:** 4324; number analysed: 4324 Specific population category: none Definition of CHD: clinical diagnosis of unstable angina or MI without ST-segment elevation **Sample characteristics** (at baseline): age (mean): 58.9 (SD 10.6); sex (% female): 951 (22)
Interventions	**Definition of smoking cessation used:** asked if currently smoking **Time point of smoking cessation categorisation:** 30, 90 and 180 days after entering trial **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality, non-fatal stroke and non-fatal MI **Follow-up time:** 6 months (mean)
Notes	Funding source: the study was funded by Sanofi-Aventis, Organon, and GlaxoSmithKline Author COI: the funding sources had no involvement in the analyses presented in the study Study/trial registry: Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)

Colivicchi 2011

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Italy
Participants	**Number of participants:** 1294; number analysed: 1294 Specific population category: none Definition of CHD: clinical validation of ACS **Sample characteristics** (at baseline): age (mean): 59.7 (SD 12.3); sex (% female): 276 (21.3)
Interventions	**Definition of smoking cessation used:** self-report of continuous abstinence

Colivicchi 2011 *(Continued)*

	Time point of smoking cessation categorisation: 1, 6, and 12 months after discharge **Smoking cessation intervention(s) used (if any):** all included participants received a brief in-hospital smoking cessation intervention delivered by either physicians or trained nurses that consisted of repeated counselling sessions lasting 5-20 min during the index admission. No pharmacological support was used. **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 12 months (median)
Notes	Funding source: Cardiovascular Department of the "San Filippo Neri Hospital" Author COI: none reported

Cordero 2012

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Spain
Participants	**Number of participants:** 365; number analysed: 365 Specific population category: none Definition of CHD: clinical diagnosis of ACS **Sample characteristics** (at baseline): age (mean): 56 (SD 10.5); sex (% female): 57 (15.6)
Interventions	**Definition of smoking cessation used:** use of bio-validation **Time point of smoking cessation categorisation:** 3 months after hospital discharge **Smoking cessation intervention(s) used (if any):** 110 smokers (30.6%) received some type of smoking cessation support - some were referred to specialised unit and others were prescribed varenicline, nicotine patches, nicotine gum and bupropion **Measure of biovalidation (if any):** exhaled carbon monoxide
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 12 months (median)
Notes	Funding source: Pfizer Author COI: none reported Study/trial registry: The smoking and risk of cardiovascular complications in patients with acute coronary syndrome-TABARCA

Daly 1985

Study characteristics	

Daly 1985 *(Continued)*

Methods	**Study design:** longitudinal cohort **Country:** Ireland
Participants	**Number of participants:** 408; number analysed: 384 Specific population category: men < 60 years Definition of CHD: clinical validation of MI or unstable angina **Sample characteristics** (at baseline): age (mean): not reported; sex (% female): 0 (0)
Interventions	**Definition of smoking cessation used:** ceased smoking for at least 3 months when asked in interview **Time point of smoking cessation categorisation:** 2 years after diagnosis **Smoking cessation intervention(s) used (if any):** rehabilitation programme, which included anti-smoking advice given at hospital and follow-up **Measure of biovalidation (if any):** measured in subsample
Outcomes	**Outcome category:** CVD death, all-cause mortality and new-onset angina **Follow-up time:** 99 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

De Boer 2013

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** the Netherlands
Participants	**Number of participants:** 806; number analysed: 497 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 54.3 (SD 8.9); sex (% female): 69 (13.9)
Interventions	**Definition of smoking cessation used:** self-report at currently not smoking **Time point of smoking cessation categorisation:** 1 year after surgery **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 19.5 years (median)
Notes	Funding source: none reported

De Boer 2013 *(Continued)*

	Author COI: the authors have no COI to disclose. Study/trial registry: none reported

Gerber 2009

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Israel
Participants	**Number of participants:** 798; number analysed: 798 Specific population category: none Definition of CHD: clinical validation of AMI **Sample characteristics** (at baseline): age (mean): 52 (SD 8); sex (% female): 104 (13.4)
Interventions	**Definition of smoking cessation used:** self-reported as non-smoker **Time point of smoking cessation categorisation:** 3-6 months, 1-2 years, 5 years and 10-13 years after diagnosis **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 13.2 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: the Israel Study of First Acute Myocardial Infarction

Grand 1992

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** France
Participants	**Number of participants:** 208; number analysed: 181 Specific population category: < 60 years Definition of CHD: clinical validation of acute MI **Sample characteristics** (at baseline): age (mean): 51 (SD not reported); sex (% female): 16 (7.7)
Interventions	**Definition of smoking cessation used:** self-report current tobacco amount smoked **Time point of smoking cessation categorisation:** within 1st year

Grand 1992 *(Continued)*

	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal stroke
	Follow-up time: 115 months (mean)
Notes	Funding source: not reported
	Author COI: none reported
	Study/trial registry: none reported
	Notes: study grouped people who completely quit with those who reduced to at least 50% consumption

Greenwood 1995

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: UK
Participants	**Number of participants:** 561; number analysed: 532
	Specific population category: none
	Definition of CHD: clinically suspected acute MI
	Sample characteristics (at baseline): age (mean): not reported; sex (% female): not reported
Interventions	**Definition of smoking cessation used:** unclear definition, “stopped smoking”
	Time point of smoking cessation categorisation: 1 month
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: 5 years (mean)
Notes	Funding source: the study was supported by a grant from the British Heart Foundation
	Author COI: none reported
	Study/trial registry: AngloScandinavian study of early thrombolysis (ASSET)

Gupta 1993

Study characteristics	
Methods	**Study design:** longitudinal cohort

Gupta 1993 *(Continued)*

	Country: India
Participants	**Number of participants:** 225; number analysed: 225 Specific population category: none Definition of CHD: clinical validation of coronary artery disease **Sample characteristics** (at baseline): age (mean): not reported (SD not reported); sex (% female): 13 (5.8)
Interventions	**Definition of smoking cessation used:** unclear definition, "given up smoking since time of diagnosis" **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD mortality and all-cause mortality **Follow-up time:** continued smoking 8.21 years (median), stopped smoking 7.39 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported Notes: patients who had received a coronary bypass surgery were excluded

Haglid 1997

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Sweden
Participants	**Number of participants:** 275; number analysed: 275 Specific population category: none Definition of CHD: surgical validation, underwent coronary bypass grafting **Sample characteristics** (at baseline): age (mean): 55.7 (SD not reported); sex (% female): 52 (19)
Interventions	**Definition of smoking cessation used:** self-report smoking habit **Time point of smoking cessation categorisation:** 3 months after entry **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 2 years (mean)
Notes	Funding source: none reported

Haglid 1997 *(Continued)*

	Author COI: none reported
	Study/trial registry: none reported

Hallstrom 1986

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: USA
Participants	**Number of participants:** 331; number analysed: 310
	Specific population category: none
	Definition of CHD: discharged from hospital due to out-of-hospital sudden cardiac arrest
	Sample characteristics (at baseline): age (mean): 56 (SD not reported); sex (% female): 61 (20)
Interventions	**Definition of smoking cessation used:** self-report smoking habit
	Time point of smoking cessation categorisation: 3 months after entry
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: 47.5 months (mean)
Notes	Funding source: supported in part by a grant from the National Center for Health Services Research and a grant from the Medic One-Emergency Medical Services Foundation
	Author COI: none reported
	Study/trial registry: none reported
	Notes: study contained individuals without prior diagnosis of CHD (25% of population) before cardiac arrest

Hammal 2014

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Canada
Participants	**Number of participants:** 2584; number analysed: 2583
	Specific population category: none
	Definition of CHD: validation through coronary angiography
	Sample characteristics (at baseline): age (mean): 58.7 (SD 9.8); sex (% female): 579 (22.4)

Hammal 2014 *(Continued)*

Interventions	**Definition of smoking cessation used:** self-report of stopping smoking **Time point of smoking cessation categorisation:** 1 year **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 42 months (mean)
Notes	Funding source: funded internally by the Department of Anaesthesiology and Pain Medicine, University of Alberta Author COI: the authors declare that they have no competing interests. Study/trial registry: APPROACH registry

Hasdai 1997

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** USA
Participants	**Number of participants:** 6424; number analysed: 5437 Specific population category: none Definition of CHD: surgical validation, underwent percutaneous coronary revascularisation **Sample characteristics** (at baseline): age (mean): not reported; sex (% female): 283 (24)
Interventions	**Definition of smoking cessation used:** self-report of stopping smoking **Time point of smoking cessation categorisation:** 6 months **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD mortality and all-cause mortality **Follow-up time:** 4.5 years (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: Mayo Clinic Registry

Hedback 1993

Study characteristics	
Methods	**Study design:** longitudinal cohort

Hedback 1993 *(Continued)*

	Country: Sweden
Participants	**Number of participants:** 157; number analysed: 157 Specific population category: none Definition of CHD: clinical validation of AMI **Sample characteristics** (at baseline): age (mean): 56.09 (SD 6.6); sex (% female): 17 (10.8)
Interventions	**Definition of smoking cessation used:** smoking habits at 1 year post-MI were used – definition unclear **Time point of smoking cessation categorisation:** 1 year post-MI **Smoking cessation intervention(s) used (if any):** smoking counselling was offered to intervention group **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 120 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported Notes: unclear grouping of 'stopped smoking' individuals, likely included people who stopped smoking before MI diagnosis. Study investigated impact of a rehabilitation programme for individuals with MI, however more than half of both intervention and reference group were smoking before and during MI.

Herlitz 1995

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Sweden
Participants	**Number of participants:** 302; number analysed: 217 Specific population category: none Definition of CHD: clinical validation of AMI **Sample characteristics** (at baseline): age (mean): 64 (33-94 range); sex (% female): 68 (22.5)
Interventions	**Definition of smoking cessation used:** self-reported having quit smoking **Time point of smoking cessation categorisation:** 1 year post-MI **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality, non-fatal stroke and non-fatal MI **Follow-up time:** 60 months (mean)

Herlitz 1995 *(Continued)*

Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported Notes: 23 individuals were excluded from study due to missing smoking status at follow up

Hickey 1983

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Ireland
Participants	**Number of participants:** 664; number analysed: 638 Specific population category: men only Definition of CHD: clinical validation of AMI or unstable angina **Sample characteristics** (at baseline): age (mean): 51 (26-59 range); sex (% female): 0 (0)
Interventions	**Definition of smoking cessation used:** self-reported having quit smoking **Time point of smoking cessation categorisation:** status recorded at 3-monthly intervals over the 1st year after discharge from hospital and thereafter annually **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 60 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported Notes: included individuals who were non-smokers before the coronary event as stopped smoking after event. 38% of non-smoking individuals at 4 years after event were non-smoking at diagnosis

Imbalzano 2018

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Italy
Participants	**Number of participants:** 231; number analysed: 231 Specific population category: none

Imbalzano 2018 *(Continued)*

	Definition of CHD: surgical validation, underwent immediate coronary revascularisation procedures **Sample characteristics** (at baseline): age (mean): 63 (11.1 SD); sex (% female): 144 (62)
Interventions	**Definition of smoking cessation used:** stopped smoking and did not start again during observation period **Time point of smoking cessation categorisation:** classified by end of observation period if still non smoking **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE **Follow-up time:** 42 months (mean)
Notes	Funding source: none reported Author COI: none declared Study/trial registry: none reported Notes: study also investigated individuals with type D personality, found individuals with type D were also more likely to have secondary MACE events

Johansson 1985

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Sweden
Participants	**Number of participants:** 161; number analysed: 156 Specific population category: women only Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (range): ≤ 44-66; sex (% female): 156 (100)
Interventions	**Definition of smoking cessation used:** stopped smoking after MI **Time point of smoking cessation categorisation:** 3 months after MI **Smoking cessation intervention(s) used (if any):** all participants were informed of the relationship between smoking and CHD, and advised to stop smoking. **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 12 years max
Notes	Funding source: supported by grants from the Swedish National Association against Heart and Chest Diseases and from the Medical Society of Goteborg Author COI: none reported

Johansson 1985 *(Continued)*

	Study/trial registry: none reported

Kievit 2009

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** the Netherlands
Participants	**Number of participants:** 317; number analysed: 317 Specific population category: none Definition of CHD: clinical validation of acute ST-elevation MI **Sample characteristics** (at baseline): age (mean): 54 (9 SD); sex (% female): 57 (18)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 60 months (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: Antithrombotics in the prevention of reocclusion in coronary thrombolysis trials Notes: study investigated whether smoking cessation had an impact on 5-year infarct-free survival however data were not shown in paper and were non-significant. We attempted to contact the study authors.

Leung 2008

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** USA, Canada, Germany, Spain, Italy, Turkey, Brazil and Argentina
Participants	**Number of participants:** 2406; number analysed: 2243 Specific population category: none Definition of CHD: clinical validation of non-ST elevation-ACS **Sample characteristics** (at baseline): age (mean): 61 (52-67 range); sex (% female): 628 (26.1)
Interventions	**Definition of smoking cessation used:** self-report of smoking status

Leung 2008 *(Continued)*

	Time point of smoking cessation categorisation: 30 days after entry
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI
	Follow-up time: 1 year (median)
Notes	Funding source: the SYNERGY trial was funded by Sanofi-Aventis
	Author COI: none reported
	Study/trial registry: SYNERGY trial

Liu 2013

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: China
Participants	**Number of participants:** 656; number analysed: 430
	Specific population category: men only
	Definition of CHD: surgical validation, underwent PCI
	Sample characteristics (at baseline): age (mean): 57 (11.63 SD); sex (% female): 0
Interventions	**Definition of smoking cessation used:** self-report of smoking status
	Time point of smoking cessation categorisation: unclear
	Smoking cessation intervention(s) used (if any): "The Ask, Advise, Assess, Assist, and Arrange" algorithm (the 5 A's framework) for smoking cessation was used
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** CVD mortality, MACE, all-cause mortality, non-fatal stroke and non-fatal MI
	Follow-up time: 27 months (median)
Notes	Funding source: none reported
	Author COI: none declared
	Study/trial registry: none reported

Lotan 2017

Study characteristics	
Methods	**Study design:** longitudinal cohort

Lotan 2017 *(Continued)*

	Country: Israel
Participants	**Number of participants:** 787; number analysed: 787
	Specific population category: none
	Definition of CHD: clinical validation of AMI
	Sample characteristics (at baseline): age (mean): 51.4 (8.3 SD); sex (% female): 100 (12.7)
Interventions	**Definition of smoking cessation used:** self-report of smoking status
	Time point of smoking cessation categorisation: 3-6 months after index hospitalisation
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: 21 years (median)
Notes	Funding source: no financial support was received
	Author COI: none declared
	Study/trial registry: Israel Study of First AMI
	Notes: study also investigated incidence of cancer

Masoudkabir 2020

Study characteristics	
Methods	**Study design:** retrospective cohort analysis
	Country: Iran
Participants	**Number of participants:** 9173; number analysed: 8990
	Specific population category: none
	Definition of CHD: surgical validation, underwent coronary bypass grafting
	Sample characteristics (at baseline): age (mean): 58.6 (9.3 SD); sex (% female): 422 (4.6)
Interventions	**Definition of smoking cessation used:** self-report of persistent abstinence from smoking after surgery
	Time point of smoking cessation categorisation: 1, 6 and 12 months after surgery
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** MACE and all-cause mortality
	Follow-up time: 60 months (median)
Notes	Funding source: financial support from the research council of Tehran University of Medical Sciences and Health Services

Masoudkabir 2020 *(Continued)*

	Author COI: none declared
	Study/trial registry: none
	Notes: included cerebrovascular events as part of MACE

Mulcahy 1982

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Greece
Participants	**Number of participants:** 665; number analysed: 663
	Specific population category: men < 60 years
	Definition of CHD: clinical validation of unstable angina or MI
	Sample characteristics (at baseline): age (mean): 51.8 (SD not reported); sex (% female): 0
Interventions	**Definition of smoking cessation used:** self-report stopping smoking
	Time point of smoking cessation categorisation: at least 3 months before the last follow-up or death
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** CVD death and MACE
	Follow-up time: 5.6 years (mean)
Notes	Funding source: none reported
	Author COI: none declared
	Study/trial registry: none

Murphy 2020

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Australia
Participants	**Number of participants:** 7376; number analysed: 7376
	Specific population category: none
	Definition of CHD: surgical validation, underwent PCI
	Sample characteristics (at baseline): age (mean): not reported; sex (% female): 6479 (23)
Interventions	**Definition of smoking cessation used:** self-report as recently quit smoking

Murphy 2020 *(Continued)*

	Time point of smoking cessation categorisation: not reported
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: not reported
Notes	Funding source: none reported
	Author COI: none declared
	Study/trial registry: none
	Notes: conference abstract

Nakatani 2007

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Japan
Participants	**Number of participants:** 1820; number analysed: 1820
	Specific population category: individuals with or without metabolic syndrome
	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): 64.7 (11.4 SD); sex (% female): 925/3858 (24) total population including those who never smoked
Interventions	**Definition of smoking cessation used:** self-report as quit smoking
	Time point of smoking cessation categorisation: 3 months after hospital discharge
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** MACE
	Follow-up time: 725 days (median)
Notes	Funding source: grant from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan, and by a research grant from the Japan Arteriosclerosis Prevention Fund, Tokyo, Japan
	Author COI: none declared
	Study/trial registry: Osaka Acute Coronary Insufficiency Study (OACIS)

Papathanasiou 2007

Study characteristics

Papathanasiou 2007 *(Continued)*

Methods	**Study design:** longitudinal cohort **Country:** Greece
Participants	**Number of participants:** 1027; number analysed: 640 Specific population category: none Definition of CHD: surgical validation, underwent coronary artery bypass grafting **Sample characteristics** (at baseline): age (mean): 57.3 (10.3 SD); sex (% female) 50/1027 (4)
Interventions	**Definition of smoking cessation used:** self-report as quit smoking **Time point of smoking cessation categorisation:** not reported, sometime after surgery **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death and MACE **Follow-up time:** 5.17 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Perkins 1985

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** UK
Participants	**Number of participants:** 119; number analysed: 119 Specific population category: none Definition of CHD: electrocardiogram validation of definite or probable MI **Sample characteristics** (at baseline): age (mean): 59.2 years for men (range 35-79 years) and 60.3 years for women (range 40-77 years); sex (% female) 29 (24.4)
Interventions	**Definition of smoking cessation used:** people who remained as a non-smoker after MI were defined as stopped smoking **Time point of smoking cessation categorisation:** 3 and 12 months after MI **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 60 months (mean)

Perkins 1985 *(Continued)*

Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Piuhola 2019

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Finland
Participants	**Number of participants:** 176; number analysed: 176 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 65 (11); sex (% female) 239/767 (31)
Interventions	**Definition of smoking cessation used:** quit smoking during 3-year follow-up **Time point of smoking cessation categorisation:** during 3-year follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE **Follow-up time:** 34.53 months (median)
Notes	Funding source: Professor Junttila received funding from Finnish Foundation for Cardiovascular Research and Sigrid Juselius Foundation Author COI: none disclosed Study/trial registry: none reported

Qi 2014

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** USA, Canada, Pakistan, Iran, Tunisia and India
Participants	**Number of participants:** 225; number analysed: 225 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 53.6 (10.2); sex (% female) 25 (11)
Interventions	**Definition of smoking cessation used:** point prevalence smoking status

Qi 2014 *(Continued)*

	Time point of smoking cessation categorisation: 12 months **Smoking cessation intervention(s) used (if any):** all participants received standardised non-pharmacologic smoking cessation intervention; half of the participants received bupropion, the other received a placebo **Measure of biovalidation (if any):** biochemically validated by an exhaled carbon monoxide level of ≤10 ppm during all clinic visits
Outcomes	**Outcome category:** QoL - EuroQoL-5D **Follow-up time:** 12 months (mean)
Notes	Funding source: the trial was funded by the Canadian Institutes of Health Research and the Heart and Stroke Foundation of Quebec. Author COI: none disclosed Study/trial registry: ZESCA

Quist-Paulsen 2006

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** Norway
Participants	**Number of participants:** 240; number analysed: 218 Specific population category: none Definition of CHD: admitted to hospital for acute MI, unstable angina or recent coronary bypass **Sample characteristics** (at baseline): age (mean): 56.5 (9); sex (% female) 45 (20.6)
Interventions	**Definition of smoking cessation used:** self-report and low nicotine metabolite concentration in urine **Time point of smoking cessation categorisation:** 12 months **Smoking cessation intervention(s) used (if any):** a smoking cessation programme initiated in the hospital and delivered by cardiac nurses was provided to half the participants, the other half received usual care. The programme was based on a booklet produced for the study, and focused on fear arousal and prevention of relapse. **Measure of biovalidation (if any):** nicotine metabolite concentration in urine
Outcomes	**Outcome category:** QoL - The Cardiac Arrhythmia Suppression Trial (CAST) quality of life scale **Follow-up time:** 12 months (mean)
Notes	Funding source: financial support provided by Vest-Agder Council for Public Health, the charity ''Sykehuset i vaare hender'' and Sørlandet Hospital HF Author COI: none reported Study/trial registry: none reported

Rallidis 2008

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Greece
Participants	**Number of participants:** 147; number analysed: 135 Specific population category: < 35 years at diagnosis Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 32.1 (3.5); sex (% female) 20 (14.8)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 6-month intervals **Smoking cessation intervention(s) used (if any):** before discharge all participants had 5–10-min of smoking cessation counselling by the attendant cardiologist that was repeated when they were seen at 6-month intervals during follow-up **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE **Follow-up time:** 3.8 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Rallidis 2015

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Greece
Participants	**Number of participants:** 257; number analysed: 237 Specific population category: < 35 years at diagnosis Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 32.2 (3.7); sex (% female) 34 (14.3)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 12-month intervals **Smoking cessation intervention(s) used (if any):** before discharge all participants had 5–10-min of smoking cessation counselling by the attendant cardiologist **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE

Rallidis 2015 *(Continued)*

	Follow-up time: 9.1 years (median)
Notes	Funding source: no extramural funding was used to support this work Author COI: none reported Study/trial registry: none reported

Rea 2002

Study characteristics	
Methods	**Study design:** retrospective cohort **Country:** USA
Participants	**Number of participants:** 808; number analysed: 808 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age: 60 (approx); sex (% female) 325 (40.8)
Interventions	**Definition of smoking cessation used:** based on inpatient smoking records before and after MI **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE **Follow-up time:** 36 months (median)
Notes	Funding source: grants from National Heart, Lung, and Blood Institute, Bethesda, Maryland Author COI: none reported Study/trial registry: none reported

Ronnevik 1985

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** Norway
Participants	**Number of participants:** 919; number analysed: 919 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): not reported; sex (% female) 400 (21.2)

Ronnevik 1985 *(Continued)*

Interventions	**Definition of smoking cessation used:** self-report of smoking status during interview **Time point of smoking cessation categorisation:** after MI for ≥ 1 month **Smoking cessation intervention(s) used (if any):** smokers were given individual advice on the relation of continued smoking and their heart disease and were encouraged to stop **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 17.3 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Salonen 1980

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Finland
Participants	**Number of participants:** 523; number analysed: 523 Specific population category: men only Definition of CHD: registered in community MI register - classified as "definite" or "possible" AMI **Sample characteristics** (at baseline): age (mean): not reported, < 65 years; sex (% female) 0
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 6 months after entry **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD mortality and all-cause mortality **Follow-up time:** 3 years max
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Sato 1992

Study characteristics	
Methods	**Study design:** longitudinal cohort

Sato 1992 *(Continued)*

	Country: Japan
Participants	**Number of participants:** 90; number analysed: 87 Specific population category: men only Definition of CHD: history of MI **Sample characteristics** (at baseline): age (mean): 50 (10 SD); sex (% female) 0
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** at entry into follow-up study and 3 years **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD mortality, all-cause mortality and non-fatal MI **Follow-up time:** 18 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Shah 2010

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** USA and Canada
Participants	**Number of participants:** 924; number analysed: 731 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 54.4 (10.5 SD); sex (% female) 0
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** smoking status was assessed at randomisation, 2 weeks after randomisation, every 3 months after randomisation for the 1st year, and every 4 months up to 5 years after randomisation **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE, all-cause mortality, non-fatal stroke and non-fatal MI **Follow-up time:** 42 months (median)
Notes	Funding source: none reported Author COI: none reported

Shah 2010 *(Continued)*

	Study/trial registry: the Survival And Ventricular Enlargement (SAVE) trial

Snaterse 2015

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** the Netherlands
Participants	**Number of participants:** 324; number analysed: 324 Specific population category: none Definition of CHD: clinical diagnosis of ACS **Sample characteristics** (at baseline): age reported in range with majority in 50-59 category; sex (% female) 72 (22)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 1-year follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** QoL - MacNew Heart Disease Health-related Quality of Life Questionnaire **Follow-up time:** 12 months
Notes	Funding source: the RESPONSE trial was sponsored by an unrestricted grant from AstraZeneca Author COI: none reported Study/trial registry: RESPONSE Trial

Sochor 2015

Study characteristics	
Methods	**Study design:** retrospective cohort **Country:** USA
Participants	**Number of participants:** 492; number analysed: 492 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 55.8 (10.7 SD); sex (% female) 132 (27)
Interventions	**Definition of smoking cessation used:** patient records of smoking status **Time point of smoking cessation categorisation:** 6 months after PCI **Smoking cessation intervention(s) used (if any):** none reported

Sochor 2015 *(Continued)*

	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 5.8 years (median)
Notes	Funding source: supported by the European Regional Development Fund Author COI: none disclosed Study/trial registry: none reported

Sparrow 1978

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** USA
Participants	**Number of participants:** 458; number analysed: 202 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 57 for persistent smoking and 55 for stopped smoking; sex (% female) 130/458 (28)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** unclear, "systematically obtained" after MI **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 72 months (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: the Framingham Study

Sun 2011

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** China
Participants	**Number of participants:** 1441; number analysed: 1441 Specific population category: none

Sun 2011 *(Continued)*

	Definition of CHD: surgical validation, underwent coronary artery bypass surgery
	Sample characteristics (at baseline): age (mean): 59 (8.9); sex (% female) 68 (4.7)
Interventions	**Definition of smoking cessation used:** self-report of smoking status after MI
	Time point of smoking cessation categorisation: 2-year follow-up
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** CVD mortality, MACE, all-cause mortality, non-fatal stroke and non-fatal MI
	Follow-up time: 5 years (mean)
Notes	Funding source: none reported
	Author COI: none reported
	Study/trial registry: none reported

Taira 2000

Study characteristics	
Methods	**Study design:** secondary analysis of RCT
	Country: USA
Participants	**Number of participants:** 442; number analysed: 442
	Specific population category: none
	Definition of CHD: surgical validation, underwent PCI
	Sample characteristics (at baseline): age (mean): 55 (9 SD) for persistent-smoking group and 57 (10) for stop-smoking group; sex (% female) 110 (24.9)
Interventions	**Definition of smoking cessation used:** self-report of smoking status
	Time point of smoking cessation categorisation: 6- and 12-month follow-up
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** QoL - Medical Outcomes Study Short-Form health status questionnaire (SF-36)
	Follow-up time: 12 months (mean)
Notes	Funding source: supported in part by a Clinician-Scientist Award from the American Heart Association. Additional support was provided by an unrestricted grant from Guidant, Inc (Santa Clara, Calif).
	Author COI: none reported
	Study/trial registry: Balloon versus optimal atherectomy trial (BOAT) and Acute coronary syndromes multi-link stent system trial (ASCENT)

Toefler 1993

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** USA
Participants	**Number of participants:** 393; number analysed: 393 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): not reported; sex (% female) not reported
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 6-month follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 4 years (mean)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: Multicentre investigation of limitation of infarct size RCT

Van Den Berg 2019

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** the Netherlands
Participants	**Number of participants:** 1506; number analysed: 1506 Specific population category: none Definition of CHD: clinical and surgical validation of coronary artery disease **Sample characteristics** (at baseline): age (mean): 57.6 (8.1 SD); sex (% female) 431 (28.6)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** year after vascular event **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** MACE and all-cause mortality **Follow-up time:** 88 months (median)

Van Den Berg 2019 *(Continued)*

Notes	Funding source: none reported Author COI: none disclosed Study/trial registry: Second Manifestations of ARTerial disease (SMART) study Notes: calculations are based on entire population (includes peripheral artery disease and cerebrovascular disease), however largest proportion of patient population were diagnosed with coronary artery disease (572), study does not report outcomes by subgroup

van Domburg 2008

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** the Netherlands
Participants	**Number of participants:** 551; number analysed: 551 Specific population category: none Definition of CHD: surgical validation, underwent coronary artery bypass grafting **Sample characteristics** (at baseline): age (mean): 51.2 (not reported SD); sex (% female) 44 (8)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 1 year after surgery **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality **Follow-up time:** 30 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Vlietstra 1986

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** USA and Canada
Participants	**Number of participants:** 4886; number analysed: 4165 Specific population category: none Definition of CHD: angiographically verified

Vlietstra 1986 *(Continued)*

	Sample characteristics (at baseline): age (mean): not reported; sex (% female) not reported
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** every year until end of follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 60 months (median)
Notes	Funding source: grant from the National Heart, Lung, and Blood Institute Author COI: none reported Study/trial registry: Coronary artery surgery study (CASS) registry

Voors 1996

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** the Netherlands
Participants	**Number of participants:** 169; number analysed: 169 Specific population category: none Definition of CHD: surgical validation, underwent coronary artery bypass surgery **Sample characteristics** (at baseline): age (mean): 51.9 (not reported SD); sex (% female) 8 (5)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** 1- and 5-year follow-up **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** all-cause mortality and non-fatal MI **Follow-up time:** 184.8 months (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Wang 2021

Study characteristics	

Wang 2021 *(Continued)*

Methods	**Study design:** longitudinal cohort **Country:** China
Participants	**Number of participants:** 8849; number analysed: 8849 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 53.14(9.6 SD) for persistent smoking and 55.47(9.94 SD) for stopped smoking; sex (% female) 264 (3.1)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** maintained abstinence until end of study **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death and all-cause mortality **Follow-up time:** 3.01 years (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: FuWai Hospital CHD registry Notes: 5% of population were randomly selected to re-collect smoking status information and high consistency of self-reported information was found.

Weng 1990

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** China
Participants	**Number of participants:** 449; number analysed: 449 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): age reported in range, < 40 to > 50; sex (% female) 222/740 (30)
Interventions	**Definition of smoking cessation used:** self-report of smoking status **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death and all-cause mortality

Weng 1990 *(Continued)*

	Follow-up time: 18 years (max)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

Wiggers 2006

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** the Netherlands
Participants	**Number of participants:** 344; number analysed: 344 Specific population category: none Definition of CHD: clinical validation of coronary artery disease **Sample characteristics** (at baseline): age (mean): 59 (12 SD); sex (% female) 126 (36.6)
Interventions	**Definition of smoking cessation used:** smoking status was assessed using a 7-day point-prevalence abstinence measure at all 4 measurement occasions **Time point of smoking cessation categorisation:** intervention, 2, 6 and 12 months after intervention **Smoking cessation intervention(s) used (if any):** participants received quit-smoking advice from their specialist and were referred to a nurse practitioner. In the experimental group nurse practitioners offered the Minimal Intervention Strategy for Cardiology Patients (C-MIS), a brief form of behavioural counselling to promote smoking cessation. Experimental group were also offered NRT if wanted. **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** QoL - Assessment of Quality of Life and Related Events Questionnaire (Aquarel) **Follow-up time:** 18 years (max)
Notes	Funding source: Netherlands Heart Foundation Author COI: "the authors thank the pharmaceutical company Novartis Consumer Health BV, Breda, The Netherlands, for providing Nicotinell TTS patches for prime cost, the nurse specialists for application of the interventions, and all medical specialists and others who contributed to this project" Study/trial registry: none reported

Wilhelmsen 1975

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** Sweden
Participants	**Number of participants:** 300; number analysed: 170

Wilhelmsen 1975 *(Continued)*

	Specific population category: none
	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): 50.6 (not reported); sex (% female) 35/300 (11.7)
Interventions	**Definition of smoking cessation used:** self-report smoking status
	Time point of smoking cessation categorisation: 3 and 12 months after MI
	Smoking cessation intervention(s) used (if any): none reported
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** all-cause mortality
	Follow-up time: 48 months (mean)
Notes	Funding source: none reported
	Author COI: none reported
	Study/trial registry: none reported

Wilhelmsson 1975

Study characteristics	
Methods	**Study design:** longitudinal cohort
	Country: Sweden
Participants	**Number of participants:** 405; number analysed: 405
	Specific population category: men only
	Definition of CHD: clinical validation of MI
	Sample characteristics (at baseline): age (mean): range 35-70; sex (% female) 0
Interventions	**Definition of smoking cessation used:** self-report smoking status
	Time point of smoking cessation categorisation: 3-month follow-up
	Smoking cessation intervention(s) used (if any): all participants were informed of the association between smoking and ischaemic heart-disease, and smokers were advised to stop smoking. Printed information was given in the form of a special brochure.
	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** CVD death, all-cause mortality and non-fatal MI
	Follow-up time: 24 months (mean)
Notes	Funding source: grants from the Swedish National Association against Heart and Chest Diseases and the Insurance Company "Forenade Liv"
	Author COI: none reported
	Study/trial registry: none reported

Xue 2017

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** China
Participants	**Number of participants:** 298; number analysed: 298 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 60.3 (9.7 SD) for persistent smoking and 60.2 (9.1 SD) for stopped smoking; sex (% female) 25 (8)
Interventions	**Definition of smoking cessation used:** self-report smoking status **Time point of smoking cessation categorisation:** follow-up at 1, 6 and 12 months after discharge **Smoking cessation intervention(s) used (if any):** none reported **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** non-fatal stroke, non-fatal MI and QoL - Medical Outcomes Study Short-Form health status questionnaire (SF-36) **Follow-up time:** 12 months (mean)
Notes	Funding source: supported by the Scientific and Technological Foundation Projects of Shanghai Jiao Tong University, School of Medicine Author COI: none reported Study/trial registry: none reported

Yudi 2017

Study characteristics	
Methods	**Study design:** longitudinal cohort **Country:** Australia
Participants	**Number of participants:** 2935; number analysed: 2935 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 56.7 (10.6 SD) for persistent smoking and 56.1 (10.2 SD) for stopped smoking; sex (% female) 597 (20)
Interventions	**Definition of smoking cessation used:** self-report smoking status **Time point of smoking cessation categorisation:** 30 days after surgery **Smoking cessation intervention(s) used (if any):** none reported

Yudi 2017 *(Continued)*

	Measure of biovalidation (if any): none reported
Outcomes	**Outcome category:** MACE, all-cause mortality, non-fatal stroke and non-fatal MI **Follow-up time:** 3.9 years (median)
Notes	Funding source: the Melbourne Interventional Group acknowledges unrestricted educational grant funding from: Abbott Vascular, Astra-Zeneca, Medtronic, MSD, Pfizer, Servier and The Medicines Company. These companies do not have access to the data and do not have the right to review manuscripts before publication. Author COI: none reported Study/trial registry: Melbourne Interventional Group registry

Zhang 2013

Study characteristics	
Methods	**Study design:** secondary analysis of RCT **Country:** Canada
Participants	**Number of participants:** 225; number analysed: 225 Specific population category: none Definition of CHD: clinical validation of MI **Sample characteristics** (at baseline): age (mean): 54 (10 SD); sex (% female) 36 (16)
Interventions	**Definition of smoking cessation used:** self-report smoking status **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** all participants received a standardised non-pharmacologic smoking cessation intervention; bupropion was given to 109 participants and 116 received placebo **Measure of biovalidation (if any):** not reported but was used
Outcomes	**Outcome category:** QoL - EuroQol-5D **Follow-up time:** 12 months (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported Notes: conference abstract

Zhu 2009

Study characteristics	
Methods	**Study design:** longitudinal cohort

Zhu 2009 *(Continued)*

	Country: China
Participants	**Number of participants:** 320; number analysed: 320 Specific population category: none Definition of CHD: surgical validation, underwent PCI **Sample characteristics** (at baseline): age (mean): 59.3 (11.8 SD); sex (% female) 8 (2.5)
Interventions	**Definition of smoking cessation used:** self-report smoking status **Time point of smoking cessation categorisation:** unclear **Smoking cessation intervention(s) used (if any):** all participants were encouraged not to smoke and informed of the harm of smoking; smokers were asked to have regular health checks and health education **Measure of biovalidation (if any):** none reported
Outcomes	**Outcome category:** CVD death, MACE, all-cause mortality and non-fatal MI **Follow-up time:** 12 months (median)
Notes	Funding source: none reported Author COI: none reported Study/trial registry: none reported

ACS: acute coronary syndrome; **AMI:** acute myocardial infarction; **CHD:** coronary heart disease; **COI:** conflicts of interest; **CVD:** cardiovascular disease; **GP:** general practitioner; **ICD-10-CM:** International Classification of Diseases, Tenth Revision, Clinical Modification; **MACE:** major adverse cardiovascular events; **MI:** myocardial infarction; **NRT:** nicotine replacement therapy; **PCI:** percutaneous coronary intervention; **QoL:** quality of life; **RCT:** randomised controlled trial; **SD:** standard deviation; **SE:** standard error

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beatty 2015	Did not compare outcomes by smoking status after MI
Dornelas 2000	Investigated rates of smoking cessation without comparing to CVD outcomes
Goldenberg 2003	Grouped individuals by if they had stopped smoking before entry to study, therefore unclear if stopped smoking before MI
Houston 2005	Compared those who received smoking cessation counselling after MI rather than comparing smoking status after MI
Ma 2016	Compared those who quit before MI versus those who were smoking at MI, no mention of smoking status after MI
Qiao 2000	Ineligible patient population, followed individuals before diagnosis of CHD
Rocha 2017	Outcomes focused on nicotine dependence, did not look at necessary CVD or QoL outcomes
Schmitz 1999	Smoking status after MI was recorded but not compared with CVD outcomes

Study	Reason for exclusion
Steele 2017	Did not assess change in smoking habit after MI, only compared those who quit smoking before MI and those who continued
Van Spall 2007	Compared those who received smoking cessation counselling after MI rather than comparing smoking status after MI

CHD: coronary heart disease; **CVD:** cardiovascular disease; **MI:** myocardial infarction; **QoL:** quality of life

DATA AND ANALYSES

Comparison 1. Death from cardiovascular disease

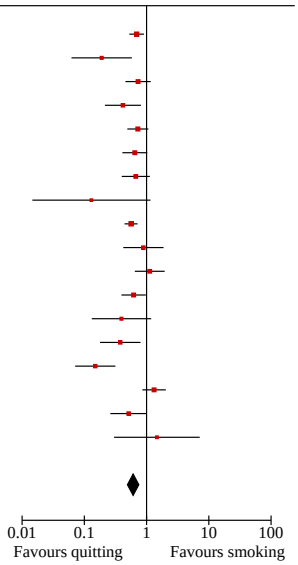
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Main data analysis for death from cardiovascular disease	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.2 Sensitivity analysis: risk of bias	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.2.1 Low and moderate risk	7	12915	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.37, 0.85]
1.2.2 Serious and critical risk	11	5067	Hazard Ratio (IV, Random, 95% CI)	0.63 [0.50, 0.81]
1.3 Sensitivity analysis: using unadjusted estimates for studies that report both adjusted and unadjusted	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.50, 0.75]
1.4 Subgroups: adjusted versus unadjusted estimates	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.4.1 HR and RR approximation unadjusted	15	7706	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.57, 0.81]
1.4.2 HR and RR approximation adjusted	3	10276	Hazard Ratio (IV, Random, 95% CI)	0.28 [0.10, 0.83]
1.5 Subgroups: reporting hazard ratios (HRs) versus approximating risk ratio (RR)	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.5.1 RR approximation	15	8448	Hazard Ratio (IV, Random, 95% CI)	0.67 [0.57, 0.80]
1.5.2 HR	3	9534	Hazard Ratio (IV, Random, 95% CI)	0.30 [0.09, 1.00]
1.6 Subgroups: biochemical validation versus no biochemical validation	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.1 Biochemical validation	2	1270	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.37, 0.94]
1.6.2 No biochemical validation	16	16712	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.47, 0.78]
1.7 Subgroups: presence of secondary medication prevention	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.7.1 Balanced or adjusted	4	2950	Hazard Ratio (IV, Random, 95% CI)	0.55 [0.28, 1.09]
1.7.2 Unbalanced and unadjusted	1	427	Hazard Ratio (IV, Random, 95% CI)	0.89 [0.42, 1.87]
1.7.3 Not reported	13	14605	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.46, 0.75]
1.8 Subgroups: sex of population	18	17982	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.49, 0.75]
1.8.1 Mixed sex	11	14985	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.45, 0.90]
1.8.2 Men only	7	2997	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.50, 0.69]
1.9 Sensitivity analysis: longer than 2-year follow-up	17	17662	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.48, 0.74]

Analysis 1.1. Comparison 1: Death from cardiovascular disease, Outcome 1: Main data analysis for death from cardiovascular disease

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Liu 2013	-2.041375	1.114226	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.573996	0.12312	282	235	9.5%	0.56 [0.44 , 0.72]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**

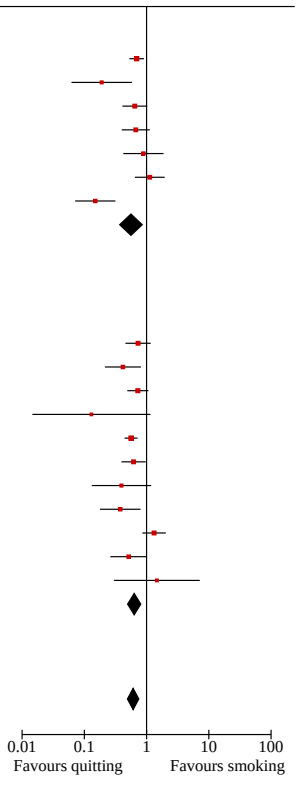
Heterogeneity: Tau² = 0.11; Chi² = 44.49, df = 17 (P = 0.0003); I² = 62%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Death from cardiovascular disease, Outcome 2: Sensitivity analysis: risk of bias

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Low and moderate risk						
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Subtotal (95% CI)			**6621**	**6294**	**40.9%**	**0.56 [0.37 , 0.85]**
Heterogeneity: Tau² = 0.22; Chi² = 24.27, df = 6 (P = 0.0005); I² = 75%						
Test for overall effect: Z = 2.71 (P = 0.007)						
1.2.2 Serious and critical risk						
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Liu 2013	-2.041375	1.113425	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.574476	0.123116	282	235	9.5%	0.56 [0.44 , 0.72]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Subtotal (95% CI)			**2720**	**2347**	**59.1%**	**0.63 [0.50 , 0.81]**
Heterogeneity: Tau² = 0.07; Chi² = 20.23, df = 10 (P = 0.03); I² = 51%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**

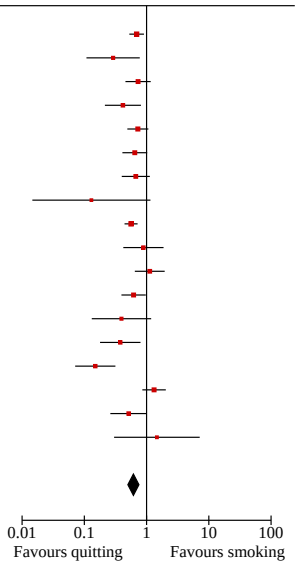
Heterogeneity: Tau² = 0.11; Chi² = 44.50, df = 17 (P = 0.0003); I² = 62%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%



Analysis 1.3. Comparison 1: Death from cardiovascular disease, Outcome 3: Sensitivity analysis: using unadjusted estimates for studies that report both adjusted and unadjusted

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Aberg 1983	-0.36749	0.137952	542	441	9.3%	0.69 [0.53 , 0.91]
Biery 2020	-1.237874	0.502956	309	309	3.1%	0.29 [0.11 , 0.78]
Boggon 2014	-0.314711	0.23815	320	645	7.0%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.1%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.1%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Liu 2013	-2.041375	1.114226	283	147	0.8%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.573996	0.12312	282	235	9.6%	0.56 [0.44 , 0.72]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.5%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.1%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.6%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.5%	0.38 [0.18 , 0.80]
Wang 2021	-1.89712	0.379618	4440	4049	4.5%	0.15 [0.07 , 0.32]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.0%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.50 , 0.75]**

Heterogeneity: Tau² = 0.10; Chi² = 42.41, df = 17 (P = 0.0006); I² = 60%
Test for overall effect: Z = 4.67 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Death from cardiovascular disease, Outcome 4: Subgroups: adjusted versus unadjusted estimates

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
1.4.1 HR and RR approximation unadjusted						
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Liu 2013	-2.041306	1.113361	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.574476	0.123116	282	235	9.5%	0.56 [0.44 , 0.72]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Subtotal (95% CI)			**4157**	**3549**	**86.2%**	**0.68 [0.57 , 0.81]**

Heterogeneity: Tau² = 0.05; Chi² = 24.57, df = 14 (P = 0.04); I² = 43%
Test for overall effect: Z = 4.22 (P < 0.0001)

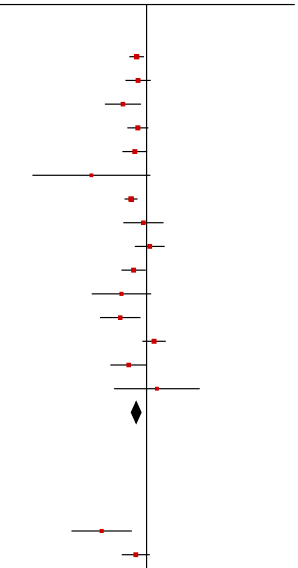
1.4.2 HR and RR approximation adjusted

Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Subtotal (95% CI)			**5184**	**5092**	**13.8%**	**0.28 [0.10 , 0.83]**

Heterogeneity: Tau² = 0.74; Chi² = 12.08, df = 2 (P = 0.002); I² = 83%
Test for overall effect: Z = 2.30 (P = 0.02)

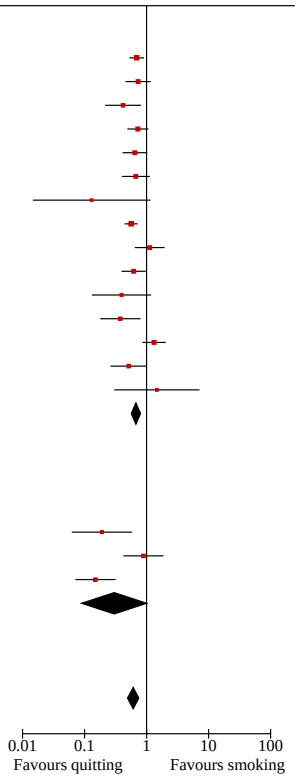
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**

Heterogeneity: Tau² = 0.11; Chi² = 44.50, df = 17 (P = 0.0003); I² = 62%
Test for overall effect: Z = 4.64 (P < 0.00001)
Test for subgroup differences: Chi² = 2.51, df = 1 (P = 0.11), I² = 60.2%



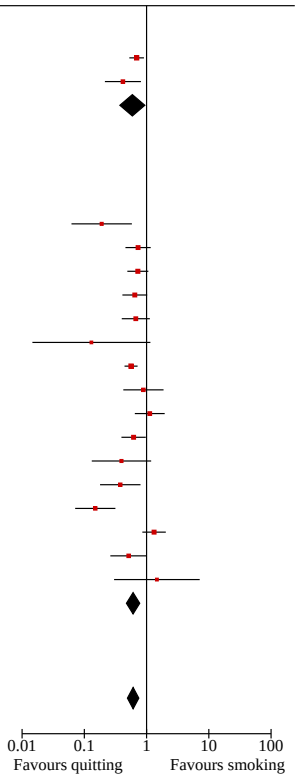
Analysis 1.5. Comparison 1: Death from cardiovascular disease, Outcome 5: Subgroups: reporting hazard ratios (HRs) versus approximating risk ratio (RR)

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
1.5.1 RR approximation						
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Liu 2013	-2.041306	1.11343	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.574476	0.123116	282	235	9.5%	0.56 [0.44 , 0.72]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Subtotal (95% CI)			**4339**	**4109**	**88.1%**	**0.67 [0.57 , 0.80]**
Heterogeneity: Tau² = 0.04; Chi² = 24.03, df = 14 (P = 0.05); I² = 42%						
Test for overall effect: Z = 4.50 (P < 0.00001)						
1.5.2 HR						
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Subtotal (95% CI)			**5002**	**4532**	**11.9%**	**0.30 [0.09 , 1.00]**
Heterogeneity: Tau² = 0.94; Chi² = 12.08, df = 2 (P = 0.002); I² = 83%						
Test for overall effect: Z = 1.95 (P = 0.05)						
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**
Heterogeneity: Tau² = 0.11; Chi² = 44.50, df = 17 (P = 0.0003); I² = 62%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.68, df = 1 (P = 0.19), I² = 40.5%						

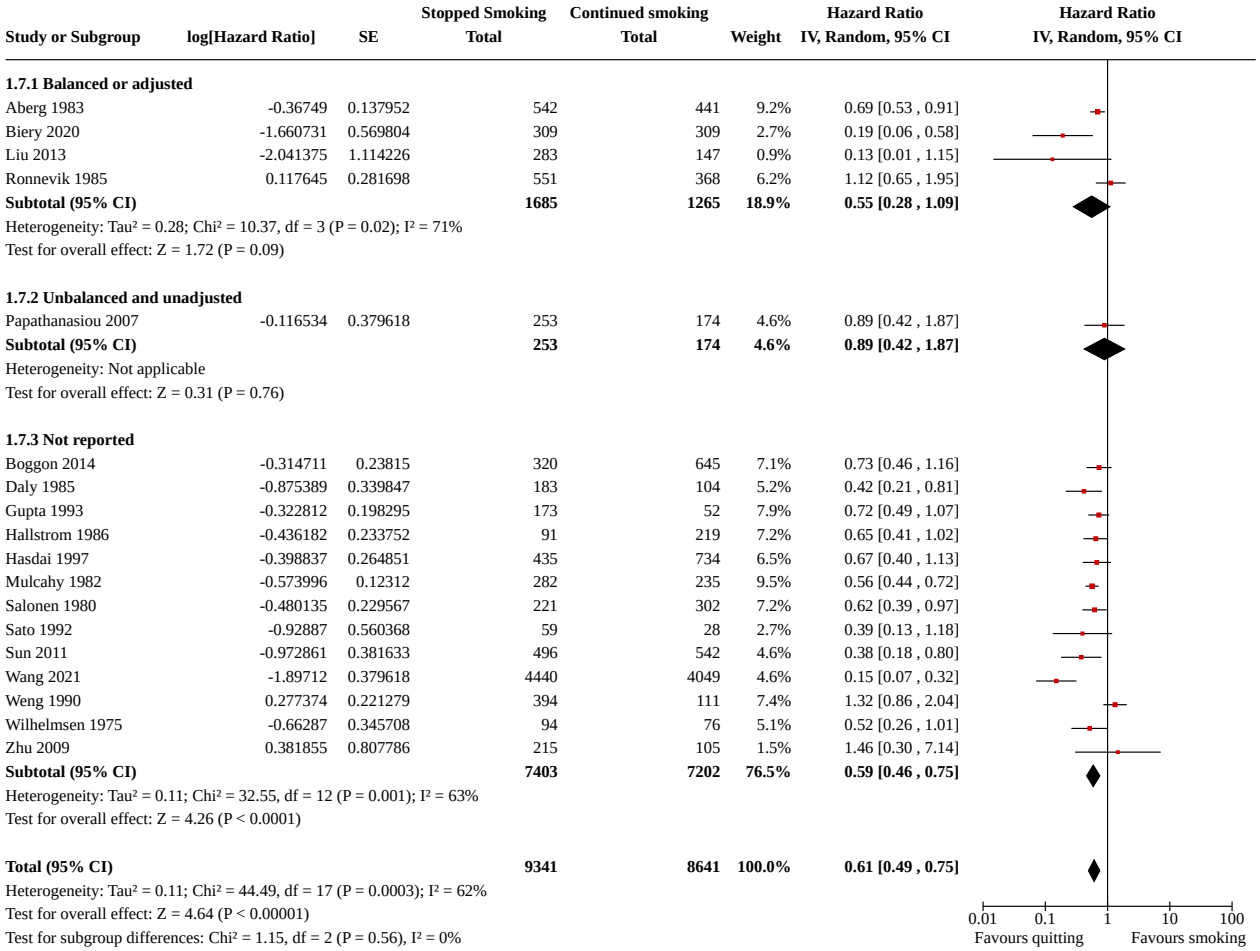


Analysis 1.6. Comparison 1: Death from cardiovascular disease, Outcome 6: Subgroups: biochemical validation versus no biochemical validation

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
1.6.1 Biochemical validation						
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Subtotal (95% CI)			**725**	**545**	**14.4%**	**0.59 [0.37 , 0.94]**
Heterogeneity: Tau² = 0.06; Chi² = 1.92, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 2.24 (P = 0.03)						
1.6.2 No biochemical validation						
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Liu 2013	-2.041308	1.11343	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.574476	0.123116	282	235	9.5%	0.56 [0.44 , 0.72]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Subtotal (95% CI)			**8616**	**8096**	**85.6%**	**0.61 [0.47 , 0.78]**
Heterogeneity: Tau² = 0.14; Chi² = 42.58, df = 15 (P = 0.0002); I² = 65%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**
Heterogeneity: Tau² = 0.11; Chi² = 44.50, df = 17 (P = 0.0003); I² = 62%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						

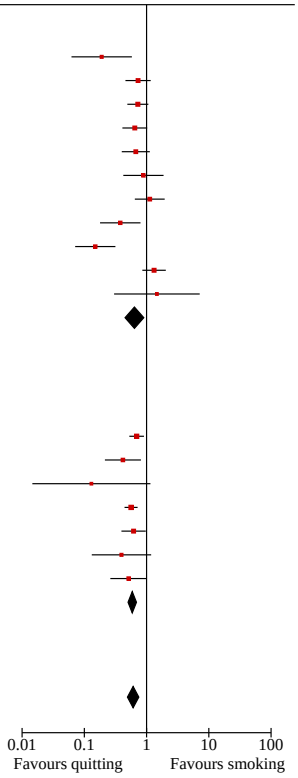


Analysis 1.7. Comparison 1: Death from cardiovascular disease, Outcome 7: Subgroups: presence of secondary medication prevention



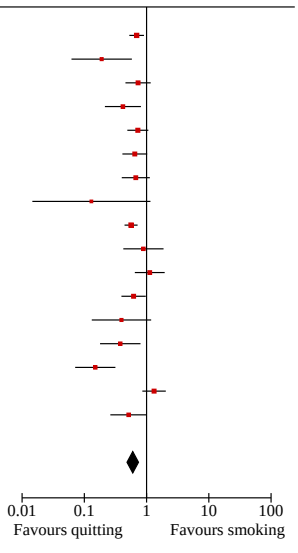
Analysis 1.8. Comparison 1: Death from cardiovascular disease, Outcome 8: Subgroups: sex of population

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
1.8.1 Mixed sex						
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Boggon 2014	-0.314711	0.23815	320	645	7.1%	0.73 [0.46 , 1.16]
Gupta 1993	-0.322812	0.198295	173	52	7.9%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.2%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.5%	0.67 [0.40 , 1.13]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.6%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.2%	1.12 [0.65 , 1.95]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Wang 2021	-1.89712	0.379618	4440	4049	4.6%	0.15 [0.07 , 0.32]
Weng 1990	0.277374	0.221279	394	111	7.4%	1.32 [0.86 , 2.04]
Zhu 2009	0.381855	0.807786	215	105	1.5%	1.46 [0.30 , 7.14]
Subtotal (95% CI)			**7677**	**7308**	**60.2%**	**0.64 [0.45 , 0.90]**
Heterogeneity: Tau² = 0.23; Chi² = 36.75, df = 10 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 2.54 (P = 0.01)						
1.8.2 Men only						
Aberg 1983	-0.36749	0.137952	542	441	9.2%	0.69 [0.53 , 0.91]
Daly 1985	-0.875389	0.339847	183	104	5.2%	0.42 [0.21 , 0.81]
Liu 2013	-2.041375	1.114226	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.573996	0.12312	282	235	9.5%	0.56 [0.44 , 0.72]
Salonen 1980	-0.480135	0.229567	221	302	7.2%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.7%	0.39 [0.13 , 1.18]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.1%	0.52 [0.26 , 1.01]
Subtotal (95% CI)			**1664**	**1333**	**39.8%**	**0.59 [0.50 , 0.69]**
Heterogeneity: Tau² = 0.00; Chi² = 5.09, df = 6 (P = 0.53); I² = 0%						
Test for overall effect: Z = 6.67 (P < 0.00001)						
Total (95% CI)			**9341**	**8641**	**100.0%**	**0.61 [0.49 , 0.75]**
Heterogeneity: Tau² = 0.11; Chi² = 44.49, df = 17 (P = 0.0003); I² = 62%						
Test for overall effect: Z = 4.64 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



Analysis 1.9. Comparison 1: Death from cardiovascular disease, Outcome 9: Sensitivity analysis: longer than 2-year follow-up

Study or Subgroup	log[Hazard Ratio]	SE	Stopped Smoking Total	Continued smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Aberg 1983	-0.36749	0.137952	542	441	9.3%	0.69 [0.53 , 0.91]
Biery 2020	-1.660731	0.569804	309	309	2.7%	0.19 [0.06 , 0.58]
Boggon 2014	-0.314711	0.23815	320	645	7.2%	0.73 [0.46 , 1.16]
Daly 1985	-0.875389	0.339847	183	104	5.3%	0.42 [0.21 , 0.81]
Gupta 1993	-0.322812	0.198295	173	52	8.0%	0.72 [0.49 , 1.07]
Hallstrom 1986	-0.436182	0.233752	91	219	7.3%	0.65 [0.41 , 1.02]
Hasdai 1997	-0.398837	0.264851	435	734	6.6%	0.67 [0.40 , 1.13]
Liu 2013	-2.041375	1.114226	283	147	0.9%	0.13 [0.01 , 1.15]
Mulcahy 1982	-0.573996	0.12312	282	235	9.6%	0.56 [0.44 , 0.72]
Papathanasiou 2007	-0.116534	0.379618	253	174	4.7%	0.89 [0.42 , 1.87]
Ronnevik 1985	0.117645	0.281698	551	368	6.3%	1.12 [0.65 , 1.95]
Salonen 1980	-0.480135	0.229567	221	302	7.4%	0.62 [0.39 , 0.97]
Sato 1992	-0.92887	0.560368	59	28	2.8%	0.39 [0.13 , 1.18]
Sun 2011	-0.972861	0.381633	496	542	4.6%	0.38 [0.18 , 0.80]
Wang 2021	-1.89712	0.379618	4440	4049	4.7%	0.15 [0.07 , 0.32]
Weng 1990	0.277374	0.221279	394	111	7.5%	1.32 [0.86 , 2.04]
Wilhelmsen 1975	-0.66287	0.345708	94	76	5.2%	0.52 [0.26 , 1.01]
Total (95% CI)			**9126**	**8536**	**100.0%**	**0.60 [0.48 , 0.74]**
Heterogeneity: Tau² = 0.11; Chi² = 43.44, df = 16 (P = 0.0002); I² = 63%						
Test for overall effect: Z = 4.72 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Comparison 2. Major adverse cardiovascular events (MACE)

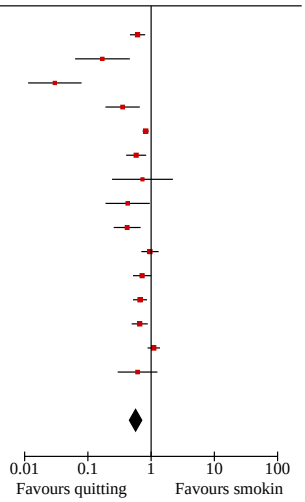
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Main data analysis for MACE	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.2 Sensitivity analysis: risk of bias	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.2.1 Low and moderate risk	9	14856	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.48, 0.76]
2.2.2 Serious and critical risk	6	5665	Hazard Ratio (IV, Random, 95% CI)	0.49 [0.28, 0.84]
2.3 Sensitivity analysis: using unadjusted estimates for studies that report both adjusted and unadjusted	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.72]
2.4 Subgroups: adjusted versus unadjusted estimates	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.4.1 HR and RR approximation unadjusted	9	9278	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.39, 0.79]
2.4.2 HR and RR approximation adjusted	6	11243	Hazard Ratio (IV, Random, 95% CI)	0.55 [0.38, 0.78]
2.5 Subgroups: reporting hazard ratios (HRs) versus approximating risk ratio (RR)	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.5.1 RR approximation	8	8547	Hazard Ratio (IV, Random, 95% CI)	0.53 [0.36, 0.78]
2.5.2 HR	7	11974	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.45, 0.78]
2.6 Subgroups: biochemical validation versus no biochemical validation	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.6.1 Biovalidation	1	199	Hazard Ratio (IV, Random, 95% CI)	0.17 [0.06, 0.46]
2.6.2 No biovalidation	14	20322	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.48, 0.74]
2.7 Subgroups: presence of secondary medication prevention	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.7.1 Balanced or adjusted	9	6097	Hazard Ratio (IV, Random, 95% CI)	0.41 [0.27, 0.63]
2.7.2 Unbalanced and unadjusted	1	2935	Hazard Ratio (IV, Random, 95% CI)	1.10 [0.88, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.3 Not reported	5	11489	Hazard Ratio (IV, Random, 95% CI)	0.73 [0.63, 0.84]
2.8 Subgroups: sex of population	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.8.1 Mixed sex	14	20091	Hazard Ratio (IV, Random, 95% CI)	0.59 [0.47, 0.74]
2.8.2 Men only	1	430	Hazard Ratio (IV, Random, 95% CI)	0.35 [0.19, 0.66]
2.9 Subgroups: definition of MACE	15	20521	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.45, 0.71]
2.9.1 MACE	8	4782	Hazard Ratio (IV, Random, 95% CI)	0.38 [0.25, 0.59]
2.9.2 Variation of MACE	7	15739	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.67, 0.96]
2.10 Sensitivity analysis: longer than 2-year follow-up	14	20201	Hazard Ratio (IV, Random, 95% CI)	0.56 [0.45, 0.71]
2.11 Sensitivity analysis: removing Imbalzano 2018	14	20290	Hazard Ratio (IV, Random, 95% CI)	0.66 [0.56, 0.78]

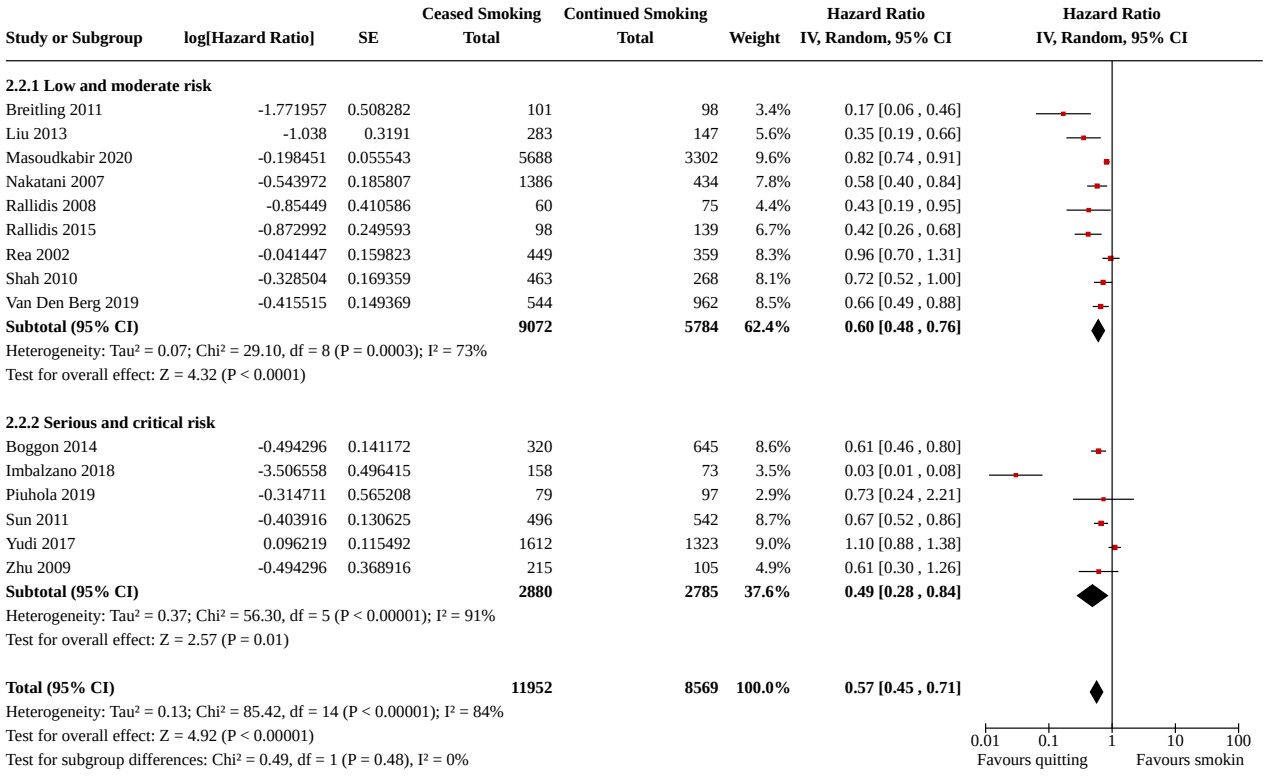
Analysis 2.1. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 1: Main data analysis for MACE

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**

Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Not applicable

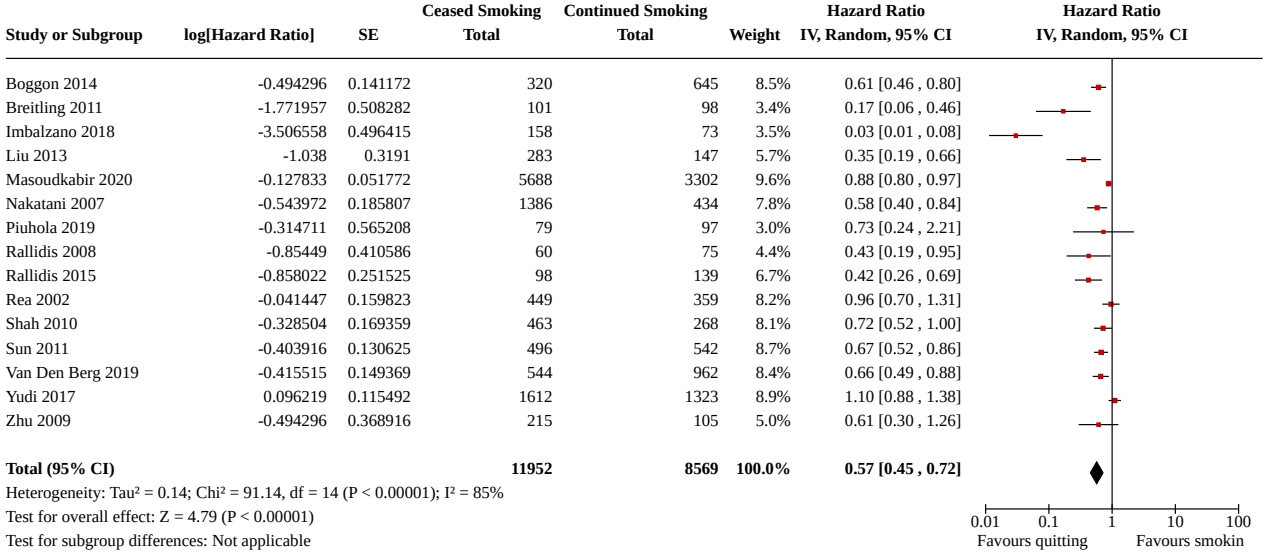


Analysis 2.2. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 2: Sensitivity analysis: risk of bias



Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.2.1 Low and moderate risk						
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Subtotal (95% CI)			**9072**	**5784**	**62.4%**	**0.60 [0.48 , 0.76]**
Heterogeneity: Tau² = 0.07; Chi² = 29.10, df = 8 (P = 0.0003); I² = 73%						
Test for overall effect: Z = 4.32 (P < 0.0001)						
2.2.2 Serious and critical risk						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**2880**	**2785**	**37.6%**	**0.49 [0.28 , 0.84]**
Heterogeneity: Tau² = 0.37; Chi² = 56.30, df = 5 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 2.57 (P = 0.01)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%						

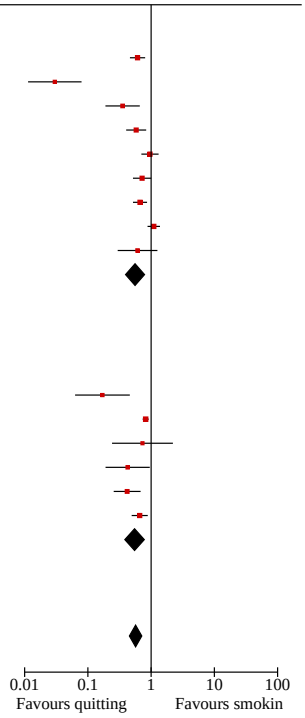
Analysis 2.3. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 3: Sensitivity analysis: using unadjusted estimates for studies that report both adjusted and unadjusted



Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Boggon 2014	-0.494296	0.141172	320	645	8.5%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.7%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.127833	0.051772	5688	3302	9.6%	0.88 [0.80 , 0.97]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	3.0%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.858022	0.251525	98	139	6.7%	0.42 [0.26 , 0.69]
Rea 2002	-0.041447	0.159823	449	359	8.2%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.4%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	8.9%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	5.0%	0.61 [0.30 , 1.26]
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.72]**
Heterogeneity: Tau² = 0.14; Chi² = 91.14, df = 14 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 4.79 (P < 0.00001)						
Test for subgroup differences: Not applicable						

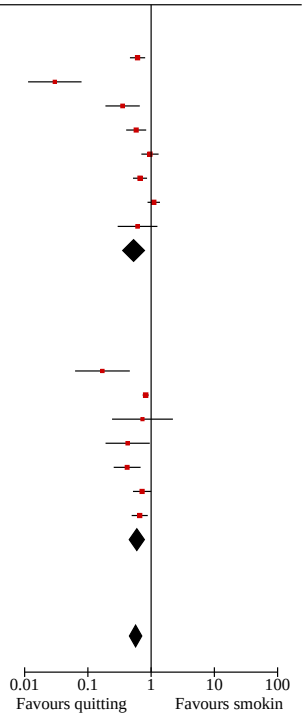
Analysis 2.4. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 4: Subgroups: adjusted versus unadjusted estimates

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.4.1 HR and RR approximation unadjusted						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**5382**	**3896**	**64.5%**	**0.56 [0.39 , 0.79]**
Heterogeneity: Tau² = 0.22; Chi² = 65.91, df = 8 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
2.4.2 HR and RR approximation adjusted						
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Subtotal (95% CI)			**6570**	**4673**	**35.5%**	**0.55 [0.38 , 0.78]**
Heterogeneity: Tau² = 0.11; Chi² = 19.19, df = 5 (P = 0.002); I² = 74%						
Test for overall effect: Z = 3.34 (P = 0.0008)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%						



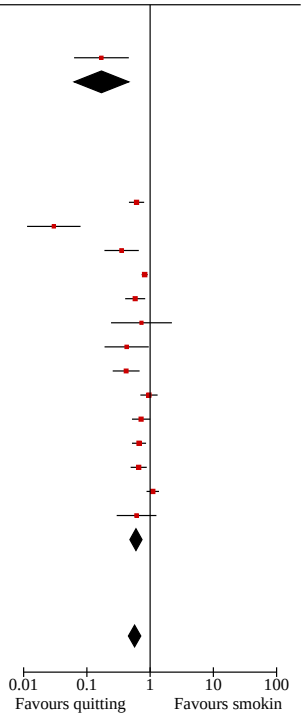
Analysis 2.5. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 5: Subgroups: reporting hazard ratios (HRs) versus approximating risk ratio (RR)

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.5.1 RR approximation						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**4919**	**3628**	**56.4%**	**0.53 [0.36 , 0.78]**
Heterogeneity: Tau² = 0.27; Chi² = 65.91, df = 7 (P < 0.00001); I² = 89%						
Test for overall effect: Z = 3.16 (P = 0.002)						
2.5.2 HR						
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Subtotal (95% CI)			**7033**	**4941**	**43.6%**	**0.59 [0.45 , 0.78]**
Heterogeneity: Tau² = 0.07; Chi² = 19.28, df = 6 (P = 0.004); I² = 69%						
Test for overall effect: Z = 3.70 (P = 0.0002)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



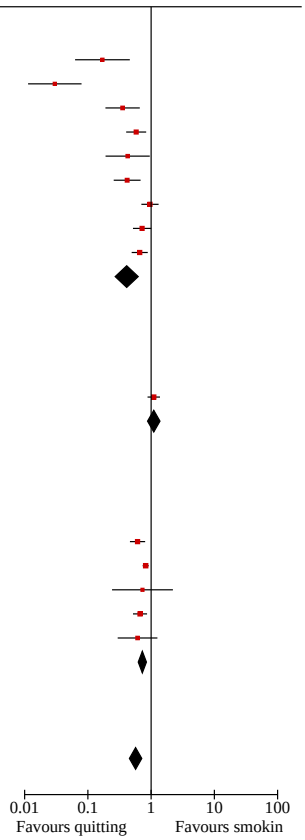
Analysis 2.6. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 6: Subgroups: biochemical validation versus no biochemical validation

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.6.1 Biovalidation						
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Subtotal (95% CI)			**101**	**98**	**3.4%**	**0.17 [0.06 , 0.46]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.49 (P = 0.0005)						
2.6.2 No biovalidation						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**11851**	**8471**	**96.6%**	**0.60 [0.48 , 0.74]**
Heterogeneity: Tau² = 0.12; Chi² = 76.93, df = 13 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 4.58 (P < 0.00001)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.82, df = 1 (P = 0.02), I² = 82.8%						



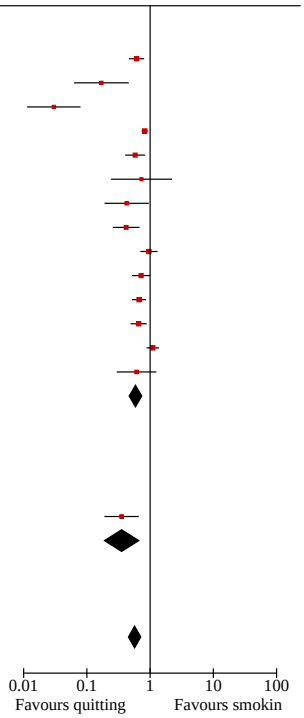
Analysis 2.7. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 7: Subgroups: presence of secondary medication prevention

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.7.1 Balanced or adjusted						
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Subtotal (95% CI)			**3542**	**2555**	**56.3%**	**0.41 [0.27 , 0.63]**
Heterogeneity: Tau² = 0.32; Chi² = 58.31, df = 8 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 4.15 (P < 0.0001)						
2.7.2 Unbalanced and unadjusted						
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Subtotal (95% CI)			**1612**	**1323**	**9.0%**	**1.10 [0.88 , 1.38]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.40)						
2.7.3 Not reported						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**6798**	**4691**	**34.8%**	**0.73 [0.63 , 0.84]**
Heterogeneity: Tau² = 0.01; Chi² = 5.60, df = 4 (P = 0.23); I² = 29%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 18.74, df = 2 (P < 0.0001), I² = 89.3%						



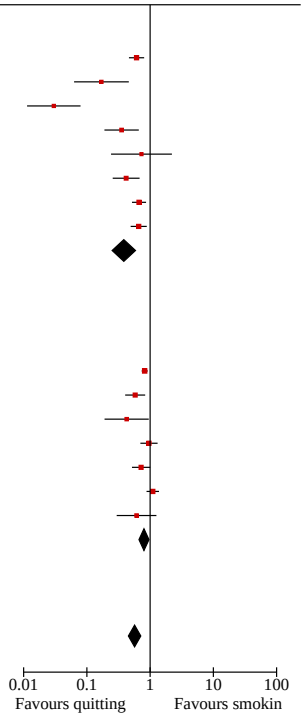
Analysis 2.8. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 8: Subgroups: sex of population

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.8.1 Mixed sex						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**11669**	**8422**	**94.4%**	**0.59 [0.47 , 0.74]**
Heterogeneity: Tau² = 0.13; Chi² = 79.92, df = 13 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.58 (P < 0.00001)						
2.8.2 Men only						
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Subtotal (95% CI)			**283**	**147**	**5.6%**	**0.35 [0.19 , 0.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.25 (P = 0.001)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.20, df = 1 (P = 0.14), I² = 54.6%						



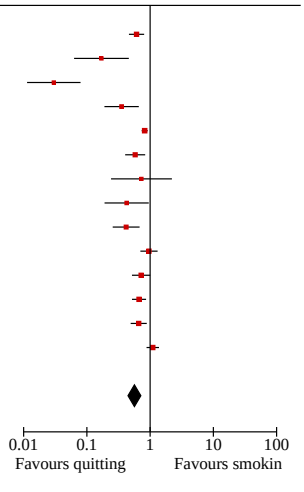
Analysis 2.9. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 9: Subgroups: definition of MACE

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
2.9.1 MACE						
Boggon 2014	-0.494296	0.141172	320	645	8.6%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	3.4%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.5%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.6%	0.35 [0.19 , 0.66]
Piuhola 2019	-0.314711	0.565208	79	97	2.9%	0.73 [0.24 , 2.21]
Rallidis 2015	-0.872992	0.249593	98	139	6.7%	0.42 [0.26 , 0.68]
Sun 2011	-0.403916	0.130625	496	542	8.7%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.5%	0.66 [0.49 , 0.88]
Subtotal (95% CI)			**2079**	**2703**	**47.9%**	**0.38 [0.25 , 0.59]**
Heterogeneity: Tau² = 0.27; Chi² = 47.27, df = 7 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
2.9.2 Variation of MACE						
Masoudkabir 2020	-0.198451	0.055543	5688	3302	9.6%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	7.8%	0.58 [0.40 , 0.84]
Rallidis 2008	-0.85449	0.410586	60	75	4.4%	0.43 [0.19 , 0.95]
Rea 2002	-0.041447	0.159823	449	359	8.3%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.1%	0.72 [0.52 , 1.00]
Yudi 2017	0.096219	0.115492	1612	1323	9.0%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	4.9%	0.61 [0.30 , 1.26]
Subtotal (95% CI)			**9873**	**5866**	**52.1%**	**0.80 [0.67 , 0.96]**
Heterogeneity: Tau² = 0.03; Chi² = 14.61, df = 6 (P = 0.02); I² = 59%						
Test for overall effect: Z = 2.42 (P = 0.02)						
Total (95% CI)			**11952**	**8569**	**100.0%**	**0.57 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.13; Chi² = 85.42, df = 14 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.69, df = 1 (P = 0.002), I² = 89.7%						



Analysis 2.10. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 10: Sensitivity analysis: longer than 2-year follow-up

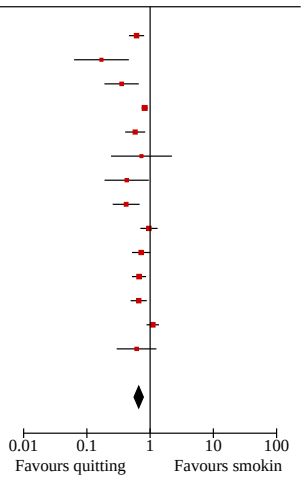
Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Boggon 2014	-0.494296	0.141172	320	645	9.0%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	3.6%	0.17 [0.06 , 0.46]
Imbalzano 2018	-3.506558	0.496415	158	73	3.7%	0.03 [0.01 , 0.08]
Liu 2013	-1.038	0.3191	283	147	5.9%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	10.1%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	8.2%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	3.1%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	4.6%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	7.1%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	8.7%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.5%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	9.2%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	8.9%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	9.4%	1.10 [0.88 , 1.38]
Total (95% CI)			**11737**	**8464**	**100.0%**	**0.56 [0.45 , 0.71]**
Heterogeneity: Tau² = 0.14; Chi² = 85.12, df = 13 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 4.80 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 2.11. Comparison 2: Major adverse cardiovascular events (MACE), Outcome 11: Sensitivity analysis: removing Imbalzano 2018

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Boggon 2014	-0.494296	0.141172	320	645	9.6%	0.61 [0.46 , 0.80]
Breitling 2011	-1.771957	0.508282	101	98	2.4%	0.17 [0.06 , 0.46]
Liu 2013	-1.038	0.3191	283	147	4.7%	0.35 [0.19 , 0.66]
Masoudkabir 2020	-0.198451	0.055543	5688	3302	12.3%	0.82 [0.74 , 0.91]
Nakatani 2007	-0.543972	0.185807	1386	434	8.1%	0.58 [0.40 , 0.84]
Piuhola 2019	-0.314711	0.565208	79	97	2.0%	0.73 [0.24 , 2.21]
Rallidis 2008	-0.85449	0.410586	60	75	3.3%	0.43 [0.19 , 0.95]
Rallidis 2015	-0.872992	0.249593	98	139	6.2%	0.42 [0.26 , 0.68]
Rea 2002	-0.041447	0.159823	449	359	9.0%	0.96 [0.70 , 1.31]
Shah 2010	-0.328504	0.169359	463	268	8.7%	0.72 [0.52 , 1.00]
Sun 2011	-0.403916	0.130625	496	542	10.0%	0.67 [0.52 , 0.86]
Van Den Berg 2019	-0.415515	0.149369	544	962	9.3%	0.66 [0.49 , 0.88]
Yudi 2017	0.096219	0.115492	1612	1323	10.5%	1.10 [0.88 , 1.38]
Zhu 2009	-0.494296	0.368916	215	105	3.9%	0.61 [0.30 , 1.26]
Total (95% CI)			**11794**	**8496**	**100.0%**	**0.66 [0.56 , 0.78]**

Heterogeneity: Tau² = 0.06; Chi² = 43.31, df = 13 (P < 0.0001); I² = 70%
Test for overall effect: Z = 4.81 (P < 0.00001)
Test for subgroup differences: Not applicable



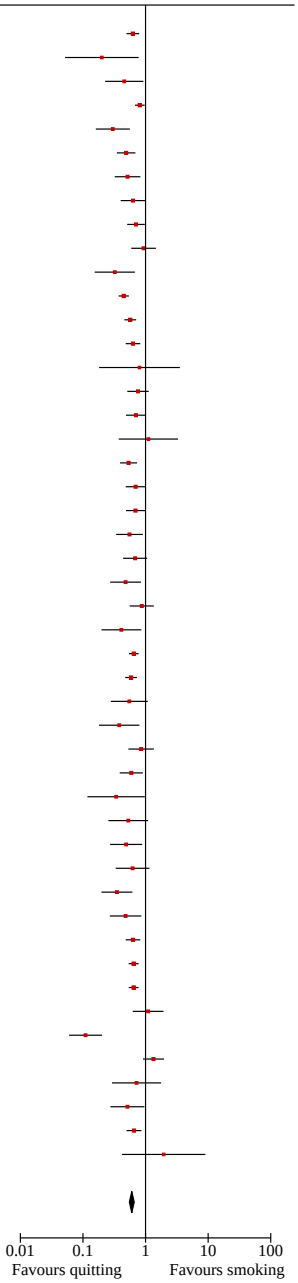
Comparison 3. All-cause mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	48	59354	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.55, 0.66]

Analysis 3.1. Comparison 3: All-cause mortality, Outcome 1: All-cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Aberg 1983	-0.467792	0.118884	542	441	3.5%	0.63 [0.50 , 0.79]
Alvarez 2011	-1.609438	0.690842	275	200	0.4%	0.20 [0.05 , 0.77]
Baughman 1982	-0.783072	0.359235	45	32	1.2%	0.46 [0.23 , 0.92]
Bednarzewski 1984	-0.211956	0.090729	455	555	3.9%	0.81 [0.68 , 0.97]
Biery 2020	-1.203973	0.319588	309	309	1.4%	0.30 [0.16 , 0.56]
Boggon 2014	-0.71335	0.173156	645	320	2.7%	0.49 [0.35 , 0.69]
Burr 1992	-0.661649	0.240789	665	521	2.0%	0.52 [0.32 , 0.83]
Cavender 1992	-0.45961	0.232927	97	187	2.1%	0.63 [0.40 , 1.00]
Cha 2018	-0.350977	0.16466	2324	1856	2.8%	0.70 [0.51 , 0.97]
Chow 2010	-0.072571	0.231144	2802	1522	2.1%	0.93 [0.59 , 1.46]
Colivicchi 2011	-1.131404	0.377053	481	813	1.1%	0.32 [0.15 , 0.68]
Daly 1985	-0.801445	0.096306	217	157	3.8%	0.45 [0.37 , 0.54]
De Boer 2013	-0.562119	0.110726	210	287	3.6%	0.57 [0.46 , 0.71]
Gerber 2009	-0.462035	0.136614	417	381	3.2%	0.63 [0.48 , 0.82]
Grand 1992	-0.223144	0.75752	115	23	0.3%	0.80 [0.18 , 3.53]
Greenwood 1995	-0.277204	0.200568	396	136	2.4%	0.76 [0.51 , 1.12]
Gupta 1993	-0.35482	0.185833	173	52	2.6%	0.70 [0.49 , 1.01]
Haglid 1997	0.10436	0.556088	99	176	0.6%	1.11 [0.37 , 3.30]
Hammal 2014	-0.624293	0.159843	1519	1064	2.9%	0.54 [0.39 , 0.73]
Hasdai 1997	-0.364707	0.185349	435	734	2.6%	0.69 [0.48 , 1.00]
Hedback 1993	-0.36976	0.178054	83	74	2.7%	0.69 [0.49 , 0.98]
Herlitz 1995	-0.589963	0.250505	115	102	1.9%	0.55 [0.34 , 0.91]
Hickey 1983	-0.382755	0.226129	299	335	2.1%	0.68 [0.44 , 1.06]
Johansson 1985	-0.733969	0.289541	81	75	1.6%	0.48 [0.27 , 0.85]
Leung 2008	-0.139262	0.22607	1397	846	2.1%	0.87 [0.56 , 1.36]
Liu 2013	-0.888714	0.37327	283	147	1.1%	0.41 [0.20 , 0.85]
Masoudkabir 2020	-0.430783	0.090517	5688	3302	3.9%	0.65 [0.54 , 0.78]
Mulcahy 1982	-0.532049	0.109667	282	235	3.6%	0.59 [0.47 , 0.73]
Papathanasiou 2007	-0.597837	0.346727	253	174	1.2%	0.55 [0.28 , 1.09]
Perkins 1985	-0.967584	0.378834	41	49	1.1%	0.38 [0.18 , 0.80]
Ronnevik 1985	-0.162519	0.238963	551	368	2.0%	0.85 [0.53 , 1.36]
Salonen 1980	-0.52408	0.217475	221	302	2.2%	0.59 [0.39 , 0.91]
Sato 1992	-1.081814	0.538709	59	28	0.6%	0.34 [0.12 , 0.97]
Shah 2010	-0.634878	0.373286	463	268	1.1%	0.53 [0.25 , 1.10]
Sochor 2015	-0.71335	0.300683	251	162	1.5%	0.49 [0.27 , 0.88]
Sparrow 1978	-0.477172	0.316149	56	139	1.4%	0.62 [0.33 , 1.15]
Sun 2011	-1.053543	0.289976	496	542	1.6%	0.35 [0.20 , 0.62]
Toefler 1993	-0.733969	0.295544	173	220	1.5%	0.48 [0.27 , 0.86]
Van Den Berg 2019	-0.462035	0.136614	544	962	3.2%	0.63 [0.48 , 0.82]
van Domburg 2008	-0.4383	0.0937	237	314	3.8%	0.65 [0.54 , 0.78]
Vlietstra 1986	-0.438505	0.092169	1490	2675	3.8%	0.64 [0.54 , 0.77]
Voors 1996	0.0953	0.2884	72	95	1.6%	1.10 [0.63 , 1.94]
Wang 2021	-2.2073	0.3093	4440	4049	1.4%	0.11 [0.06 , 0.20]
Weng 1990	0.291923	0.196556	390	109	2.4%	1.34 [0.91 , 1.97]
Wilhelmsen 1975	-0.330353	0.460759	94	76	0.8%	0.72 [0.29 , 1.77]
Wilhelmsson 1975	-0.666349	0.319454	231	174	1.4%	0.51 [0.27 , 0.96]
Yudi 2017	-0.425413	0.139589	1612	1323	3.2%	0.65 [0.50 , 0.86]
Zhu 2009	0.669367	0.78158	215	105	0.3%	1.95 [0.42 , 9.04]
Total (95% CI)			**32338**	**27016**	**100.0%**	**0.60 [0.55 , 0.66]**

Heterogeneity: Tau² = 0.04; Chi² = 111.50, df = 47 (P < 0.00001); I² = 58%
Test for overall effect: Z = 11.27 (P < 0.00001)
Test for subgroup differences: Not applicable



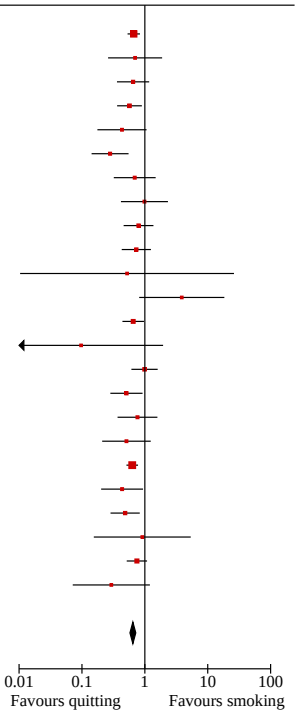
Comparison 4. Non-fatal myocardial infarction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Non-fatal myocardial infarction	24	23264	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.58, 0.72]

Analysis 4.1. Comparison 4: Non-fatal myocardial infarction, Outcome 1: Non-fatal myocardial infarction

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Aberg 1983	-0.406018	0.11566	542	441	19.6%	0.67 [0.53 , 0.84]
Alvarez 2011	-0.356675	0.504689	275	200	1.2%	0.70 [0.26 , 1.88]
Boggon 2014	-0.430783	0.300683	320	645	3.2%	0.65 [0.36 , 1.17]
Chow 2010	-0.562119	0.230902	2802	1522	5.4%	0.57 [0.36 , 0.90]
Cordero 2012	-0.837249	0.458967	248	117	1.4%	0.43 [0.18 , 1.06]
Grand 1992	-1.272966	0.345316	115	23	2.4%	0.28 [0.14 , 0.55]
Hasdai 1997	-0.370658	0.391034	435	734	1.9%	0.69 [0.32 , 1.49]
Herlitz 1995	-0.014606	0.438905	109	115	1.5%	0.99 [0.42 , 2.33]
Johansson 1985	-0.231113	0.278387	81	75	3.7%	0.79 [0.46 , 1.37]
Leung 2008	-0.311975	0.272539	1397	846	3.9%	0.73 [0.43 , 1.25]
Liu 2013	-0.651762	1.997504	283	147	0.1%	0.52 [0.01 , 26.13]
Perkins 1985	1.352065	0.79532	52	67	0.5%	3.87 [0.81 , 18.37]
Ronnevik 1985	-0.426132	0.201038	551	368	7.0%	0.65 [0.44 , 0.97]
Sato 1992	-2.336142	1.532819	59	28	0.1%	0.10 [0.00 , 1.95]
Shah 2010	-0.011263	0.245292	463	268	4.8%	0.99 [0.61 , 1.60]
Sochor 2015	-0.673345	0.300683	162	251	3.2%	0.51 [0.28 , 0.92]
Sparrow 1978	-0.26958	0.372037	56	139	2.1%	0.76 [0.37 , 1.58]
Sun 2011	-0.673541	0.45351	496	542	1.4%	0.51 [0.21 , 1.24]
Vlietstra 1986	-0.461815	0.108169	1490	2675	22.1%	0.63 [0.51 , 0.78]
Voors 1996	-0.832915	0.391262	72	95	1.9%	0.43 [0.20 , 0.94]
Wilhelmsson 1975	-0.721619	0.272917	231	174	3.9%	0.49 [0.28 , 0.83]
Xue 2017	-0.094311	0.905326	126	172	0.4%	0.91 [0.15 , 5.37]
Yudi 2017	-0.291101	0.189974	1612	1323	7.8%	0.75 [0.52 , 1.08]
Zhu 2009	-1.227503	0.72054	215	105	0.6%	0.29 [0.07 , 1.20]
Total (95% CI)			**12192**	**11072**	**100.0%**	**0.64 [0.58 , 0.72]**

Heterogeneity: Tau² = 0.00; Chi² = 23.54, df = 23 (P = 0.43); I² = 2%
Test for overall effect: Z = 8.07 (P < 0.00001)
Test for subgroup differences: Not applicable



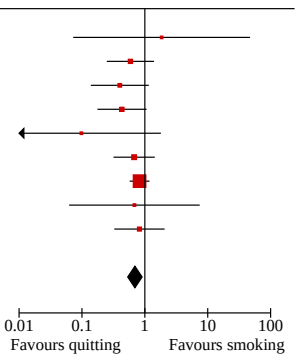
Comparison 5. Non-fatal stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Non-fatal stroke	9	11352	Hazard Ratio (IV, Random, 95% CI)	0.70 [0.53, 0.90]

Analysis 5.1. Comparison 5: Non-fatal stroke, Outcome 1: Non-fatal stroke

Study or Subgroup	log[Hazard Ratio]	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Hazard Ratio IV, Random, 95% CI
Alvarez 2011	0.615186	1.651983	275	200	0.7%	1.85 [0.07 , 47.13]
Boggon 2014	-0.527633	0.441305	320	645	9.3%	0.59 [0.25 , 1.40]
Chow 2010	-0.916291	0.541621	2802	1522	6.2%	0.40 [0.14 , 1.16]
Cordero 2012	-0.837249	0.458895	248	117	8.6%	0.43 [0.18 , 1.06]
Herlitz 1995	-2.322788	1.484786	115	102	0.8%	0.10 [0.01 , 1.80]
Shah 2010	-0.392598	0.38585	463	268	12.2%	0.68 [0.32 , 1.44]
Sun 2011	-0.193585	0.185129	496	542	52.9%	0.82 [0.57 , 1.18]
Xue 2017	-0.381936	1.219157	126	176	1.2%	0.68 [0.06 , 7.45]
Yudi 2017	-0.197598	0.469964	1612	1323	8.2%	0.82 [0.33 , 2.06]
Total (95% CI)			**6457**	**4895**	**100.0%**	**0.70 [0.53 , 0.90]**

Heterogeneity: Tau² = 0.00; Chi² = 5.31, df = 8 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



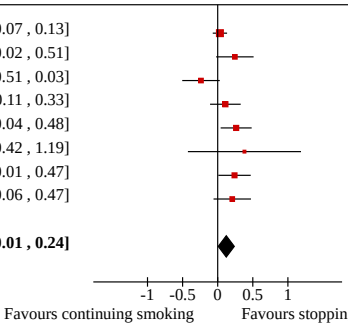
Comparison 6. Quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Quality of life	8	3182	Std. Mean Difference (IV, Random, 95% CI)	0.12 [0.01, 0.24]

Analysis 6.1. Comparison 6: Quality of life, Outcome 1: Quality of life

Study or Subgroup	SMD	SE	Ceased Smoking Total	Continued Smoking Total	Weight	Std. Mean Difference IV, Random, 95% CI
Buchanan 2015	0.031493	0.052086	683	801	23.4%	0.03 [-0.07 , 0.13]
Qi 2014	0.24461	0.136102	92	133	11.2%	0.24 [-0.02 , 0.51]
Quist-Paulsen 2006	-0.237987	0.13631	101	117	11.2%	-0.24 [-0.51 , 0.03]
Snaterse 2015	0.109429	0.111271	156	168	14.0%	0.11 [-0.11 , 0.33]
Taira 2000	0.262892	0.112662	121	231	13.9%	0.26 [0.04 , 0.48]
Wiggers 2006	0.381106	0.410969	15	41	1.9%	0.38 [-0.42 , 1.19]
Xue 2017	0.239704	0.117678	126	172	13.2%	0.24 [0.01 , 0.47]
Zhang 2013	0.207226	0.135961	92	133	11.2%	0.21 [-0.06 , 0.47]
Total (95% CI)			**1386**	**1796**	**100.0%**	**0.12 [0.01 , 0.24]**

Heterogeneity: Tau² = 0.01; Chi² = 13.58, df = 7 (P = 0.06); I² = 48%
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Secondary manifestations of arterial disease (SMART) risk scores

	HDL (mg/dL)		Total cholesterol (mg/dL)		eGFR (mL/min/1.73 m2)		C reactive protein (mg/L)	
	Smoking	Cessation	Smoking	Cessation	Smoking	Cessation	Smoking	Cessation
Biery 2020	36 (9)[a]	36 (9)[a]	193 (66)[a]	192 (45)[a]	90 (19)[a]	90 (18)[a]		
Gupta 1993			250(45)[a]	240 (45)[a]				
Van Den Berg 2019					83 (70-94)[b]	81 (69-92)[b]	3.1 (1.5–6.1)[b]	2.0 (1.1–4.1)[b]

[a]Mean (standard deviation).
[b]Median (interquartile range).

APPENDICES

Appendix 1. Search strategies

Cochrane Tobacco Addiction Specialised Register (vias CRS-Web)

1. (myocardial infarct*):TI,AB,MH,EMT,KY,XKY
2. (acute coronary syndrome):TI,AB,MH,EMT,KY,XKY
3. ((coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease)):TI,AB,MH,EMT,KY,XKY

Cochrane Central Register of Controlled Trials (CENTRAL) via CRS-Web

1. (myocardial infarct*):TI,AB,MH,EMT,KY,XKY
2. (acute coronary syndrome):TI,AB,MH,EMT,KY,XKY
3. ((coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease)):TI,AB,MH,EMT,KY,XKY
4. MESH DESCRIPTOR Tobacco Use Disorder EXPLODE ALL NOT SRTAG
5. MESH DESCRIPTOR Tobacco Use Cessation EXPLODE ALL NOT SRTAG
6. MESH DESCRIPTOR Tobacco Smoke Pollution EXPLODE ALL NOT SRTAG
7. MESH DESCRIPTOR Tobacco Use Cessation Products EXPLODE ALL NOT SRTAG
8. MESH DESCRIPTOR Tobacco, Smokeless EXPLODE ALL NOT SRTAG
9. (SMOKING* or TOBACCO or TOBACCO-USE-DISORDER* or TOBACCO-SMOKELESS* or TOBACCO-SMOKE-POLLUTION* or TOBACCO-USE-CESSATION* or NICOTINE*):MH NOT SRTAG
10. (smoking cessation):MH NOT SRTAG
11. (SMOKING CESSATION or ANTISMOK*):TI,AB NOT SRTAG
12. (quit* or smok* or nonsmok* or cigar* or tobacco* or nicotine*):TI NOT SRTAG
13. MESH DESCRIPTOR Smoking Cessation EXPLODE ALL NOT SRTAG
14. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15. #14 AND #3

MEDLINE (via Ovid)

1. smoking cessation.mp. or exp Smoking Cessation/
2. tobacco cessation.mp. or "Tobacco-Use-Cessation"/
3. (nicotine dependence or tobacco dependence).mp.
4. exp Smoking/th
5. "Tobacco Use Disorder"/
6. Smoking reduction/ or Smoking reduction.mp.
7. exp Pipe smoking/ or exp Tobacco smoking/ or exp Tobacco Products/ or exp Smoking/
8. ((quit$ or stop$ or ceas$ or giv$ or abstain* or abstinen*) adj5 (smoking or smoke* or tobacco)).ti,ab.
9. exp Tobacco/ or exp Nicotine/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. myocardial infarct*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mh]
12. acute coronary syndrome.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mh]
13. (coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease).mp.
14. 11 or 12 or 13
15. 14 and 10
16. Epidemiologic studies/
17. exp case control studies/
18. exp cohort studies/
19. Case control.tw.
20. (cohort adj (study or studies)).tw.
21. Cohort analy$.tw.

22. (Follow up adj (study or studies)).tw.
23. (observational adj (study or studies)).tw.
24. Longitudinal.tw.
25. Cross sectional.tw.
26. Cross-sectional studies/
27. Retrospective.tw.
28. Follow-up studies/
29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 28
30. 15 and 29

Embase (via Ovid)

1. smoking cessation.mp. or exp Smoking Cessation/
2. tobacco cessation.mp. or "Tobacco-Use-Cessation"/
3. (nicotine dependence or tobacco dependence).mp.
4. exp Smoking/th
5. "Tobacco-Use-Disorder"/
6. Smoking reduction/ or Smoking reduction.mp.
7. exp *Pipe smoking/ or exp *Tobacco smoking/ or exp *Tobacco Products/ or exp *Smoking/
8. ((quit$ or stop$ or ceas$ or giv$ or abstain* or abstinen*) adj5 (smoking or smoke* or tobacco)).ti,ab.
9. exp Tobacco/ or exp Nicotine/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. myocardial infarct*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mh]
12. acute coronary syndrome.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mh]
13. (coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease).mp.
14. 11 or 12 or 13
15. 14 and 10
16. Epidemiologic studies/
17. exp case control studies/
18. exp cohort studies/
19. Case control.tw.
20. (cohort adj (study or studies)).tw.
21. Cohort analy$.tw.
22. (Follow up adj (study or studies)).tw.
23. (observational adj (study or studies)).tw.
24. Longitudinal.tw.
25. Cross sectional.tw.
26. Cross-sectional studies/
27. Retrospective.tw.
28. Follow-up studies/
29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 28
30. 15 and 29

CINAHL (via EBSCOhost)

1. TI (((quit* or stop* or ceas* or giv* or abstain* or abstinen*) N5 (smoking or smoke* or tobacco))) OR AB (((quit* or stop* or ceas* or giv* or abstain* or abstinen*) N5 (smoking or smoke* or tobacco)))
2. TI (“Smoking reduction” or “smoking cessation” or “tobacco cessation” or “nicotine dependence” or “tobacco dependence”) OR AB (“Smoking reduction” or “smoking cessation” or “tobacco cessation” or “nicotine dependence” or “tobacco dependence”)
3. MW smoking or tobacco or nicotine
4. TI (“myocardial infarct*” or “acute coronary syndrome” or coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease) OR AB (“myocardial infarct*” or “acute coronary syndrome” or coronary heart disease or MI or myocardial iscahemia or myocardial ischemia or CHD or CAD or heart attack or heart disease or NSTEMI or STEMI or angina or coronary artery disease)

5. TI (Case control or (cohort N1 (study or studies)) or Cohort analy* or (Follow up N1 (study or studies)) or (observational N1 (study or studies)) or Longitudinal or Cross sectional or Retrospective) OR AB (Case control or (cohort N1 (study or studies)) or Cohort analy* or (Follow up N1 (study or studies)) or (observational N1 (study or studies)) or Longitudinal or Cross sectional or Retrospective) OR MH (“Epidemiologic studies” or “case control studies” or “cohort studies” or “Cross-sectional studies” or “Follow-up studies”)
6. 1 or 2 or 3
7. 4 and 6
8. 5 and 7

WHAT'S NEW

Date	Event	Description
20 July 2022	New citation required and conclusions have changed	This new review supersedes a previous Cochrane Review (now withdrawn) on this topic.

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

ADW wrote the review with comments and revisions from AT, ET, CL, JHB, NL, and PA.

For this review, ADW, AH, AT, AW, ET, and CL screened studies or extracted data, or both.

ADW entered data for analysis.

DECLARATIONS OF INTEREST

ADW: none

JHB: none

NL: none

PA: none

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- NIHR Applied Research Collaboration, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods section was updated to clarify that we would run sensitivity and subgroup analyses only on our primary outcomes. This was for reasons of pragmatism.

We had initially planned to run additional analyses, but did not conduct them due to a lack of data, as previously discussed in the review. We had planned to compare studies that used more stringent smoking cessation definitions, however we could not compare between point prevalence versus continuous smoking cessation as the studies did not report sufficient data. We did, however, run post hoc analyses to explore the impact of controlling for secondary prevention medication and the definition of MACE on outcomes. Additionally, we planned to run post hoc analyses to remove studies that did not have clinically validated coronary heart disease definitions, however no studies presented such, therefore we did not run the analysis.

While we had collected outcome data at two follow-up time points for studies that reported such data, we did not use these outcome data in our analysis. Again, this was for reasons of pragmatism.