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## **Interventions to reduce harm from continued tobacco use (Review)**

Lindson-Hawley N, Hartmann-Boyce J, Fanshawe TR, Begh R, Farley A, Lancaster T

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Interventions to reduce harm from continued tobacco use.

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# Interventions to reduce harm from continued tobacco use

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## ABSTRACT

### Background

Although smoking cessation is currently the only guaranteed way to reduce the harm caused by tobacco smoking, a reasonable secondary tobacco control approach may be to try and reduce the harm from continued tobacco use amongst smokers unable or unwilling to quit. Possible approaches to reduce the exposure to toxins from smoking include reducing the amount of tobacco used, and using less toxic products, such as pharmaceutical, nicotine and potential reduced-exposure tobacco products (PREPs), as an alternative to cigarettes.

### Objectives

To assess the effects of interventions intended to reduce the harm to health of continued tobacco use, we considered the following specific questions: do interventions intended to reduce harm have an effect on long-term health status?; do they lead to a reduction in the number of cigarettes smoked?; do they have an effect on smoking abstinence?; do they have an effect on biomarkers of tobacco exposure?; and do they have an effect on biomarkers of damage caused by tobacco?

### Search methods

We searched the Cochrane Tobacco Addiction Group Trials Register (CRS) on the 21st October 2015, using free-text and MeSH terms for harm reduction, smoking reduction and cigarette reduction.

### Selection criteria

Randomized or quasi-randomized controlled trials of interventions to reduce the amount smoked, or to reduce harm from smoking by means other than cessation. We include studies carried out in smokers with no immediate desire to quit all tobacco use. Primary outcomes were change in cigarette consumption, smoking cessation and any markers of damage or benefit to health, measured at least six months from the start of the intervention.

### Data collection and analysis

We assessed study eligibility for inclusion using standard Cochrane methods. We pooled trials with similar interventions and outcomes (> 50% reduction in cigarettes a day (CPD) and long-term smoking abstinence), using fixed-effect models. Where it was not possible to meta-analyse data, we summarized findings narratively.

## Main results

Twenty-four trials evaluated interventions to help those who smoke to cut down the amount smoked or to replace their regular cigarettes with PREPs, compared to placebo, brief intervention, or a comparison intervention. None of these trials directly tested whether harm reduction strategies reduced the harms to health caused by smoking. Most trials (14/24) tested nicotine replacement therapy (NRT) as an intervention to assist reduction. In a pooled analysis of eight trials, NRT significantly increased the likelihood of reducing CPD by at least 50% for people using nicotine gum or inhaler or a choice of product compared to placebo (risk ratio (RR) 1.75, 95% confidence interval (CI) 1.44 to 2.13; 3081 participants). Where average changes from baseline were compared for different measures, carbon monoxide (CO) and cotinine generally showed smaller reductions than CPD. Use of NRT versus placebo also significantly increased the likelihood of ultimately quitting smoking (RR 1.87, 95% CI 1.43 to 2.44; 8 trials, 3081 participants; quality of the evidence: low). Two trials comparing NRT and behavioural support to brief advice found a significant effect on reduction, but no significant effect on cessation. We found one trial investigating each of the following harm reduction intervention aids: bupropion, varenicline, electronic cigarettes, snus, plus another of nicotine patches to facilitate temporary abstinence. The evidence for all five intervention types was therefore imprecise, and it is unclear whether or not these aids increase the likelihood of smoking reduction or cessation. Two trials investigating two different types of behavioural advice and instructions on reducing CPD also provided imprecise evidence. Therefore, the evidence base for this comparison is inadequate to support the use of these types of behavioural advice to reduce smoking. Four studies of PREPs (cigarettes with reduced levels of tar, carbon and nicotine, and in one case delivered using an electronically-heated cigarette smoking system) showed some reduction in exposure to some toxicants, but it is unclear whether this would substantially alter the risk of harm. We judged the included studies to be generally at a low or unclear risk of bias; however, there were some ratings of high risk, due to a lack of blinding and the potential for detection bias. Using the GRADE system, we rated the overall quality of the evidence for our cessation outcomes as 'low' or 'very low', due to imprecision and indirectness. A 'low' grade means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. A 'very low' grade means we are very uncertain about the estimate.

## Authors' conclusions

People who do not wish to quit can be helped to cut down the number of cigarettes they smoke and to quit smoking in the long term, using NRT, despite original intentions not to do so. However, we rated the evidence contributing to the cessation outcome for NRT as 'low' by GRADE standards. There is a lack of evidence to support the use of other harm reduction aids to reduce the harm caused by continued tobacco smoking. This could simply be due to the lack of high-quality studies (our confidence in cessation outcomes for these aids is rated 'low' or 'very low' due to imprecision by GRADE standards), meaning that we may have missed a worthwhile effect, or due to a lack of effect on reduction or quit rates. It is therefore important that more high-quality RCTs are conducted, and that these also measure the long-term health effects of treatments.

## PLAIN LANGUAGE SUMMARY

**Can smokers be helped to reduce the harm caused by cigarette smoking by smoking fewer cigarettes or using different tobacco products?**

### Background

The best thing to do to reduce the harms caused by smoking is to quit, but some people may not want to do this or may feel that they are unable to stop smoking completely. Cutting down the number of cigarettes smoked daily or using different tobacco products, such as chewing tobacco or low-tar cigarettes, may reduce some of the harm caused by smoking. It may also help people to stop smoking completely in the long term. On the other hand, reducing smoking or using other tobacco products may not improve health and could reduce a person's motivation to quit smoking altogether. It is important that we review the evidence to find out whether these approaches could help smokers who do not want to or cannot quit to reduce the harm caused by their smoking. We were mainly interested in whether these approaches improved the health of smokers, but also looked at smoking reduction and quitting rates.

### Study characteristics

We found 20 randomised controlled trials that tested ways to help people to cut down the number of cigarettes they smoked. Some of these just advised smokers to smoke less, but most also provided them with a product to help them cut down: nicotine replacement therapy (NRT), varenicline, bupropion, electronic cigarettes (ecigs), or snus (a form of smokeless, oral tobacco). We also found four randomized controlled trials that tested the effects of using cigarettes designed to reduce the damage caused by smoking: reduced tar,

carbon or nicotine cigarettes. Most of the studies used NRT to help people to reduce their smoking. All of the studies included people who were not planning to quit smoking soon. The research is current to October 2015.

### **Key results**

Eight studies (with 3081 smokers) found that using NRT roughly doubled the likelihood of halving the number of cigarettes smoked each day, compared to using a placebo. Using NRT in this way also nearly doubled the likelihood of quitting completely. One trial each tested bupropion, varenicline, ecigs and snus to help reduce the harms caused by smoking, and there was no evidence that any of these treatments helped smokers to reduce the number of cigarettes they were smoking each day. This may be because there has not yet been enough research into these methods. Only one of the trials testing cigarettes designed to reduce risk measured their effect on the number of people quitting smoking. It found that people were not more likely to quit smoking if they used reduced-nicotine cigarettes than if they smoked their usual cigarettes. We did not find any trials which reported the long-term health effects of the treatments, and so it remains uncertain how much health benefit there is from reducing the number of cigarettes smoked each day or smoking cigarettes designed to be less harmful.

### **Quality of evidence**

The tobacco industry funded three of the included studies of cigarettes designed to reduce risk. None of the studies looked at whether there had been a long-term change in the health of the users. We rate the quality of the evidence looking at how many people quit smoking as 'low' or 'very low', generally because the findings are based on a small number of studies. We need more studies to investigate methods of reducing the harm caused by continued smoking. These need to measure the health of the users over a long period.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Interventions to reduce the harms caused by continued smoking							
<b>Patient or population:</b> Smokers who cannot or do not want to quit smoking <b>Setting:</b> Varied <b>Intervention:</b> Various harm reduction aids (NRT, behavioural advice, bupropion, varenicline, ecigs, snus, low-nicotine cigarettes) <b>Comparison:</b> <b>Various controls</b> (placebo, usual care, brief advice, self-help, regular cigarettes)							
Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with control	Risk with harm reduction aid				
Long-term change in health status		We found no studies that reported this primary outcome		Not applicable	(0 RCTs)	Not applicable	
Cessation: NRT vs placebo follow-up: 12 to 24 months		Study population		RR 1.87 (1.43 to 2.44)	3081 (8 RCTs)	⊕⊕○○ LOW <sup>1</sup>	
		5 per 100	10 per 100 (7 to 13)				
Cessation: Bupropion vs. placebo follow up: 6 months		Study population		RR 1.27 (0.67 to 2.40)	594 (1 RCT)	⊕⊕○○ LOW <sup>2</sup>	
		5 per 100	7 per 100 (4 to 13)				
Cessation: Varenicline vs placebo follow-up: 6 months		Study population		RR 1.95 (0.86 to 4.40)	218 (1 RCT)	⊕⊕○○ LOW <sup>2</sup>	
		7 per 100	14 per 100 (6 to 32)				
Cessation: Ecigs vs placebo follow-up: 12 months		Study population		RR 2.75 (0.97 to 7.76)	300 (1 RCT)	⊕⊕○○ LOW <sup>2</sup>	

	4 per 100	11 per 100 (4 to 31)			
Cessation: Snus vs placebo follow-up: 6 months	Study population		RR 3.06 (0.84 to 11.08)	319 (1 RCT)	⊕⊕○○ LOW <sup>2</sup>
	2 per 100	6 per 100 (2 to 21)			
Cessation: Low-nicotine cigarettes vs regular cigarettes follow-up: 6 months	Study population		RR 1.38 (0.13 to 14.79)	135 (1 RCT)	⊕○○○ VERY LOW <sup>23</sup>
	2 per 100	3 per 100 (0 to 27)			
Cessation: Behavioural reduction advice vs health mailings follow-up: 12 months	Study population		RR 1.49 (0.59 to 3.76)	320 (1 RCT)	⊕○○○ VERY LOW <sup>24</sup>
	4 per 100	7 per 100 (3 to 17)			

\***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; RR: Risk ratio; NRT: nicotine replacement therapy; Ecigs: electronic cigarettes

#### GRADE Working Group grades of evidence

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** 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 quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

<sup>1</sup>Downgraded two levels due to imprecision. Small number of events (< 300), and wide confidence intervals.

<sup>2</sup>Downgraded two levels due to imprecision. Small number of events (< 300), and small number of studies.

<sup>3</sup>Downgraded one level due to risk of bias. The study was intentionally unblinded to simulate a 'real world' situation, but this provides potential for detection bias. There were more dropouts in the intervention arm than the control arm, due to "not liking the cigarettes".

<sup>4</sup>Downgraded one level due to indirectness. Participants were awaiting surgery and so a very specific population, which may differ from the general population.

## BACKGROUND

### Description of the condition

The morbidity and mortality associated with smoking is well established. People who stop smoking can reduce their risk of developing smoking-related diseases (Anthonisen 2005; Doll 2004), so the primary strategy for reducing harm due to tobacco smoking must be to encourage cessation. However, despite the fact that most people who smoke say that they want to stop, the prevalence of smoking is declining very slowly, even in those countries where tobacco control policies are well developed, and in some cases prevalence is still rising (Bilano 2015). In 2005 the World Health Organization (WHO) Framework Convention on Tobacco Control formalized a global commitment to reduce tobacco use worldwide and make tobacco control a global health priority (WHO 2003). In 2014, based on this Framework, the WHO member states went on to agree a target of a 30% relative reduction in tobacco use worldwide by 2025 (WHO 2013). However, based on the actual decline in smoking prevalence, predictions of trends to 2025 suggest that only 25% of countries worldwide will be likely to experience this decrease in smoking men, and only 52% will be likely to experience this decrease in smoking women from 2010 to 2025. This means fewer than half of countries globally are likely to meet the WHO targets, and this issue is not limited only to low- and middle-income countries (Bilano 2015). Although it is important to continue to motivate and assist people to quit, it may therefore be reasonable to seek ways to reduce the harm from continued smoking for people who are not ready to or cannot quit, as a secondary strategy to improve global health.

### Description of the intervention

There are multiple approaches that may have potential for harm reduction for people who do not want to give up tobacco or nicotine use completely. Shiffman 2002 has provided a catalogue of these with a conceptual structure of their characteristics. They cover many different intended intermediate effects and mechanisms. They also differ in the likely ease of the behaviour change needed to adopt them and related appeal to smokers, and their expected population risk. Shiffman 2002 categorizes tobacco harm reduction into the following four approaches:

1. Methods to establish and adhere to tobacco abstinence, as acknowledged above;
2. The use of tobacco products in a way or in a form that is less harmful than traditional products;
3. The use of pharmaceutical products to reduce tobacco use or the harm caused; and
4. Changes in behaviours that will reduce harm.

Categories two to four are the subject of this review.

Products that fall within the second category are referred to as potential reduced-exposure products (PREPs), which are:

“(a) modified tobacco products that contain reduced levels of one or more toxins (for example, cigarettes with reduced tobacco-specific nitrosamines through new curing processes, the addition of catalysts to reduce polycyclic aromatic hydrocarbon carcinogens produced by smoke, the use of genetically modified plants to reduce nicotine or nitrosamines, or the use of filters to selectively reduce toxicants), (b) cigarette-like devices, such as those that heat rather than burn tobacco, and (c) oral non-combustible products, such as snus” (Hatsukami 2005a).

Some oral smokeless tobacco products have been estimated to be approximately 90% less harmful than smoking cigarettes (Levy 2004). Research on alternative tobacco products has largely been conducted within the tobacco industry and has generally attempted to modify the characteristics of existing tobacco-containing products, or to design new types of commercial tobacco products, to make tobacco use less dangerous. Very large, independently-conducted, long-term trials are required to fully evaluate their effects (Murrelle 2010).

The use of pharmaceutical products to reduce harm could, for example, refer to using any of the existing pharmacotherapies already available to help people to quit smoking, such as nicotine replacement therapy (NRT), varenicline or bupropion, to reduce tobacco consumption. There is variation in whether NRT is licensed for use as a reduction aid across countries; for example, the US Food and Drug Administration (FDA) have not approved the use of NRT for smokers who wish to cut down the amount they smoke without wanting to quit. However, the Medicines and Healthcare Regulatory Authority (MHRA) in the UK have licensed it for this purpose. Finally, “changes in behaviours that will reduce harm” applies to behaviour change interventions such as reducing the number of cigarettes smoked each day (CPD), otherwise known as ‘controlled smoking’, which could be carried out alongside the use of other aids, such as PREPs or pharmaceutical products.

### How the intervention might work

There are two major routes through which we would expect the above harm reduction approaches to work: 1) by promoting subsequent smoking cessation, as a by-product of harm reduction (rather than encouraging quitting specifically); and 2) by reducing the health effects of smoking without quitting completely. There is evidence that the smoking reduction potentially promoted by the majority of harm reduction approaches is associated with an increase in subsequent cessation. A qualitative systematic review (Hughes 2006) of 19 observational studies and randomized controlled trials (RCTs) showed no indication that CPD reduction had a negative impact on future cessation; in fact, 16 of the 19 studies found reduction was associated with higher eventual quit rates. This association may be because reduction increases self-efficacy, disrupts pharmacological conditioning or reduces depen-



dence, or both. However, there is also evidence that attempts at smoking reduction can be undermined by other unconscious adjustments to smoking behaviour, for example taking longer, deeper puffs of a cigarette to maintain previous nicotine levels (Scherer 1999). Using an alternative reduced-harm nicotine source (such as NRT, snus, electronic cigarettes (ecigs)) to support behavioural reduction could help to compensate for this, by reducing nicotine withdrawal and subsequent cravings. In Sweden the use of snus as a cigarette substitute has been credited for a reduction in smoking among men, which is associated with lower tobacco-related mortality rates in Sweden than in other European countries (Ramstrom 2014). There is mixed evidence for the effects of smoking reduction on disease and health markers. For example, a systematic review reports that their largest included study found a reduction in lung cancer risk in smokers who reduced consumption compared with those who maintained their smoking behaviour (Pisinger 2007); however, a later study found no evidence of a reduction in risk (Hart 2013). There is some evidence that smoking reduction can reduce biomarkers related to the risk of cancer or carcinogen exposure, or both; however, it is unclear whether this reduces the incidence of cancer (Pisinger 2007).

### Why it is important to do this review

Most evidence investigating the link between smoking reduction and health currently comes from observational, epidemiological studies, and there are issues with this. Firstly, because smoking is generally measured at two time points and if the later one demonstrates a lower rate than the initial one, it is assumed that smoking reduction has been maintained throughout the follow-up period, which may not be the case. Secondly, many of the studies have not used biomarkers to validate smoking consumption, which could mean that compensatory smoking (such as deeper puffs) is not accounted for. Finally, many of these studies have not included people who used alternative nicotine products to compensate for smoking, which may impact on the success of reduction, and therefore on the associated changes in health risks (Begh 2015). The nature of RCTs means that all of these factors can be controlled for more effectively (although this is not always the case), and where this has been done we can be more confident that results indicating associations between reduction and health are causal. By reviewing these studies, we can make a valuable contribution to the literature and to the debate surrounding harm reduction approaches.

However, the use of harm reduction strategies in relation to tobacco smoking is a controversial topic, which divides opinion. There are concerns that encouraging people to reduce their smoking may undermine their motivation to quit smoking in the long term, and that this may encourage the tobacco industry to market 'reduced risk' products and carry out biased research on their effectiveness (Hatsukami 2004). The availability of ostensibly less harmful tobacco products could even lead never-smokers to start

smoking, or ex-smokers to relapse, in the belief that the risks are acceptable. These are questions that cannot be answered by RCTs alone, and are outside the scope of this review; the results of this review should therefore be considered alongside research which investigates any potential negative impact of promoting harm reduction.

Despite the ongoing debate regarding the promotion of tobacco use harm reduction, in 2013 the UK National Institute for Health and Care Excellence (NICE) published their first version of guidance on how to offer harm reduction approaches to smokers unwilling or unable to quit in one step, who may want to use a long-term safer substitute for smoking, or may only be ready to reduce the amount they smoke (NICE 2013). This guidance therefore recommends some non-traditional interventions where the ultimate goal is still to quit (reducing smoking to quit), but also recommends behavioural smoking reduction with or without the use of NRT, and temporary abstinence with or without NRT for smokers who need to stop smoking for a set period of time, for example, during working hours, a long-haul flight, or a hospital stay. The guidance highlights that the health benefits of smoking reduction, rates of relapse and progression to stopping smoking among people who have opted to reduce the amount they smoke are still unclear, and that better evidence is therefore still required to support and inform the harm reduction approach. In addition, new products, such as ecigs, that have the potential to be used in a harm-reduction capacity have also become available since the last update of this review. Evidence is needed to inform whether these harm reduction interventions could be useful in reducing tobacco-related harm in smokers who cannot, or do not wish to, quit.

## OBJECTIVES

To assess the effects of interventions intended to reduce the harm to health of continued tobacco use. We considered the following specific questions:

- Do interventions intended to reduce harm have an effect on long-term health status?
- Do interventions intended to reduce harm lead to a reduction in the number of cigarettes smoked?
- Do interventions intended to reduce harm have an effect on smoking abstinence?
- Do interventions intended to reduce harm have an effect on biomarkers of tobacco exposure?
- Do interventions intended to reduce harm have an effect on biomarkers of damage caused by tobacco?

## METHODS

## Criteria for considering studies for this review

### Types of studies

Randomized or quasi-randomized controlled trials.

### Types of participants

People who smoke tobacco, but have no immediate intention to quit all tobacco use. We included trials which did not assess motivation if an aim was to reduce cigarette consumption, but not to quit entirely.

### Types of interventions

Interventions to reduce the amount smoked, or to reduce harm from smoking by means other than cessation, including switching to a potential reduced-exposure product (PREP), or making other changes to cigarette characteristics. We excluded interventions where a reduction in the number of cigarettes smoked over a short period, or a change in type of cigarette smoked (e.g. nicotine fading), was intended as a precursor to quitting completely. We deemed studies eligible for inclusion if they compared these interventions to any 'standard control', such as brief advice, no treatment or placebo, or compared one type of harm reduction intervention to another.

### Types of outcome measures

#### Primary outcomes

The preferred primary outcome was long-term change in health status, but we expected that this was unlikely to be assessed in randomized trials. The most appropriate proxy indicator to demonstrate a reduction in toxin intake from tobacco use, sufficient to lead to a clinically useful long-term health benefit is not known (Hatsukami 2005a). We have therefore considered and extracted any attempt made to measure a health marker.

In the absence of better health indicators, we have also assessed both the change in smoking rate from baseline and smoking cessation as primary outcomes. For smoking reduction outcomes, we preferred prolonged or continuous rates to point prevalence rates. Where studies did not incorporate abstinent participants in their reduction rates we have done this for the purposes of our meta-analyses, as participants who have quit smoking have by definition reduced to zero. As there was no expectation that participants would quit at the start of the intervention, we have favoured measures of abstinence based on behaviour towards the end of the follow-up period (i.e. point prevalence rates) over continuous or sustained abstinence rates (Hughes 2003). We preferred biochemically-validated rates to self-reported rates for both reduction and cessation outcomes. To be eligible for inclusion, a study had to

report at least one of these outcomes at least six months following baseline.

#### Secondary outcomes

We extracted information on any biochemical indicators of the amount of tobacco use, and on adverse events when the intervention being tested included the use of a pharmaceutical, nicotine- or tobacco-based substitute for tobacco smoking.

### Search methods for identification of studies

We searched the Cochrane Tobacco Addiction Group Trials Register (CRS), which includes controlled trials and other evaluations of interventions to change tobacco use behaviour, derived from systematic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO. At the time of search (21<sup>st</sup> October 2015) the Register included the results of searches of CENTRAL (Issue 10, 2015); MEDLINE (via OVID) to update 20151012; Embase (via OVID) to week 201541; PsycINFO (via OVID) to update 20151005.

The MeSH terms 'Harm reduction' and 'Risk reduction behavior' were only introduced in 2003, so free-text searches were the main method for identifying earlier relevant trials. Original terms used were 'harm reduction', 'smoking reduction', 'reduce\* smoking', 'tobacco harm', 'cigarette consumption near (reduction or reduce\*)', 'controlled smoking'. Risk Assessment [MeSH], Harm reduction [MeSH], Risk reduction behavior [MeSH]. The most up-to-date, full search strategy for identifying studies for this review update in the CRS is shown in [Appendix 1](#).

We also searched the reference lists of studies found in the literature search and the metaRegister of controlled trials database ([www.isrctn.com/page/mrct](http://www.isrctn.com/page/mrct)) to October 2015.

### Data collection and analysis

#### Selection of studies

Two authors (from AF, JHB, NLH, RB for this update; TL & previous author LS for previous versions) independently screened papers identified by the search strategy for possible relevance in two stages (titles and abstracts, and full-text). Both authors discussed any differences between them, and where necessary had recourse to a third author.

#### Data extraction and management

Two authors (from AF, JHB, NLH, RB for this update; TL & previous author LS for previous versions) independently extracted data from full-text papers deemed eligible for inclusion.

We checked for agreement, and discussed and resolved any differences within the author team.

We collected the following information for each trial:

- Country and setting of intervention
- Method of participant recruitment and main inclusion criteria in relation to motivation to change tobacco use
- Other participant characteristics, including age, sex, previous smoking habit, quit attempt history
- Description of intervention and control conditions
- Outcomes assessed, including all measures of tobacco use reduction and quitting, and all measures of exposure to tobacco and measures of potential harm
- The definition of 'harm reduction', and quitting
- Adverse events (where the intervention included the use of a pharmaceutical, nicotine- or tobacco-based substitute for tobacco smoking)

One author then entered the data into Review Manager 5 software for analysis, and another checked them.

### Assessment of risk of bias in included studies

Two authors (from AF, JHB, NLH, RB for this update; TL & previous author LS for previous versions) independently assessed the risk of bias for each included study, following the approach recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used domain-based evaluation to address the following areas: random sequence generation; allocation concealment; blinding (of participants, providers and assessors); and incomplete outcome data. We assigned a grade (low, high, or unclear) for risk of bias for each domain, resolving disagreements by discussion with a third author where necessary.

### Measures of treatment effect

For outcomes measured using continuous variables, for example carbon monoxide (CO) levels, the preferred outcome was the difference between the average change from baseline in the intervention and control groups.

For dichotomous outcomes, we summarized results of each study as a risk ratio (RR), with a 95% confidence interval (CI).

### Dealing with missing data

We assessed the potential for bias due to loss to follow-up. Where outcomes for individuals were missing, we planned to include them and assume that they had not stopped smoking or had not changed their behaviour in a favourable direction. This conservative approach is standard for the Cochrane Tobacco Addiction Group. We planned to note any exceptions to this, and to consider the sensitivity of results to different assumptions about missing data.

### Assessment of heterogeneity

We assessed whether trials used comparable interventions and measured similar outcomes, to guide our decision whether to pool data. Where we did decide to pool data we assessed statistical heterogeneity using the  $I^2$  statistic (Higgins 2003). We would deem a value greater than 50% as evidence of substantial heterogeneity.

### Assessment of reporting biases

We intended to assess reporting bias using funnel plots; however, this is only a robust approach where 10 or more RCTs contribute to an outcome. There are currently too few studies to support this approach.

### Data synthesis

We planned to pool data for meta-analysis where appropriate, i.e. where we did not detect substantial clinical and methodological heterogeneity. For example, we did not intend to pool harm reduction interventions using different classes of pharmacotherapy (such as NRT, bupropion, varenicline). Where data was pooled the decision whether to use random or fixed-effect models was partly informed by the statistical heterogeneity detected, with an  $I^2$  of 50% or over classed as substantial. Ultimately, we pooled studies using a Mantel-Haenszel fixed-effect model. We considered pooling behavioural interventions if they were of comparable intensity in terms of the presence or absence of face-to-face contact, and the number of contacts.

### Subgroup analysis and investigation of heterogeneity

In the event of heterogeneity, we considered subgroup analyses based on the intervention type (in both the experimental and control groups) and the characteristics of participants.

### Sensitivity analysis

We considered assessment of the sensitivity of meta-analysis results to the exclusion of studies that we rated as being at high risk of bias.

### 'Summary of findings' table

Our aim was to create a 'Summary of findings' table for the primary outcome of long-term change in health status. However, there were no studies which reported this outcome. As the only other outcome measured that we know to have a positive impact on health is complete abstinence, we created a table to summarize the smoking abstinence outcomes for the primary comparisons of each intervention. Following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

## RESULTS

### Description of studies

#### Results of the search

Full details of search results are not available for the previous versions of this review; however, the search we carried out for this update identified 659 non-duplicate records. We assessed the titles and abstracts of all of these studies and acquired the full text of 60 (representing 48 studies) to conduct a further eligibility assessment. We found nine studies to be eligible after this stage, of which three were ongoing (Caponetto 2014; NCT02124187; Taskila 2012; see [Characteristics of ongoing studies](#) table for more details). We therefore performed full data extraction on six completed studies, and have added them to the review for this update (Benowitz 2012; Caponetto 2013; Chan 2011; Hughes 2011; Joksic 2011; Nackaerts 2009), giving a total of 24 included studies.

#### Included studies

We include 24 studies, which aimed to test interventions to reduce the harm caused by continued tobacco smoking. Across studies, this involved behaviour change to reduce tobacco consumption or to replace traditional tobacco use with alternative products of (potentially) lower risk, or both. Studies typically recruited between 100 and 200 participants in each intervention or control group. The smallest had 93 participants in total (Riley 2002).

#### Participants

The methods of recruitment were varied. Most studies relied on advertising to attract community volunteers. One study proactively recruited participants by telephoning households and identifying people who smoked (Carpenter 2004). One study used multiple approaches, including direct mail to households (Etter 2004). One small study (Hanson 2008) was in adolescents in particular, and another specifically recruited electively hospitalized patients from a variety of wards in academic hospitals (Nackaerts 2009). Most studies excluded people currently interested in quitting smoking, but the assessments and cut-off points used to establish eligibility varied. Participants generally had to lack current interest in quitting, but some studies (e.g. Batra 2005; Bolliger 2000; Hausteine 2003; Joseph 2008) also required past failure in a serious quit attempt. This criterion was intended to exclude people likely to quit easily without assistance. Exceptions were Kralikova 2009, where participants were recruited on the basis that they did not have to be motivated to quit (cessation was recommended but not mandatory), and Joksic 2011, where participants did have to

be motivated to quit smoking but the intervention was smokeless tobacco and therefore participants were not willing to quit tobacco completely. However, despite using criteria to exclude people willing to attempt immediate quitting in the main, the long-term motivation to stop smoking often appeared high. For example, Wennike 2003 reported participants as having an average motivation to quit of 6.6 on a visual analogue scale of 0 to 10. Little information was available on the participants in two of the studies (Australia NNCG-017; Nackaerts 2009). Participants in the studies of PREPs (excluding smokeless tobacco) were volunteers who were paid for participation in research studies (Benowitz 2012; Mendes 2008; Roethig 2008; Sarkar 2008). In most studies participants had a baseline average smoking rate of between 20 and 30 CPD; however, participants had a baseline rate of 12 CPD in Hanson 2008, 19 CPD in Hughes 2011, and 18 CPD in Sarkar 2008.

#### Interventions and controls

##### Nicotine replacement therapy

Fourteen included trials provided or offered nicotine replacement therapy (NRT). They took place in the USA (Carpenter 2003; Carpenter 2004; Hanson 2008; Joseph 2008; Rennard 2006); Australia (Australia NNCG-017); Germany and/or Switzerland (Batra 2005; Bolliger 2000; Etter 2004; Hausteine 2003); the Czech Republic (Kralikova 2009); Denmark (Wennike 2003); Belgium (Nackaerts 2009); and China (Chan 2011).

Nine of these trials provided behavioural support to encourage smoking reduction, and randomized participants to NRT or placebo (Australia NNCG-017; Batra 2005; Bolliger 2000; Etter 2004; Hanson 2008; Hausteine 2003; Kralikova 2009; Rennard 2006; Wennike 2003), including one (Etter 2004) which also had a control group receiving only minimal behavioural support. Etter 2004 and Kralikova 2009 offered participants a choice of products, and in one of these participants could use a combination of types (Etter 2004). Bolliger 2000 and Rennard 2006 used an inhaler alone; Australia NNCG-017 and Wennike 2003 provided 2 mg or 4 mg gum, depending on baseline dependence, while Batra 2005 and Hausteine 2003 used 4 mg gum only. Hausteine 2003 involved additional stratification to arms, supporting reduction for a maximum of either four weeks or six months (resulting in a 2x2 study design). In the short-term reduction arms participants were asked at baseline to quit at week four, while in the long-term arm participants were asked simply to reduce as much as possible over six months. At the end of the six months, participants were advised that it was preferable to quit altogether; however, this was not the original goal and a specific cessation intervention was not offered. For the purposes of this review we are solely interested in the two long-term reduction arms (comparing nicotine gum to placebo gum). Hanson 2008 was borderline for inclusion, and so not included in meta-analyses. This was because after a short

period of reduction (four weeks) participants were offered a cessation intervention where they set a quit date and were provided with NRT. There were two intervention arms: one used nicotine gum and the other used nicotine patch; however, these were only provided in the second phase of the study, if participants decided to set a quit day after the period of reduction.

One study (Nackaerts 2009) investigated the use of nicotine patches versus placebo patches as a substitute for smoking, to induce “temporary abstinence”, during hospitalization.

A further two studies (Chan 2011; Joseph 2008) provided repeated counselling and encouragement to use NRT, compared to a control group that received only brief advice on the importance of quitting. Chan 2011 further split their counselling + NRT group, so that one group also received add-on counselling to encourage adherence to the NRT. However, for the purposes of our analysis we combined the two counselling + NRT groups and compared them to the brief-advice control. Joseph 2008 provided participants with nicotine gum, or, if this did not suppress withdrawal, with nicotine patch.

Two other NRT studies did not have a placebo control and were borderline for inclusion. As a result we have not included them in our meta-analyses. In Carpenter 2003 participants were recruited on the basis that they were not interested in quitting immediately, but that they were interested in quitting within the next six months. This was a pilot study, assessing whether assistance with cutting down increased the impact of subsequent brief advice to quit completely. Intervention participants were given a choice of NRT products and a target of reducing their daily cigarette consumption by at least 50% in four weeks, after which they were advised to quit, and given self-help materials to do so if desired. The control group received brief advice to quit at the initial visit, and those who set a quit date were offered NRT but no further support. In Carpenter 2004 the initial intervention focused on reduction, but participants were advised to quit and those that set a quit date were provided with additional support (i.e. a cessation intervention). Carpenter 2004 had three arms: a no-intervention control, motivational interviewing intended to increase interest in quitting, and advice to reduce with an offer of NRT. Both intervention arms included eligibility for free NRT if a quit date was set. Both Carpenter 2003 and Carpenter 2004 provided participants with a choice of NRT products (gum, patch or inhaler; and gum or patch respectively).

Across all NRT studies, the maximum length of time NRT could be used to aid reduction ranged from nine months (Haustein 2003) to 18 months (Bolliger 2000). In Nackaerts 2009 the nicotine patch was used as a complete substitute for smoking rather than whilst reducing. Participants were provided with patches until they were discharged from hospital, for a maximum of seven days.

## Bupropion

One USA study (Hatsukami 2004a) offered bupropion or placebo for 26 weeks to people attempting to reduce their smoking, with a target of 50% reduction in cigarettes smoked a day. Final follow-up was six months after the end of treatment. Participants who indicated a willingness to quit at any time remained on assigned treatment but enrolled in a seven-week cessation programme with weekly counselling visits followed by 19 weeks of follow-up.

## Varenicline

Hughes 2011, carried out in the USA, randomized participants to either varenicline or placebo for two to eight weeks. Participants were also provided with four counselling sessions (baseline, two weeks, four weeks and eight weeks) on methods that could be used to reduce the amount of cigarettes smoked. The aim of the study was to see whether varenicline would induce quit attempts in smokers who were not currently planning to quit. Final follow-up was six months after baseline.

## Electronic cigarettes

Another single study (Caponnetto 2013) encouraged participants who did not intend to quit to reduce their cigarette-smoking using electronic cigarettes (ecigs). There were three arms, all of which were instructed to use an ecig *ad libitum*; the difference between the three study arms was the nicotine content of the ecig nicotine cartridges provided (7.2 mg; 5.4 mg; 0 mg). Participants received 12 weeks-worth of cartridges. The identical appearance of the ecigs and cartridges was intended to blind participants and investigators to their treatment allocation. The study took place in Italy, at the Università di Catania, and had a follow-up of one year.

## Snus

Joksić 2011, which took place in Serbia, used the smokeless tobacco product, snus, to encourage participants to reduce their smoking. Although participants were told that their ultimate goal should be to quit, the aim in the first 24 weeks was solely cigarette reduction. We included this study despite the goal to quit cigarettes, as it instructed participants to switch to snus, and therefore not to quit tobacco completely. Participants were told to use a sachet of snus every time they felt the urge to smoke. The control group received placebo sachets of smokeless tobacco, which were almost identical to the snus product in appearance, feel, pH and taste, but contained no nicotine or tobacco. Study follow-up took place up to two years post-baseline. Joksić 2011 was sponsored by Swedish Match.

## Other PREPs (excluding smokeless tobacco)

There were also four studies comparing PREPs (excluding smokeless tobacco) to conventional cigarette use (Benowitz 2012; Mendes 2008; Roethig 2008; Sarkar 2008). For the purposes of this review we present studies of smokeless tobacco separately from



these other PREPs, which were all products mimicking cigarette smoking whilst potentially reducing the intake of harmful components. Three of the PREP studies were funded by a tobacco company (Mendes 2008; Roethig 2008; Sarkar 2008), and the fourth was funded by the National Cancer Institute and National Institute on Drug Abuse, National Institutes of Health, but a tobacco company provided the research cigarettes (Benowitz 2012). All four studies investigated products designed to reduce the risks of smoking in different ways. Mendes 2008 evaluated light and ultra-light tar cigarettes compared to continued use of conventional cigarettes; Sarkar 2008 investigated carbon-filtered cigarettes; Benowitz 2012 investigated reduced-nicotine content cigarettes, and Roethig 2008 evaluated an electrically-heated cigarette smoking system (EHCSS), a device used to smoke regular cigarettes, rather than an ecig. These studies had six- to 12-month follow-up, including regular research clinic visits for collection of samples for biochemical assessment of levels of markers of exposure and risk.

### Behavioural interventions

Two studies investigated behavioural interventions to change smoking behaviour without the use of pharmaceutical aids, nicotine or tobacco substitutes for cigarettes. Riley 2002, involving community volunteers only interested in reduction, compared two guided methods to reduce the number of cigarettes smoked. One intervention used computerized scheduled smoking to achieve a gradual reduction to 50% of baseline in two weeks. The comparison condition provided a treatment guide instructing in gradual reduction by selectively eliminating cigarettes. Glasgow 2009 provided an intervention for members of a Health Maintenance Organization who were due to have outpatient surgery or a diagnostic procedure via telephone. The individualized counselling consisted of participants being advised to gradually reduce their cigarette smoking by 50% or more, with cessation encouraged following reduction. This intervention was compared to usual care in the form of usual care plus generic health mailings.

### Outcomes

The main outcomes in most of the included studies were reduction or cessation, and these all had follow-up of at least six months. However, three of the studies investigating PREPs measured neither reduction nor cessation, and instead used biochemical assessments to measure potential markers of health risk. The smoking reduction and cessation outcomes used in this review were all assessed at least one month after the end of the treatment period, as well as being at least six months after the start of the intervention. The most consistently used reduction outcome was a reduction in self-reported cigarettes a day of more than 50% from baseline. Most studies used sustained reduction at multiple follow-ups, validated by any level of reduction in baseline CO. Other reduction

measures reported in some studies were average reduction in CPD, and average reduction in CO levels, cotinine levels and thiocyanate levels. These reductions could be expressed as absolute or percentage reductions, and were typically calculated using available data without imputing values for dropouts, and included people who were no longer smoking at assessment.

In those studies that did investigate health outcomes, analyses of changes in biomarker levels amongst reducers did not always distinguish between treatment groups. In addition, the wide variation in the markers used and the ways these were assessed meant that we could not attempt meta-analysis for these outcomes.

### Ongoing studies

During the 2016 update we also identified three studies deemed to be ongoing (Caponetto 2014; NCT02124187; Taskila 2012), where results are not currently available. These may be eligible for inclusion in a subsequent update. Caponetto 2014 is another ecig study which recruited people with schizophrenia with no intention of quitting. It has three trial arms: 1) high-nicotine ecig (24 mg); 2) ecig with no nicotine; and 3) nicotine-free inhalator. NCT02124187 is a very similar ecig study with the same investigator, recruiting participants with major depressive disorder, with the same study arms. Both of these studies began in 2014 and have a planned 52-week follow-up. Taskila 2012 is a completed but currently unpublished study assessing the effectiveness of pharmacist-delivered behavioural reduction programmes. Planned length of follow-up was six months. For further detail see [Characteristics of ongoing studies](#).

### Excluded studies

We found a variety of other studies which were potentially relevant but did not meet our inclusion criteria because they recruited participants that wanted to quit as a short-term aim, or the aim of the study was to quit smoking rather than to simply to reduce smoking or harm. Another common reason for exclusion was that the long-term change in smoking behaviour and associated change in biomarkers of harm were not a target of the study. Many of these were very short-term within-subject cross-over studies of smokers switching to PREPs developed by the tobacco industry. Another short-term excluded study used payment for reduced levels of carbon monoxide to encourage smoking reduction (Lamb 2005). One study estimated the amount of compensatory smoking in people switching to lower-tar cigarette brands (Frost 1995). For more detail on excluded studies and the reasons for exclusion, see [Excluded studies](#).

### Risk of bias in included studies

See [Characteristics of included studies](#) and [Figure 1](#).

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)
Australia NNCG-017	?	?	?	?
Batra 2005	?	?	?	+
Benowitz 2012	?	?	-	-
Bolliger 2000	+	+	+	+
Caponnetto 2013	+	+	?	+
Carpenter 2003	?	?	+	?
Carpenter 2004	?	?	-	?
Chan 2011	+	+	+	+
Etter 2004	+	?	+	+
Glasgow 2009	+	?	+	+
Hanson 2008	?	?	?	?
Hatsukami 2004a	+	?	?	+
Haustein 2003	+	+	+	+
Hughes 2011	?	+	+	?
Joksić 2011	+	+	+	+
Joseph 2008	+	+	-	+
Kralikova 2009	?	?	?	?
Mendes 2008	?	?	-	-
Nackaerts 2009	?	?	?	?
Rennard 2006	?	?	?	+
Riley 2002	?	?	-	?
Roethig 2008	?	?	-	+
Sarkar 2008	?	?	-	-
Wennike 2003	?	?	?	+

## Allocation

We judged 15 of the included studies to be at unclear risk of bias for random sequence generation. This was simply because the studies stated that they were randomized but then did not specify how the randomization sequence was generated, making it impossible to judge whether or not this was done adequately. We judged all other studies to be at low risk of bias for sequence generation, as they reported being randomized with a robust method of sequence generation (Bolliger 2000; Caponnetto 2013; Chan 2011; Etter 2004; Glasgow 2009; Hatsukami 2004a; Hausteine 2003; Joksic 2011; Joseph 2008).

When assessing allocation concealment, we rated most trials at unclear risk, due to a lack of reporting, i.e. 18 studies did not specify how participant allocation to study groups was concealed prior to and during randomization. However, we judged the remaining seven studies to be at low risk, as treatment was either organized and/or distributed by an independent pharmacist or researcher with no further involvement in the study (Bolliger 2000; Caponnetto 2013; Hughes 2011; Joksic 2011), or allocations were concealed up to treatment delivery in opaque sealed envelopes (Chan 2011; Hausteine 2003; Joksic 2011).

## Blinding

In seven cases we deemed blinding to be insufficient and rated the studies at high risk (Benowitz 2012; Carpenter 2004; Joseph 2008; Mendes 2008; Riley 2002; Roethig 2008; Sarkar 2008). Carpenter 2004 tested a behavioural intervention, which would be impossible to blind. Potential bias would have been minimized if the study arms had received the same level of support and if outcomes were biochemically verified, but this was not the case. In the other studies rated as high risk, group allocation was not blinded and the products provided across groups differed in nature so that there was a risk of performance bias. For example, in Joseph 2008 there were differences between the arms in the counselling provided, and in whether NRT was supplied. In nine cases we judged blinding to be at an unclear risk of bias (Australia NNCG-017; Batra 2005; Caponnetto 2013; Hanson 2008; Hatsukami 2004a; Kralikova 2009; Nackaerts 2009; Rennard 2006; Wennike 2003). This was because the study was described as “blinded”, “double-blinded”, or used a placebo, but with no details given as to who was blinded or how this was achieved, or both.

## Incomplete outcome data

Loss to follow-up was high in some trials. Although this is also a problem in cessation trials where participants wish to quit, study reports indicate that it was a larger problem in this population of smokers who were not as motivated to change their smoking

behaviour. We rated three studies (Benowitz 2012; Mendes 2008; Sarkar 2008) at high risk of bias for this domain, as there was a substantial difference in dropout rates between study groups.

Outcomes derived from continuous variables (mainly markers of health outcomes) were generally reported for continuing participants only. If dropouts are less likely to have changed their behaviour, these outcomes will overestimate the change in the trial population. In using a dichotomous outcome for reduction in cigarettes and calculating rates on an intention-to-treat basis, we, like the trialists, made the assumption that dropouts had not reduced by more than 50%. This will underestimate the change in the population if our assumption is incorrect. It does not remove the potential to introduce bias if the true change in behaviour amongst dropouts is confounded by treatment group. The trials of PREPs had particularly high losses to follow-up, which was higher in groups using the unfamiliar products.

## Other potential sources of bias

Studies typically reported sustained reduction measured by a self-reported cigarette consumption of less than 50% of baseline, validated by reduced levels of CO at follow-up visits. However, Hanson 2008, Hughes 2011 and Nackaerts 2009 did not report full information on smoking reduction in the long term. Hanson 2008 did not report reduction or cessation rates to the full length of follow-up (six months), or split by arm. Hughes 2011 covered self-reported smoking reduction at two-month follow-up and then CO-validated abstinence at six months, and Nackaerts 2009 gave self-reported abstinence at six months. Etter 2004, a study in the NRT group, did not report sustained abstinence at the longest (two-year) follow-up, and did not use biochemical validation because there was no personal contact with participants. Since these factors could overestimate the true reduction we tested the sensitivity of the relevant meta-analysis to exclusion of this trial.

Three of the included studies remain unpublished; two were presented at conferences (Hausteine 2003; Nackaerts 2009) and one was identified from internal reports provided by Pfizer (Australia NNCG-017).

## Effects of interventions

See: [Summary of findings for the main comparison](#)  
[Interventions to reduce the harms caused by smoking in people who cannot or do not want to quit smoking](#)

## Type of intervention

### Nicotine replacement therapy

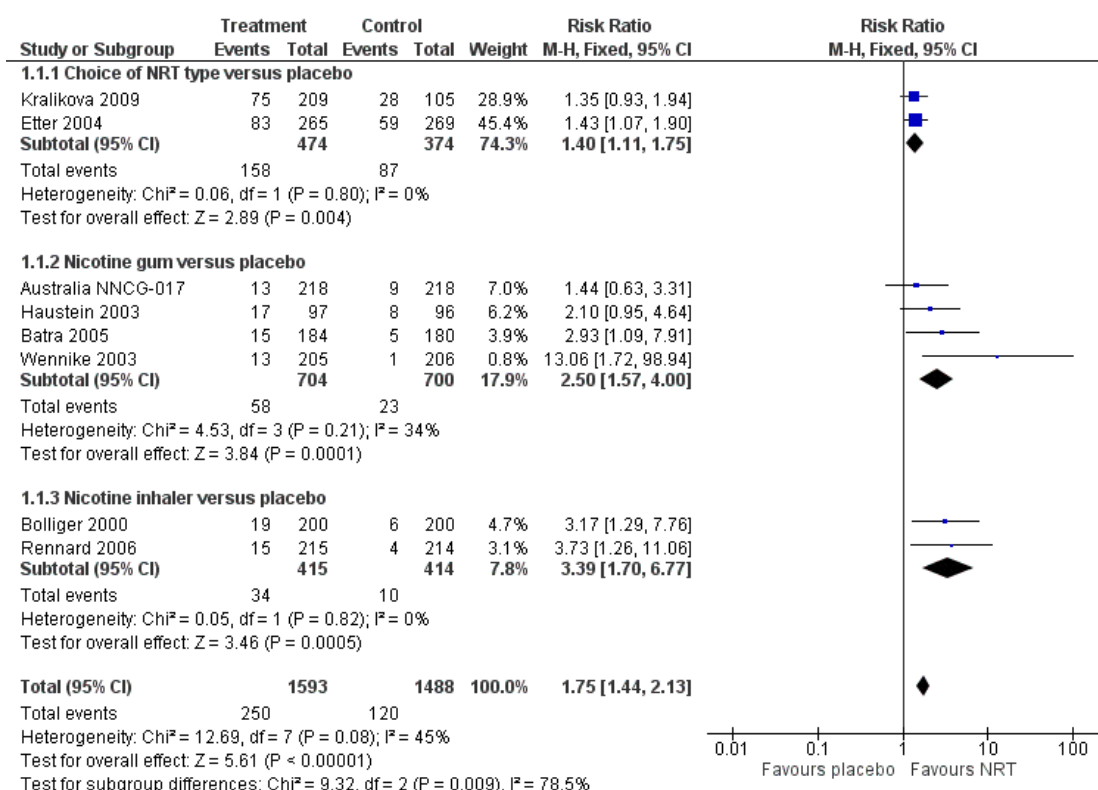


## Smoking reduction outcomes

We pooled eight trials of nicotine replacement therapy (NRT) versus placebo in adults. Overall there was a statistically significant effect of NRT on the likelihood of reducing cigarette use by 50% or more from baseline (risk ratio (RR) 1.75, 95% confidence interval (CI) 1.44 to 2.13; 3081 participants; [Analysis 1.1](#); [Figure 2](#)). There was moderate heterogeneity ( $I^2 = 45\%$ ). Two studies, [Etter 2004](#); [Kralikova 2009](#), contributed most weight to the analysis. [Etter 2004](#) used self-reported reduction and many more participants claimed to have reduced than in other studies, although the relative effect of treatment was smaller. We used data from the two-year follow-up in the analyses but also tested the sensitivity to

the use of five-year follow-up data. [Kralikova 2009](#) was not typical because participants appear to have been more motivated to quit than to reduce, and many did so. We conducted a sensitivity analysis to assess the impact of excluding these two studies. Since they showed relatively less effect on reduction, the effect was to increase the point estimate whilst widening the confidence intervals and reducing heterogeneity. However, the effect was still statistically significant (RR 2.77, 95% CI 1.88 to 4.08,  $I^2 = 9\%$ ; 2233 participants). [Etter 2004](#) also had a non-placebo control group, not included in the analyses above. Including this group in the control condition would have increased the effect. Using the five-year data for this study did not substantially alter the result.

**Figure 2. Forest plot of comparison: 1 Nicotine replacement therapy to assist smoking reduction versus placebo, outcome: 1.1 Reduction in cigarettes/day of > 50% of baseline or cessation.**



We performed a subgroup analysis to see whether the effect differed according to the type of NRT being used (i.e. a choice of NRT, nicotine gum, or nicotine inhaler; [Figure 2](#)), and found that NRT resulted in significantly more reducers than placebo in all cases. However, there is evidence of between-group differences ( $P$

$= 0.009$ ) with nicotine gum (RR 2.50, 95% CI 1.57 to 4.00,  $I^2 = 34\%$ ; 1404 participants; [Analysis 1.1.2](#)) and nicotine inhaler (RR 3.39, 95% CI 1.70 to 6.77,  $I^2 = 0\%$ ; 829 participants; [Analysis 1.1.3](#)), resulting in more reducers than choice of NRT (RR 1.40, 95% CI 1.11 to 1.75,  $I^2 = 0\%$ ; 848 participants; [Analysis 1.1.3](#))

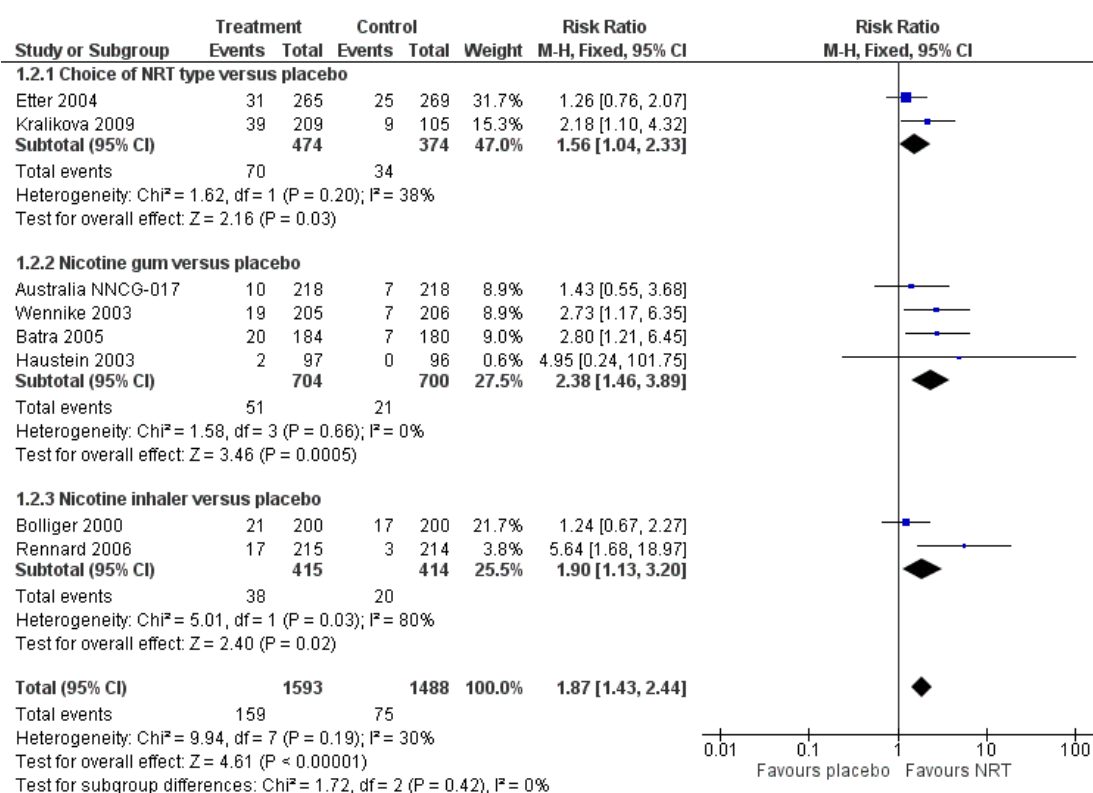
relative to placebo.

Joseph 2008 and Chan 2011 differed from the other studies in combining NRT and counselling versus a brief advice control, so we pooled these trials separately (RR 1.75, 95% CI 1.26 to 2.43,  $I^2 = 32\%$ ; 1306 participants; Analysis 2.1). Again, there was a statistically significant effect on reduction; however, Chan 2011 was a larger study and therefore contributed much of the weight. Joseph 2008 as a single study found a small non-significant effect.

### Cessation outcomes

Pooling the eight NRT-versus-placebo trials in adults, we found a statistically significant effect of NRT in increasing quit rates by the end of follow-up (RR 1.87, 95% CI 1.43 to 2.44; 3081 participants; Analysis 1.2) with moderate heterogeneity ( $I^2 = 30\%$ ). We again produced a subgroup analysis to assess any effect of the type of NRT used. No significant differences emerged between subgroups. For all three subgroups NRT resulted in statistically significantly higher pooled quit rates than placebo (Analysis 1.2.2; Figure 3).

**Figure 3. Forest plot of comparison: 1 Nicotine replacement therapy to assist smoking reduction versus placebo, outcome: 1.2 Cessation at long-term follow-up (subgroups by type of NRT).**



Pooling the two studies which compared NRT with behavioural support to brief advice found no statistically significant effect (RR 1.49, 95% CI 0.89 to 2.50,  $I^2 = 27\%$ ; 1306 participants; Analysis 2.2), with neither study individually finding a significant effect on quit rates (Chan 2011; Joseph 2008).

Nackaerts 2009 was the only study in the review which investigated the use of NRT (specifically nicotine patches) to aid temporary

abstinence. This study only reports abstinence at long-term (six-month) follow-up and found almost identical quit rates in the patch (44/150; 29%) and placebo (41/146; 28%) groups.

In two studies the control groups did not get a placebo and there was the option of a cessation intervention at the end of the short-term reduction intervention (as previously discussed, these studies were borderline included and therefore not pooled in meta-analysis).

ses). In the first (Carpenter 2003), cessation rates were non-significantly different (5/32 versus 3/35, RR 1.82, 95% CI 0.47 to 7.02) and non-quitters reduced their CPD compared to controls. In the second (Carpenter 2004), reduction and quit rates were significantly higher in the NRT and behavioural support group than in the no-treatment control, but advice to reduce before quitting had similar effects on reduction and cessation to the motivational interviewing intervention designed to increase interest in quitting. We did not pool one small pilot study amongst adolescents (Hanson 2008), which also gave the option of a cessation intervention after a four-week reduction intervention. Furthermore, cessation was not reported by group and a reduction of more than 50% was not reported at six-month+ follow-up. There was no evidence of any treatment effects, and although average CPD was smaller in all three conditions at six months, average CO and cotinine levels were non-significantly higher than at baseline.

### **Adverse events (AEs)**

Nine of the fourteen NRT studies compared one arm receiving NRT to another arm receiving placebo or no NRT, and reported on adverse events (Batra 2005; Bolliger 2000; Carpenter 2004; Etter 2004; Hausteine 2003; Joseph 2008; Kralikova 2009; Rennard 2006; Wennike 2003). The reporting across studies was generally sparse and varied. There was some evidence of a small elevation in non-serious adverse events in the study arms receiving active treatment; for example, Hausteine 2003 found that nausea and vomiting were more common in the active (59/193) than in the placebo group (17/192); Kralikova 2009 found that 82 adverse events occurred in the active arm versus 26 in the placebo arm (N = 209 and 105 respectively); and Batra 2005 reported 506 AEs in the active group and 370 in the control group (N = 184 and 180 respectively). However, this is also true for NRT used for cessation (Stead 2012), and there were no reports of any serious adverse events that might have been attributed to NRT use alongside continued smoking in any of the studies reporting safety outcomes.

### **Other markers of cigarette consumption**

We summarize reported changes in CPD, CO, thiocyanate and cotinine, expressed as percentage or absolute differences from baseline values, for the studies for which data were available in Analysis 1.3 (NRT versus placebo) and Analysis 2.3 (NRT + counselling versus brief advice). Studies typically showed reductions from baseline in both treatment and control groups, but this was usually based on continuing participants only. Differences between groups where reported were not always statistically significant. Because of the multiple differences in the ways in which changes were calculated and reported, we did not attempt any formal meta-analysis. People who reduce their cigarette consumption may inadvertently compensate for the reduction in nicotine by smoking the remaining cigarettes more 'efficiently' and therefore do not reduce their

intake of toxins as much as might be suggested from CPD. Using NRT to assist reduction may help avoid this compensation, so that toxin levels are reduced more for a similar level of CPD reduction. We found relatively little data about either compensation generally amongst reducers, or differential levels of compensation for NRT and placebo users. Bolliger 2000 reported that at 24 months sustained reducers had an average CPD of 25% of baseline, whilst CO and cotinine levels were only about 50% of baseline. The same study presented data on cigarette and CO reduction in the subgroup of intervention and placebo participants who were still using inhalers daily at various points during the treatment phase. After 18 months, the 22 active inhaler-users had an average reduction in CPD of 64% of baseline with a range of 0% to 100%. CO levels were only reduced by an average of 29% of baseline. Changes in CO levels ranged from a decrease of 92% to an increase of 222%. The eight placebo-users had a significantly smaller (P = 0.02) percentage reduction in CPD than the active inhaler-users (reduced to 33% of baseline, range 20% to 100%) and a non-significantly smaller percentage reduction in CO (reduced to 82% of baseline, range 50% to 177%). Batra 2005 reported the proportion of participants with a sustained reduction in CO levels of over 20% from baseline at 13-month follow-up. The proportions achieving this (13.6% active versus 5.6% placebo) were higher in both conditions than the proportion reporting sustained reduction greater than 50% in CPD, suggesting that all the reducers had achieved at least a 20% reduction in CO.

### **Health markers**

Six studies (Batra 2005; Bolliger 2000; Hausteine 2003; Joseph 2008; Kralikova 2009; Rennard 2006) assessed some biomarkers of disease risk, and we report these narratively in Analysis 1.4. Changes from baseline were assessed in those with available data and typically showed improvements over time but not between groups. Bolliger 2000 and Hausteine 2003 assessed differences between those participants who successfully reduced and those who did not, rather than between randomized groups. Again, there were not consistent between-group differences. One study (Rennard 2006) found no differences across treatment groups in any markers of cardiovascular risk, but also reported changes in cardiovascular risk factors from baseline to four-month follow-up in individuals who had reduced by more than 50%, including quitters. Results were not reported by treatment group, and we cannot separate the benefit of quitting from that of reducing; there was a significant increase in high-density lipoprotein (HDL) cholesterol. It was not possible to meta-analyse any of the reported data due to variations in the markers measured, the ways these were measured and the comparison groups used.

### **Bupropion**

Hatsukami 2004a, the single study testing bupropion, did not de-

test a long-term effect on reduction or cessation. Participants who became willing to make a quit attempt entered a cessation programme. When using all randomized participants as the denominator, long-term cessation rates were not statistically significantly different between the bupropion and placebo groups (RR 1.27, 95% CI 0.67 to 2.40; 594 participants; [Analysis 4.1.1](#)), although those in the bupropion group made their quit attempts sooner and had better short-term quit rates. Smoking reduction in participants who never attempted to quit, as defined by a reduction in urinary cotinine of more than 50%, was greater during the treatment phase but did not differ significantly at 12-month follow-up (RR 1.01, 95% CI 0.62 to 1.67; 594 participants; [Analysis 4.1.2](#)). Reduction in cotinine more than 50%: 2% (3/153) bupropion versus 5% (8/174) placebo, not statistically significant ( $P = 0.17$ ) excludes participants who entered the cessation arm of the study. The between-group difference in cotinine measured continuously was also non-significant at 12-month follow-up ([Analysis 4.2](#)).

Health markers were not assessed in this study.

Eight participants in the bupropion group and three in the placebo group reported adverse events that met study criteria for serious events. One of these was thought to be related to the bupropion treatment.

### Varenicline

[Hughes 2011](#) assessed point prevalence CO-verified quit rates at six-month follow-up, and found that 14% of the varenicline group and 7% of the placebo group were abstinent; however, this difference was not statistically significant (RR 1.95, 95% CI 0.86 to 4.40; 218 participants; [Analysis 5.1](#)). Smoking reduction was only reported at two-month follow-up, with statistically significant differences in self-reported CPD and exhaled CO.

Health markers were not assessed at all in this study.

There was no significant difference in adverse events between groups, with 12% of the active group and 10% of the placebo group stopping their medication due to an AE.

### Electronic cigarettes

[Caponnetto 2013](#) was the only completed study investigating ecigs as a harm reduction aid at the time of the searches. The study compared nicotine and non-nicotine ecigs, and found that there was a reduction in the number of regular cigarettes smoked, but without statistically significant between-group differences. The RR for more than a 50% reduction at one-year follow-up was 1.28 (95% CI 0.76 to 2.17; 300 participants; [Analysis 6.1.1](#)), and for abstinence 2.75 (95% CI 0.97 to 7.76; 300 participants; [Analysis 6.1.2](#)); both were statistically non-significantly in favour of ecigs with nicotine cartridges. The CPD reduction finding was mirrored by non-significant between-group differences in CO at 12-month follow-up ([Analysis 6.2](#)).

[Caponnetto 2013](#) also assessed whether weight, resting heart rate, systolic blood pressure (SBP) or diastolic blood pressure (DBP)

changed over time or between groups. There were no significant differences for any of these outcomes ([Analysis 6.3](#)). The frequency of adverse events was reported to be comparable across groups at each of the three assessment time points during the study (baseline, week 12, week 52). All symptoms were significantly reduced between baseline and week 52 in all groups ( $P < 0.001$ ). In particular, the rates of shortness of breath were reduced from 20% to 4% two weeks into the study. No serious adverse events were reported during the study.

### Snus

The one study ([Joksić 2011](#)) that investigated replacing cigarette smoking with another form of tobacco (smokeless, snus) found that there was not a significant difference in the number who achieved more than a 50% cigarette reduction (RR 0.94, 95% CI 0.81 to 1.11; 319 participants; [Analysis 7.1.1](#)) and complete abstinence (RR 3.06, 95% CI 0.84 to 11.08; 319 participants; [Analysis 7.1.2](#)) between the active and placebo groups at six months. However, statistically significantly more participants in the snus group achieved more than a 75% reduction at six-month follow-up (15/158, 9.5% in the snus group and 4/161, 2.5% in the placebo group;  $P = 0.01$ ). It should be noted that the last of these analyses was the result of an exploratory, post hoc investigation. Although this study went on to 48-month follow-up, we only use the data up to 24 months here, as after this point anyone who had not reduced by more than 50% or quit was excluded. When we assessed markers of consumption (CPD, CO and cotinine) as continuous measures, there were no significant between-group differences at 48 weeks; however, in both groups CPD and cotinine reduced by approximately a third, and CO reduced by around half ([Analysis 7.2](#)).

A number of health markers were measured; however, in no case did we find any differences over time or between groups ([Analysis 7.3](#)). Only two adverse events were reported in the snus arm of the study, and neither was judged to be associated with the use of snus.

### Other PREPs (excluding smokeless tobacco)

We summarize the main findings of these four studies narratively. All reported data on multiple biomarkers at multiple follow-up points ([Analysis 8.1](#)). Difficulties in interpreting the results include the large variation between participants, and the loss to follow-up of participants who did not maintain use of the test products. Some measures showed marked changes from baseline to the end of follow-up; for example, CPD typically increased in both experimental and control groups. Switching from full-strength (F) to low- (L) or very low-tar (UL) cigarettes ([Mendes 2008](#)) led to significantly lower average nicotine levels in the UL than in the F groups. CPD increased in all groups, possibly because cigarettes were provided free in a residential clinic. Carboxyhaemoglobin

(COHb) levels were similar between the F and UL groups, but higher in the L groups. Overall, although some exposures were reduced in the heavy smokers who switched to lower-tar alternatives, the absolute differences were not large, even when statistically significant. Use of carbon-filtered low- and medium-tar cigarettes led to reduced levels of gas phase biomarkers, but had no impact on particulate phase biomarkers (Sarkar 2008). Using an electrically-heated cigarette smoking system (EHCSS) reduced exposure to tobacco smoke constituents, especially carboxyhaemoglobin. Nicotine levels were reduced, which, combined with the higher dropout in the EHCSS group, suggests that the device may not have been very acceptable to smokers (Roethig 2008). In this study markers of cardiovascular risk factors including white blood cell counts and levels of HDL and LDL did show significant change in favourable directions compared to conventional cigarette use. Benowitz 2012 conducted bi-weekly clinics in a community clinic setting, a slightly different context to the aforementioned studies. This may account for the fact that cigarette consumption stayed relatively stable in both study conditions (reduced nicotine content-cigarettes versus usual cigarettes). Markers of consumption, such as CO, and cardiovascular biomarkers also stayed approximately the same in both groups. However, markers of nicotine consumption decreased in the group receiving reduced nicotine content-cigarettes. It would seem that, although nicotine consumption was successfully reduced in the experimental group, this did not result in participants compensating for this by smoking more cigarettes and thereby increasing their CO consumption. None of the four studies of PREPs reported reduction as a binary outcome (with a 50% cut-off), and only Benowitz 2012 assessed and reported smoking cessation. Only very small numbers quit (2/80 in the experimental, reduced nicotine cigarettes group, and 1/55 in the control, regular cigarettes group), resulting in a statistically non-significant effect, with very wide confidence intervals (RR 1.38, 95% CI 0.13 to 14.79; 135 participants; Analysis 8.2). A summary of measures of health markers across studies of PREPs can be found in Analysis 8.3.

### Behavioural interventions

In a study comparing computerized scheduled reduction to reduction by selective elimination of cigarettes (Riley 2002), both groups achieved statistically significant reductions in cigarettes from baseline, but there was no difference between the groups (RR 0.99, 95% CI 0.42 to 2.34; 93 participants; Analysis 9.1.1). There were also reductions in CO which did not differ between groups (Analysis 9.2). Point prevalence quit rates were higher at 12-month follow-up than at the end of treatment in both groups, suggesting no deterrent effect on quitting. At 12 months quit rates were statistically non-significantly higher in the computer scheduled group than the selective reduction group (RR 1.86, 95% CI 0.47 to 7.32; 93 participants; Analysis 9.1.2). An intervention of repeated telephone counselling and mailings

was not shown to assist reduction after 12 months relative to a control of health mailings in Glasgow 2009. No indicators of reduction were significantly higher in the intervention than in the control group at 12 months (25% vs 18.6% for 50% or more CPD reduction, 11% versus 7% for abstinence). The proportions reducing CO by more than 50% were also similar across groups at 12 months (14.0% versus 14.1%). When we looked at the overall continuous rates of CPD and CO reduction, both groups had reduced their cigarette consumption (by approximately a quarter of their baseline rate) and CO levels (by approximately a sixth of their baseline rate) on average (Analysis 10.2).

## DISCUSSION

### Summary of main results

The studies included in this review assess ways to help people who smoke to potentially reduce the harm caused by their smoking, either by reducing the number of cigarettes they smoke (with the help of behavioural methods to encourage change, or using pharmaceutical, nicotine or reduced-risk tobacco products as partial substitutes, or both), or by fully substituting regular tobacco products with 'reduced-risk' alternatives.

Studies included tested a wide range of approaches in the form of harm reduction interventions: nicotine replacement therapy (NRT); bupropion; varenicline; ecigarettes (ecigs); snus; other potential reduced-exposure tobacco products (PREPs); behavioural reduction advice; and a computerized smoking reduction programme. The opportunities for meta-analyses were limited, but there is evidence that NRT has an effect on successful smoking reduction (50%+ reduction in cigarettes a day (CPD)) and quit rates. There is insufficient evidence to suggest whether or not other harm reduction interventions are effective in reducing the harm caused by tobacco. Included trials suggest that people who use NRT to reduce their smoking are more likely to be able to reduce their cigarette consumption than people attempting to reduce with placebo. All the trials included a follow-up period when NRT was no longer provided, and one trial had follow-up 20 months after the end of NRT provision. There was no evidence that using NRT, with an aim to assist reduction, diverted people from attempting to quit, since cessation rates were also higher in NRT-treated groups. Whilst the trial evidence supports the concept of using NRT to reduce the amount smoked, showing a significant effect and an effect size that would be clinically important in many treatments, the absolute benefit from this use of NRT seems to be small. NRT increased the number of long-term sustained reducers, but against a background of very little reduction amongst the control group. Treatment typically increased the proportion of successful reducers from 1 - 3% to 6 - 9%, and the health benefit even for these people is unclear.



Some of the included studies allowed a comparison between change in CPD and changes in other measure of exposure to tobacco smoke. Data on markers of consumption are typically reported in different ways across studies, which makes it difficult to produce pooled across-study estimates of changes. However, these studies confirm that the extent to which participants reduced their CPD consumption was typically greater than the observed percentage reduction in other measures of their exposure to tobacco smoke, such as carbon monoxide (CO) and cotinine (Batra 2005; Joksic 2011 Rennard 2006; Wennike 2003; Glasgow 2009). Another review has estimated that the reduction in CO is typically about a third less than the reduction in CPD (Hughes 2005). However, it should be noted that as the baseline CO reading in a non-smoker is typically not zero, one would not necessarily expect percentage reductions in CO and CPD to map directly on to each other, even in the absence of compensatory smoking.

As predicted, studies provided very little information on changes in health or markers of this. Where this was reported, between-group comparisons were generally not made. Where they were made, there appeared to be no evidence of consistent benefits resulting from any of the interventions in terms of health and markers of health. Reporting on adverse effects was limited, but those studies that did report on them found nothing that has not already been detected when using the medications tested for their more traditional indication of cessation. This suggests that there is no additional risk of using NRT, bupropion, ecigs or varenicline for the purposes of harm reduction.

### Overall completeness and applicability of evidence

The field of harm reduction has progressed since the last update of this review was published in 2007 (partially demonstrated by the NICE harm reduction guidance published in the interim (NICE 2013). As a result, there is a wider range of interventions aiming for tobacco harm reduction (for example, ecigs). We took this into account and expanded our search terms for this update, making the search less sensitive and allowing us to broaden our reach for relevant studies. As a result we are confident that we have accounted for changes in the research field and have found the available, relevant literature. As expected we identified studies testing interventions new to this review (e.g. varenicline, snus, ecigs); however, in most cases we found only one study for each intervention, limiting the power needed to detect an effect, and hence the strength of the conclusions we can draw, due to imprecision. NRT therefore remains the only intervention for which there were multiple studies and for which we could produce meta-analyses. The lack of investigation into alternative approaches could account for the lack of effects observed in reducing smoking and increasing abstinence rates. The effect estimates with their corresponding 95% confidence intervals for harm reduction interventions other than NRT overlap with those in our meta-analysis of NRT studies, so

it is plausible that all medications work equally to support reduction, but further high-quality research would need to test this assumption.

The primary outcome which we wished to test in this review was long-term health, and it was impossible to do so. This would have given us a clearer idea of any benefits of harm reduction for those people who do not achieve cessation. Some studies measured biomarkers of health risk, but these were typically measured at short-term follow-up, inconsistently across studies, and only in those participants who had not dropped out earlier from the study. In many cases comparisons were only between those who had successfully changed their behaviour versus those who had not, rather than across randomized groups, making it impossible to assess the effects of the intervention in comparison to the control condition. However, cessation results in substantial health benefits (Anthonisen 2005; Doll 2004), so this was still a valuable outcome to assess.

### Quality of the evidence

For a number of 'Risk of bias' domains across studies, we rated the risks of bias as unclear, due to a lack of reporting. For instance, a number of trials (particularly those of NRT versus placebo) were described as "blinded", but without full details of how this was carried out, i.e. who was blinded and how it was done. In these cases bias is probably not a problem, but we cannot be sure. Some studies provided different harm reduction aids, or administered aids differently across study groups, meaning the studies were impossible to blind; we judged them to be at high risk of performance bias. Another key concern for research in the field of harm reduction is that it may motivate those with a stake in the tobacco industry to manufacture and test 'reduced-harm' alternatives to tobacco, in order to provide an alternative to complete cessation. All of the studies testing PREPs (including snus) in this review were in some way linked to the tobacco industry: Joksic 2011; Mendes 2008; Roethig 2008 and Sarkar 2008 were all sponsored by the tobacco industry. Benowitz 2012 was not, but the test cigarettes were supplied directly by the tobacco industry.

We planned to assess the quality of the evidence contributing to long-term health status outcomes using the GRADE approach (GRADE 2012). However, this proved impossible, as no studies reported on this outcome. As cessation is the only other outcome that we know can be used as an accurate measure of harm reduction, we have used the GRADE approach to assess the quality of the evidence contributing to the main comparison for each harm reduction aid (Summary of findings for the main comparison). In most cases we rated the evidence as 'low', and in some cases (low-nicotine cigarettes versus regular cigarettes; behavioural reduction advice versus health mailings) 'very low'. Across all outcomes this was due to imprecision, i.e. a small number of studies, resulting in a small number of events and wide confidence intervals around the effect size. In the case of the low-nicotine cigarettes versus

regular cigarettes cessation outcome this was also due to the fact that the study treatments were unblinded, providing the potential for detection bias, and that there were differential participant dropout rates between study groups. In the case of the behavioural reduction advice versus health mailings cessation outcome we also downgraded the evidence due to indirectness. The only study investigating this comparison was conducted in a very specific population (people awaiting surgery), and so the findings may not be applicable to the general population.

## Agreements and disagreements with other studies or reviews

The literature investigating the potential health benefits of interventions aimed at reducing smoking behaviour is very conflicted, and no clear conclusions have been drawn (Begh 2015; Hughes 2006; Tverdal 2006), leaving the overall public health benefit uncertain. Unfortunately, the data on biomarkers of health reviewed here do not resolve these problems. This is largely due to the design and reporting of the studies, which could be improved in future research.

An earlier review of the use of PREPs specifically to reduce harm concluded that “there is no evidence to suggest that there is enough of a reduction in tobacco toxin exposure with any of the existing PREPs to expect a significant reduction in disease risk, nor do we know the extent of toxin exposure reduction that is necessary to result in reduction of disease” (UMN TTURC 2005). Of particular note is that some participants using some types of PREPs had higher levels of CO than they had when smoking normally (for example, Fagerström 2000; Fagerström 2002b; Rennard 2002; Strasser 2007). This may be because smokers overestimate the ‘reduced risk’ of PREPs and compensate for this by consciously smoking more, or because smokers using PREPs are withdrawing from the component of the PREP that has been reduced and are increasing their cigarette consumption to compensate for this.

Aside from the direct health benefits that could be achieved by reducing smoking and the harmful components of cigarettes, harm reduction interventions could improve public health by ultimately leading to greater cessation rates in the long term. Limited evidence means this is currently difficult to assess across harm reduction interventions; however, the pooled group of studies comparing NRT to placebo in adults provides support for this hypothesis. This may occur because smoking reduction acts as a mediator of the effect of harm reduction interventions on cessation. Our review also found that the studies comparing NRT to placebo demonstrated a positive association between successful reduction and the intervention. Reviews by Hughes 2006 and Asfar 2011, also investigating the association between reduction and quitting, have found that the two are positively linked. However, in Asfar 2011 (which, like us, only looked at studies of smokers unwilling or unable to quit) this was only the case when interventions involved

pharmacotherapy to aid reduction; the evidence was inconclusive for interventions offering only behavioural support.

NRT, bupropion, varenicline and behavioural reduce-to-quit interventions have all been found to be effective cessation interventions in smokers who would like to quit (Cahill 2016; Hughes 2014; Lindson-Hawley 2012; Stead 2012). The evidence for ecigs as a quitting aid is sparse, but the two randomized controlled trials included in the Cochrane Review on the subject indicate that they also have a favourable effect on quitting (Hartmann-Boyce 2016).

## AUTHORS’ CONCLUSIONS

### Implications for practice

- Some people who smoke and do not wish to quit can be helped to cut down the number of cigarettes smoked and their intake of carbon monoxide by using NRT as a harm reduction aid.
- There is not enough evidence on whether varenicline, bupropion, ecigarettes, behavioural advice alone, snus or other potential reduced-exposure tobacco products (PREPs) help to reduce smoking rates, enhance quit rates, or reduce harm in any way when used as a harm reduction aid.
- There is insufficient evidence of a long-term health benefit of any interventions intended to help people reduce or alter but not quit tobacco use. However, there is evidence that reduction supported by NRT can increase the chances of complete cessation. Bearing this potential benefit in mind, alongside the strong safety profile of NRT, the benefits of advising smokers unwilling or unable to quit smoking to reduce their smoking using NRT are likely to outweigh any disadvantages, given that the alternative is likely to be no action.

### Implications for research

- The tobacco research field has developed a standard for assessing smoking abstinence (the Russell Standard) aimed at improving the reporting of smoking cessation trials (West 2005). The tobacco harm reduction field would benefit from developing similar standards to improve the consistency, quality and relevance of outcomes reported in this area.
- More high-quality studies with long-term follow-up are required, to aid the development of public health guidance, particularly considering the debate in the field and the emergence of ecigarettes.
- New studies should ensure that they report all outcomes across randomized groups, so that all of the intervention effects can be considered. This should accompany comparisons between successful and unsuccessful reducers, as this will help to explore the role of smoking reduction in mediating any effects of harm reduction interventions on cessation.

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\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

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

#### Australia NNCG-017

Methods	Country: Australia Recruitment: community volunteers Design: Double-blind, placebo-controlled randomized trial Dates of study: 1999-2001	
Participants	436 smokers ( $\geq 15$ CPD) not intending to quit (218 placebo; 218 NRT) Av. age 44, av. CPD 28, CO 26	
Interventions	1. Nicotine gum, 2mg or 4mg according to dependence score, for 4m 2. Placebo	
Outcomes	Reduction in CPD: sustained > 50% at 12m Abstinence: PP at 12m Validation: Reduction by reduced CO from baseline	
Notes	Unpublished study. Data from Pfizer summary; therefore limited details Funding declaration and conflict of interest: the study was conducted by Pfizer- the drug company who manufacture Nicorette NRT products	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as randomized but method not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind with placebo control, but no other details specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	436 participants were equally distributed in comparable groups. 276 attended the last follow-up; but N in each group not specified

## Batra 2005

Methods	Country: Germany and Switzerland Recruitment: community volunteers Design: Double-blind, placebo-controlled randomized trial Study dates: 2001-2002
Participants	364 smokers ( $\geq 20$ CPD) not intending to quit, at least 1 failed quit attempt within 2 yrs but not within 6m (184 NRT; 180 placebo) 41% F, av age 43, av. CPD 28
Interventions	1. Nicotine gum, 4 mg for up to 12m, 6 - 24 pieces daily 2. Placebo gum Aim to reduce as much as possible, 50% not given as objective. Counselling on reduction provided at 9 clinic visits
Outcomes	Reduction in CPD: sustained > 50% at 13m Reduction in CO: Sustained > 20% at 13m % CO reduction from baseline at 13m (For 55 intervention, 39 control participants including quitters who completed all visits) Also % reduction in CPD, cotinine, thiocyanate Abstinence: PP at 13m Validation: CO at all visits
Notes	Sustained quitters (2 intervention, 0 control) included with reducers Attrition: 138 (75%) gum vs 111 (62%) placebo reached at 13m Funding declaration: the study was funded by Pfizer- the drug company who manufacture Nicorette NRT products Conflicts of interest: "Anil Batra has received research funding from Pfizer Consumer Healthcare for this and other research projects. Karl Klingler has received research funding from Pfizer Consumer Healthcare for this research project. Björn Landfeldt, Åke Westin, and Tobias Danielsson are employees of Pfizer Consumer Healthcare. Hubertus M. Friederich has no conflict of interest to declare."

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind with placebo control, but no other details specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	98 nicotine participants (53%) and 69 placebo participants (38%) were seen for the 13m follow-up. A further 82 participants were followed up by telephone or let-

		ter at 13m, yielding a total of 249 participants who completed the study (n = 138 in nicotine group and n = 111 in placebo group)
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**Benowitz 2012**

Methods	Country: USA (community-based clinic) Recruitment: newspaper advertisements Design: parallel-group RCT Study dates: not stated	
Participants	135 smokers (80 PREP group; 55 usual smoking group) of at least 10 CPD for past year, not interested in quitting in next 6m, CO ≥ 25 ppm or saliva cotinine ≥ 100 ng/ml, 18 - 70 years old, healthy based on medical history and screening blood tests 53% F; av. age 37; av. CPD 23; CO 21 ppm	
Interventions	1. Reduced nicotine content-cigarettes (RNC): participants provided with 5 types of progressively lower nicotine content-cigarettes. First 4 levels smoked for 4 weeks each, lowest then smoked for 6m. Target nicotine level per cigarette 12, 8, 4, 2 and 1 mg as progressed through study. Were told to smoke study cigarettes as desired, but not to smoke any other type of cigarette and not to use other forms of tobacco or nicotine medications 2. Usual brand control: smoke own cigarettes as normal Both groups attended face-to-face bi-weekly visits at a community based clinic	
Outcomes	Markers of consumption: CPD, plasma nicotine, plasma cotinine, expired carbon monoxide Markers of carcinogens: urine NNAL, urine 3 + 4 hydroxyphenanthrenes, urine 2-Naphol, urine 2-hydroxyfluorene, urine 1-hydroxypyrene Health markers: SBP, heart rate, WBC count, haemoglobin, HDL cholesterol, fibrinogen Abstinence: 7-day PP, verified biochemically as plasma cotinine concentration of < 14 ng/ml or, if taking nicotine replacement medication, an expired CO concentration of < 5 ppm All measured up to 6m	
Notes	Funding declaration: the National Cancer Institute and National Institute on Drug Abuse, National Institutes of Health Philip Morris provided research cigarettes. Conflicts of interest: "N.L. Benowitz is a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expertwitness in litigation against tobacco companies. S. Hall has received material support for an ongoing clinical trial from Pfizer. No potential conflicts of interest were disclosed by the other authors."	
Risk of bias		
Bias	Authors' judgement	Support for judgement

**Benowitz 2012** (Continued)

Random sequence generation (selection bias)	Unclear risk	Randomized in blocks of 10, but method of sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	"The study was not blinded because we wanted to simulate a real world regulatory situation in which the nicotine content of cigarettes is progressively decreased with the knowledge of the smoker." Non-blinded so at risk of detection bias. Biomarkers of exposure were used
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on losses to follow-up somewhat unclear, but significantly higher proportion lost to follow-up in intervention than control group (27/80 lost intervention, 5/55 lost control). 17 of intervention dropouts left study due to "not liking the cigarettes"

**Bolliger 2000**

Methods	Country: Switzerland (2 hospital pulmonary clinics) Recruitment: community volunteers Design: Double-blind, placebo-controlled randomized trial Study dates: 1997-1999
Participants	400 smokers (200 NRT; 200 placebo), smoking > 15 CPD for 3+ yrs, failed at least 1 serious quit attempt in past 12m, wanting to reduce smoking as much as possible 52.5% F, av age 46, av. CPD 29, CO 27 ppm
Interventions	1. Nicotine inhalator, 6 - 12 cartridges over 24 hrs. Encouraged to decrease after 4m but use permitted up to 18m 2. Placebo inhalator (contained menthol only) Counselling on smoking reduction provided at each clinic visit (1, 2, 3, 6 wks, and 3, 4, 6, 12, 18, 24m). Smoking cessation was recommended as ultimate goal throughout study
Outcomes	Reduction in CPD: > 50%, sustained from week 5 at 24m Abstinence: sustained from wk 6 at 24m, PP cessation at 24m (Paper reports outcomes after 4m and 12m, also PP rates) Validation: Reduction validated by reduced CO from baseline (at 6 wks, 3m, 4m), but amount of reduction not specified, abstinence verified by CO < 10 ppm from wk 6 Bolliger 2002 reports on health risk markers for 25 successful sustained reducers compared to unsuccessful participants

**Bolliger 2000** (Continued)

Notes	PP rates of cessation increased through the study Attrition: 166 (83%) inhaler vs 144 (72%) completed 24m Funding declaration: Pharmacia and Upjohn Consumer Healthcare, Sweden Conflicts of interest: “TD, ÅW, and US are all employed by Pharmacia and Upjohn, Sweden, and AR, CTB, and JPZ have received funds for research from them.”	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated central list
Allocation concealment (selection bias)	Low risk	“Independent pharmacists dispensed either active or placebo inhalers”. The placebo inhalers were identical in appearance to the intervention inhalers
Blinding (performance bias and detection bias) All outcomes	Low risk	“double blind, placebo controlled”. The placebo inhalers were identical in appearance to the intervention inhalers
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 24m follow-up 83% were followed up in the intervention group and 72% in the placebo group

**Caponnetto 2013**

Methods	Country: Italy Recruitment: through local newspaper. Study took place at smoking cessation clinic at the Università di Catania Design: parallel-group RCT Study dates: 2010-2012
Participants	300 smokers (200 in ecig groups; 100 in placebo group). Inclusion criteria: smoked $\geq$ 10 factory-made CPD, for at least the past 5 years, aged 18 - 70 years, in good general health; not currently attempting to quit smoking or wishing to do so in the next 30 days, committed to follow trial procedures 37% F; av. age 44, av. CPD 21, CO 20
Interventions	1. 7.2 mg e-cig: "Categoria" e-cigarette (model "401") 3-piece e-cig model that closely resembles a tobacco cigarette. Loaded with "Original" 7.2 mg nicotine cartridges. 12-wk supply of cartridges provided Participants were given a free e-cigarette kit and were permitted to use the study product ad libitum throughout the day (up to a maximum of 4 cartridges a day, as recommended by the manufacturer) in anticipation of reducing the number of CPD smoked. Participants were also asked to fill in a 2-wk study diary. No emphasis on encouragement, motivation and reward for the smoking cessation effort

	<p>were provided, since this study was intended to monitor smokers (not wishing to quit) using e-cigs. After 12 wks participants were informed that no more cartridges would be provided by the investigators, but that they were advised to continue using their ecigarette if they wished to do so</p> <p>2. 5.4 mg e-cig: as for group 1 apart from participants received 6 wks of 7.2 mg cartridges and then 6 weeks of "Categoria" 5.4 mg nicotine (1.71, SD 0.09% nicotine)</p> <p>3. 0 mg e-cig: as for group 1 apart from cartridges were "Original" without nicotine (sweet tobacco aroma), supplied for 12 wks</p>
Outcomes	<p>Consumption: CPD; 50%+ reduction in CPD; expired CO</p> <p>Quit rates: complete self-reported abstinence from tobacco smoking - not even a puff (together with an exhaled CO concentration of 7 ppm or less) since the previous study visit</p> <p>All measured to 12m follow-up</p>
Notes	<p>Funding declaration: "This research was supported by a grant-in-aid from Lega Italiana AntiFumo. The study sponsor had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. The e-cigarette supplier had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. The "Categoria" electronic cigarette kit and cartridges were provided free of charge by the local distributor, Arbi Group Srl, Italy."</p> <p>Conflicts of interest: "RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl, the distributor of the Categoria<sup>TM</sup> e-Cigarette. The other authors have no relevant conflict of interest to declare in relation to this work. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials."</p>

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization sequence was computer-generated by using block size of 15 with an allocation ratio of 5:5:5 for each of the 3 study conditions (A, B, and C)
Allocation concealment (selection bias)	Low risk	The hospital pharmacy was in charge of randomization and packaging of the cartridges
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was ensured by the identical external appearance of the cartridges

**Caponnetto 2013** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	At 52-wk follow-up 35 of Group A, 37 of group B and 45 of Group C had dropped out. All participants received their allocated intervention. Overall 225 participants (75.0%) returned at wk 12, 211 (70.3%) at wk 24, and 183 (61.0%) for their final follow-up visit at wk 52. Baseline characteristics of those who were lost to follow-up were not significantly different from participants who completed the study, with the exception of gender: at wk 52, men were 71% of participants lost to follow-up, while 58% among those still present at wk 52 ( $P = 0.03$ , $\text{Chi}^2$ test). No significant difference was evident in dropout rates among study groups at any study visit ( $\text{Chi}^2$ test)
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**Carpenter 2003**

Methods	Country: USA Recruitment: community volunteers Design: randomized pilot trial Study dates: not stated	
Participants	67 smokers (brief advice 35; reduction 32), smoking > 10 CPD, with an interest in quitting eventually but not in next 30 days. At least 1 previous attempt. 69% F; av. age 44; av. CPD 24	
Interventions	1. Behavioural support to reduce by > 50% in 4 wks. NRT (gum or patch or inhaler) described and offered At 4 wks given brief advice to quit based on US guideline; weekly visits 2. Brief advice to quit at initial visit, NRT provided only if quit date set; weekly visits	
Outcomes	Change in CPD (50% reduction outcome only given for intervention group) Abstinence for 7 days at 6m (average reduction in CO only reported at 4 wks)	
Notes	Main objective of study was to assess whether assistance to reduce enhanced quit rates compared to advice to quit. Not included in meta-analysis as participants were willing to quit within 6 months (although not immediately) Funding declaration: “The study was supported by NIDA Grant DA 11557, NIDA Training Grant DA 07242, and NIDA Senior Scientist Award DA 00450.” Conflicts of interest: not stated	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

**Carpenter 2003** (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	Non-blinded, behavioural: participants were either asked to reduce with NRT or given brief advice to quit and used NRT if set a quit date. However, both groups were provided with NRT and smoking behaviour was biochemically verified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly reported

**Carpenter 2004**

Methods	Country: USA Recruitment: proactive calls to identify households with smokers Design: randomized controlled trial Study dates: not stated
Participants	616 smokers (212 reduction group; 197 motivation group; 207 no intervention), smoking $\geq 10$ CPD, not interested in cessation. 71% F, av. age 40, av. CPD 22, 65% precontemplators
Interventions	1. Behavioural support to reduce by either scheduled or hierarchical reduction. NRT (gum or patch) described and offered. At 6 wks given brief advice to quit based on US guideline. NRT offered at wk 6 if quit date set, NRT no longer available otherwise. 12 - 17 mins at each call 2. Motivational interviewing. '5 Rs' approach (Relevance/ Risks/ Rewards/ Roadblocks/ Repeated). Eligible for free NRT if quit date set. Mailed self-help materials, counsellor call within 5 days of TQD 3. Control. No intervention, assessment calls only. Common components: Phone contacts at 0, 3, 6, 24 wks
Outcomes	Reduction in CPD excl quitters at 24 wks PP abstinence at 24 wks Quit attempts, over 24 hrs and in 6m
Notes	Similar objective to <a href="#">Carpenter 2003</a> . Not included in meta-analysis as participants were offered a cessation intervention after 6 wks of reduction Funding declaration: "This study was supported by National Institute on Drug Abuse (NIDA) Grant DA 11557 and NIDA Training Grant DA 07242 to Matthew J. Carpenter, and NIDA Senior Scientist Award DA 00450 to John R. Hughes." The nicotine replacement therapy was supplied by GlaxoSmithKline Consumer Healthcare Conflicts of interest: not stated



<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Behavioural intervention, unblinded; level of support was not equivalent across all groups, and quit rates were not biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

## Chan 2011

Methods	Country: China Recruitment: through announcements in local media and contacting previous cohorts of smokers who had had cessation counselling. Study took place in smoking cessation clinics with face-to-face counselling Design: parallel-group RCT Study dates: 2004-2007
Participants	1154 smokers (928 reduction groups; 226 control group). Inclusion criteria: Chinese, aged 18+ years, smokes at least 2 CPD, no intention to quit in next 4 wks but interested in reducing smoking, no contraindication to NRT, not following other forms of smoking cessation or reduction interventions 16% F, av. age 42, av. CPD 20, av. CO 17
Interventions	1. Reduction & adherence (full intervention): 8 wks free supply of NRT (gum or patch according to participant preference). Counselling in smoking reduction and adherence to NRT given. Told to reduce their smoking; emphasized achieving the ultimate goal of complete cessation by focusing on the importance of smoking reduction before quitting, how reduction is useful and effective when quitting is difficult, and on how to reduce. A participant-centred intervention utilizing motivational interviewing techniques and the 5R approach (relevance, risk, rewards, roadblocks and repetition) was used to boost motivation. The 3-min ADIN adherence counselling was developed from the guidelines on adherence interventions by the World Health Organization, which emphasizes the importance of adherence to prescribed NRT dosage in the treatment of tobacco dependence, advantages of adherence and disadvantages of non-adherence, assessment and discussion of the ways to overcome barriers and a problem-orientated approach to improving adherence. Counselling was provided at baseline, wk 1 and wk 4. Participants also received a self-help quitting pamphlet, 'Tips for Quit Smoking', produced by Hong Kong Council on Smoking and Health 2. Reduction only: Participants were provided with the same 8-wk free supply of NRT

	<p>as group 1; however they were provided counselling in smoking reduction only, with no adherence element. Participants were told simply to reduce their smoking as in group 1 and were provided with specific reduction counselling. Counselling was provided at baseline, wk 1 and wk 4. They also received the self-help quitting pamphlet</p> <p>3. Control: Participants were not provided with any NRT. They were given simple advice on the health hazards of smoking and the importance of smoking cessation at baseline, and also received the pamphlet supplied to groups 1 and 2</p> <p>For the purposes of analyses we combined the intervention groups (1 and 2)</p>
Outcomes	<p>Consumption: reduction in CPD of at least 50% (validated by exhaled CO level reduction of 1 ppm+ compared to baseline); reduction in CO of at least 50%</p> <p>Quitting: 7-day point prevalence (validated by exhaled CO level of 9 ppm or less, or urinary cotinine concentration of 115 ng/ml or less)</p> <p>All measured at 6m follow-up</p>
Notes	<p>Funding declaration and conflicts of interest: "This study was funded by the Health and Health Services Research Fund, Hong Kong SAR (Project no. 01030611). Nicotine patches/gum provided free of charge to the subjects were provided free from Pfizer, later named as McNeil AB. Pfizer was not involved in the design and conduct of the study, in the collection, management, analysis or interpretation of the data, or in the preparation, review or approval of the manuscript. Moreover, we do not have any connection of any of the researchers with the tobacco, alcohol, pharmaceutical or gaming industries or anyone funded substantially by one of these organizations."</p>

### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random numbers for group assignment were generated by the research assistant (not the counsellors) of the project using a personal computer before participant recruitment
Allocation concealment (selection bias)	Low risk	Randomization was performed by opening of a serially-labelled, opaque and sealed envelope with a card inside indicating the randomly-allocated group by a trained smoking cessation counsellor
Blinding (performance bias and detection bias) All outcomes	Low risk	Behavioural interventions, so blinding impossible; however, biochemical validation places results at low risk. All participants including control group B were contacted at 6m by telephone by research assistants blind to group assignment of the participants

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no statistical difference in retention rates at all 3 time points between groups A1 and A2 (1 wk: 84.3% vs 83.7%; 4 wks: 72.4% vs 73.7%; 3m: 86.0% vs 85.7%). The retention rate at 6m was statistically higher in group B (A1: 89.1%; A2: 90.2%; B: 95.6%) but analysis was intention-to-treat
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#### Etter 2004

Methods	Country: Switzerland Recruitment: community volunteers Design: Randomized placebo-controlled trial Study dates: 1999-2007 (including 5 year follow-up)
Participants	923 smokers (265 NRT group; 269 placebo group; 389 no treatment group), smoking $\geq 20$ CPD, not intending to quit in next 6m, willing to commit to reduce consumption by half 52% F; av.age 43; av. CPD 29
Interventions	1. Choice of nicotine patch, 4 mg gum, inhaler or combination. 5-day supply of each provided initially, more could be ordered every 2 wks for 6m 2. Same choice, placebo products 3. Control, no products Minimal behavioural support: 20-page booklets after enrolment and after 3m survey, 2-page information leaflet at each mailing
Outcomes	Reduction in CPD: $\geq 50\%$ at 2 yrs (6m and 5-yr outcomes also reported in separate papers). Average reduction in CPD also reported Abstinence: 4 wks at 18m Validation: none
Notes	Placebo group only as control in meta-analysis (the no treatment control group was not included in meta-analyses); this is conservative for effect of NRT on reduction, but increases effect on abstinence By 5 yrs there was no significant difference in cessation rates or CPD due to increased cessation and reduction in controls Funding declaration: "This study was supported by grants from the Swiss National Science Foundation to JFE (3233-054994.98 and 3200-055141.98) and by the Swiss Federal Office of Public Health. Nicotine and placebo products were provided by Pharmacia Inc (Helsingborg, Sweden)." Conflicts of interest: not stated

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
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**Etter 2004** (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	Nicotine and placebo products were sent to participants in unbranded packaging, similar in the 2 groups, labelled "nicotine or placebo." The investigators had no in-person contact with participants and had only minimal (reactive) telephone contact. All documents sent by mail were identical in the nicotine and placebo groups. Thus, participants were not aware of the nature of the products they received, but the investigators were not blinded. After the end of the 6m intervention, participants were informed of whether they had received nicotine or placebo products
Incomplete outcome data (attrition bias) All outcomes	Low risk	93%, 93% and 90% of the nicotine, placebo and control groups respectively were followed up at 2 years

**Glasgow 2009**

Methods	Country: USA Recruitment: HMO members scheduled for outpatient surgery or diagnostic procedure Design: Randomized controlled trial Study dates: 2004-2006
Participants	320 smokers (164 intervention; 156 control), smoking > 20 CPD, not interested in quitting smoking; 73% F, av. age 55, av. CPD 21
Interventions	1. Telephone-based, individualized graduated reduction to 50% or more. Cessation encouraged following reduction. 4 phone sessions over 6m, 4 individually-tailored newsletters, 1 targeted newsletter 2. Usual care plus 3 generic health education mailings
Outcomes	Reduction: > 50% in CPD, > 50% in CO at 12m (and 3m) Abstinence: 12m PP
Notes	Funding declaration: "Funding was provided by the National Cancer Institute, grant # RO1 CA90974-01." Conflicts of interest: not stated
<b><i>Risk of bias</i></b>	

**Glasgow 2009** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using computer algorithm
Allocation concealment (selection bias)	Unclear risk	Randomized after baseline telephone assessment. Participants who did not attend in person for baseline biochemical samples were excluded from analyses
Blinding (performance bias and detection bias) All outcomes	Low risk	Behavioural intervention, so blinding was impossible; however, an attempt was made to match the intensity and contacts made in the 2 arms and biochemical measurements were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	71/391 without baseline samples excluded, similar across groups. 37% intervention and 18% control lost to follow-up, treated as continuing smokers

**Hanson 2008**

Methods	Country: USA, 14 high schools, Minneapolis St Paul Recruitment: Adolescents smoking $\geq 5$ CPD for at least 6m, wanting to reduce, no quit date set for next 2m Design: randomized, open-label trial Study dates: 2002-2004
Participants	103 adolescents (34 nicotine patch group; 33 nicotine gum group, 36 placebo group); 58% F, av. age 17, av. CPD 11.8
Interventions	All participants 6 weekly visits 20 - 30 mins incl 10 - 15 mins CBT, medication and reduction from visit 3. At end of 6 weeks, option to set quit date with medication 1. Nicotine Patch 2. Nicotine gum 3. Folic acid pill (placebo)
Outcomes	Reduction: average CPD, average CO, cotinine at 6m Cessation: 30-day abstinence at 6m (Outcomes also assessed at end of treatment and 3m)
Notes	Not combined with adult NRT studies. Cessation intervention offered after 4 wks of reduction. Cessation not reported by group, 50% reduction only reported at end of treatment, and not by group. No treatment effects detected at any follow-up. CPD lower than baseline in all groups at 6m but CO and cotinine higher, raising possibility that reducing cigarettes had increased smoke exposure, but could also have been due to greater free time, variability in smoking patterns and possibly the trajectory towards increased

**Hanson 2008** (Continued)

	smoking behaviour. 5/103 reported 30-day abstinence at 6m Funding declaration: "Funding for this project was provided by NIH Grants: R01-DA014538 and P50 DA013333. The funding sources did not contribute to developing or conducting the study" Conflicts of interest: "All authors except Dorothy Hatsukami stated that they have no conflicts of interest. Dorothy Hatsukami has the following conflicts of interest: (a) she received an honorarium and travel expense from Pfizer for consulting on their smoking cessation medication, Chantix (12/05), and (b) she received a joint grant from Nabi Biopharmaceuticals and the National Institute on Drug Abuse to conduct a clinical trial on the nicotine vaccine."	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	A placebo was used but this was not matched to either patch or gum (it was in pill form). Biological validation was used, but rates were not reported split by group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Of participants, 91.3% (n = 94/103) completed the study until the end-of-treatment, 85.1% (n = 80/94) completed the 3-month follow-up visit and 71.3% (n = 67/94) completed the 6-month follow-up visit." Follow-up rates were high in general, but not split by treatment arm

**Hatsukami 2004a**

Methods	<p>Country: USA 12 sites</p> <p>Recruitment: community volunteers</p> <p>Design: double-blind, randomized, placebo-controlled trial</p> <p>Study dates: not stated</p>
Participants	<p>594 smokers (295 bupropion; 299 placebo), smoking <math>\geq 20</math> CPD, wanting to reduce amount smoked. Not quit for &gt; 3m in previous year, at least 2 failed quit attempts including 1 with NRT</p> <p>45% F; av.age 42; av. CPD 29; av. CO 28</p>
Interventions	<p>1. Bupropion 300 mg/day, 26 wks</p> <p>2. Placebo</p>

**Hatsukami 2004a** (Continued)

	Common components: written materials suggesting reduction techniques, monthly brief individual counselling, telephone contact day 2, day 12, wk 5 after target reduction date. Participants indicating a willingness to quit at any time were enrolled in a 7-wk cessation programme with weekly counselling visits followed by 19 wks of follow-up	
Outcomes	Reduction > 50% in urine cotinine at 1 yr (denominator 327 excludes 214 who entered cessation arm, and 53 with missing baseline cotinine) Reduction > 50% in CPD at 1 yr Abstinence 6m (denominator 594; 214 entered cessation phase)	
Notes	38% of bupropion and 34% of placebo group entered cessation phase. Median time to attempting cessation shorter in bupropion group Funding declaration: “This study was supported by GlaxoSmithKline, Research Triangle Park, North Carolina. The sponsor was responsible for finalizing the design of the study and oversight of the research project, had primary responsibility for conducting the data analyses, and reviewed the final paper.” Conflicts of interest: not stated	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Specified to be double-blind trial with matching placebo acting as control, but no further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a high loss to follow-up rate with 31% of the bupropion group and 34% of the placebo group followed up at the 12m visit. However, the rates did not differ greatly between groups

**Haustein 2003**

Methods	Country: Germany Recruitment: community volunteers Design: double-blind randomized, placebo-controlled trial Study dates: 2000-2002
Participants	385 (193 of interest in our analyses) healthy adult smokers (96 short-term gum; 96 short-term placebo; 97 long-term gum; 96 long-term placebo), happy to make attempt to change smoking behaviour but not to quit in the next month; smoked $\geq 15$ CPD; had smoked for $\geq 3$ yrs; had a CO level of $\geq 15$ ppm; had failed at least 1 serious attempt

**Haustein 2003** (Continued)

	to quit within the last 24m 50% F; av. age 42; av. CPD 25, av. CO 28	
Interventions	1. Nicotine gum, short-term reduction over 4 wks 2. Nicotine gum, long-term reduction up to 9m 3. Placebo, short-term reduction over 4 wks 4. Placebo, long-term reduction up to 9m	
Outcomes	Reduction > 50% in CPD with CO reduction, sustained at 12m Abstinence at 12m (PP abstinence used) Validation: CO < 10 ppm	
Notes	Included a comparison of 2 schedules of NRT-assisted reduction. Change for 2016 update: participants in short-term reduction group instructed to reduce and quit over 4 wks, so we have not analysed short-term reduction group. Comparison made between long-term reduction with gum and long-term reduction with placebo (2 and 4) Funding declaration: study conducted by Pharmacia and Upjohn (now merged with and known as Pfizer) Conflicts of interest: not stated	
<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomization list generated using a computer programme
Allocation concealment (selection bias)	Low risk	Sealed envelopes were provided by Pharmacia for each participant and held by the investigator
Blinding (performance bias and detection bias) All outcomes	Low risk	All study medication was identical in appearance and packaging. The designated person who held the list of participants and medications, and dispensed medication, was not involved in any other aspect of the study. Investigators and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	48% of the active groups and 42% of the placebo groups attended the 12m visit



Methods	<p>Country: USA</p> <p>Recruitment: smokers in 2008 - 2009 in Burlington, VT, USA and Omaha, NE, USA, via newspaper, radio, and flyer advertisements. Study took place in smoking clinics</p> <p>Design: parallel-group RCT</p> <p>Study dates: recruitment 2008-2009</p>
Participants	<p>218 smokers (107 varenicline; 111 placebo). Inclusion criteria: wish to eventually stop smoking, no intention to quit smoking in the next month, daily smoking <math>\geq 8</math> CPD, no history of use of varenicline, not currently using a smoking cessation medication, not currently or planning to be pregnant or breastfeeding and negative pregnancy test, <math>\geq 18</math> years old, no current or past history of medical or psychological problems that would, in the judgement of the investigators, place the participant at significant risk of an AE, including lifetime suicidal attempt or current depression, drink fewer than 16 alcoholic beverages per week, no current use of a sedating medication (to minimize possible psychiatric AEs from varenicline), no current kidney disease or frequent nausea</p> <p>36% F; av. age 42; av. CPD 19</p>
Interventions	<p>1. Varenicline: participants provided with varenicline for 2 - 8 wks - 1 pill/day (0.5 mg/day) for the first 3 days, then 2 pills/day (0.5 mg each) for 4 days, and then 2 pills/day (1.0 mg each) for the remainder of treatment. The clinician stated participants should take the medication for at least 2 weeks unless they had significant side effects, and they were encouraged to use it for up to 8 weeks. Brief counselling about reduction was given at baseline, 2, 4 and 8 wks. Participants were told varenicline would help them to reduce CPD, but it is unclear whether reducing improves health. At wk 2 they were encouraged to reduce CPD for the next 2 wks; however the clinician encouraged smoking reduction only to a degree that did not cause significant craving or withdrawal. If they agreed the clinician discussed 2 reduction methods: (a) systematically increasing the minimum amount of time between cigarettes, and (b) rank-ordering cigarettes from easiest to give up to hardest and systematically foregoing easiest to hardest cigarettes. The clinician suggested the participant set a very achievable initial goal (e.g. reduce by 5 cigarettes over the next 2 wks) to increase the chances of initial success. At all sessions, participants were asked if they had made a quit attempt since the last session but were never explicitly advised to quit. At the 4-wk visit, the clinician encouraged smokers to either maintain that level of smoking, or set a new reduction goal. At the last visit at 8 wks, the clinician reminded participants that they would not be provided with further medication unless they set a quit date in the next 2 wks. If during any visit, participants stated they planned to try to stop smoking or had recently quit and were still abstinent, the session did not focus on reduction but rather on methods to prepare for or maintain abstinence</p> <p>2. Placebo: as in group 1 but participants were provided with placebo medication rather than varenicline</p>
Outcomes	<p>Consumption: self-report 50%+ reduction in CPD (only measured to 2m follow-up)</p> <p>Quitting: 7-day PP at 6m follow-up (validated by exhaled CO &lt; 10 ppm)</p> <p>Adverse effects: serious adverse events (monitored throughout study)</p>
Notes	<p>Funding declaration: "Pfizer Inc. via an unrestricted grant plus provided medication and placebo; Senior Scientist Award DA-000490 to J.R.H. and grant DA011557 to J.R.H.; and the Larson Endowment at the University of Nebraska Medical Center to S.I.R."</p> <p>Conflicts of interest: "Dr Hughes is currently employed by The University of Vermont</p>

and Fletcher Allen Health Care. In the last 3 years, he received research grants from the National Institute on Health and Pfizer Pharmaceuticals and accepted honoraria or consulting fees from Abbot Pharmaceuticals, Academy for Educational Development, Acrux DDS, Aradigm, American Academy of Addiction Psychiatry, American Psychiatric Association, Atrium, Cambridge Consulting, Celtic Pharmaceuticals, Cline, Davis, and Mann, Constella Group, Concepts in Medicine, Consultants in Behavior Change, Cowen Inc., Cygnus, Edelman PR, EPI-Q, Evotec, Exchange Limited, Fagerstrom Consulting, Free and Clear, Health Learning Systems, Healthwise, Insyght, Invivodata, Johns Hopkins University, J Reckner, Maine Medical Center, McNeil Pharmaceuticals, Nabi Pharmaceuticals, Novartis Pharmaceuticals, Oglivy Health PR, Pfizer Pharmaceuticals, Pinney Associates, Reuters, Shire Health London, Temple University of Health Sciences, United Biosource, University of Arkansas, University of Auckland, University of Cantabria, University of Greifswald, University of Kentucky, University of Madrid Medical School, U.S. National Institutes of Health, and Xenova and ZS Associates. Dr. Rennard is currently employed by the University of Nebraska Medical Center, Omaha Nebraska. In the last 3 years, he has received research grants/contracts from Almirall, Biomark, Centocor, GSK, the Institute for Science and Health, Lorillard, Mpex, Nabi, Novartis, Pfizer, RJReynolds, Roche, Astellas, AstraZeneca, Philip Morris, the National Heart Lung and Blood Institute, and the National Institute for Environmental Health Sciences. He has received honoraria for consulting or for speaking from Abbott, Almirall, Altana, Anthera, Aradigm, AstraZeneca, Bioli-pos, BoehringerIngelheim, Centocor, Critical Therapeutics, GSK, Johnson and Johnson, Novartis, Otsuka, Parengenix, Pfizer, Quintiles, Roche, Sanofi, Schering, TargeGen, Theravance, UBS, Talecris, Dey, Nycomed, Pharmaxis the American College of Chest Physicians, the American Board of Internal Medicine, and the American Thoracic Society. Karl Fagerstrom is president of Fagerstrom Consulting and has, over the last 3 years, received honoraria and speaking fees from Novartis, Nicovum, Pfizer, Independent Pharmaceutica, McNeil, Institute for Science and Health and various professional networks, universities, and scientific organizations. Peter Callas, James Fingar, and Sandy Talbot have no disclosures."

### ***Risk of bias***

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	"One of the authors (PC) randomized study IDs, stratifying by study site. Block sizes of four were used within each site to ensure an approximately equal distribution to active and placebo groups within site." However, does not specify how participants were randomized
Allocation concealment (selection bias)	Low risk	The list of IDs and assignment was sent to either a pharmacist (at Nebraska site) or a research assistant (at Vermont site) who prepared the appropriate aliquot of pills for each ID. Neither PC nor the pharmacist/research assistant had contact with partic-

**Hughes 2011** (Continued)

		ipants during the study. At each site, consented participants were assigned to the next ID in sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo control used for blinding. Clinicians were unaware of the randomization details (e.g. block size) and were blinded to participant condition. Follow-up phone calls were made by research assistants blind to study conditions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study flow diagram only goes up to 2m follow-up, i.e. no information to 6 months However, dropout is almost equal at this point

**Joksić 2011**

Methods	Country: Serbia Recruitment: Participants were recruited through posters and other printed material distributed at near the study sites, and by word-of-mouth. The 2 sites were occupational health centres located at the head office of a large Serbian corporation (NIS-Jugopetrol) and at a major research institution in Belgrade (Vinča Institute of Nuclear Sciences) Design: Parallel-group RCT Study dates: 2008-2010
Participants	319 smokers (158 snus; 161 placebo). Inclusion criteria: aged between 20 and 65 years, history of daily smoking for < 1 yr, an average consumption of > 10 CPD during the past month, motivation to substantially reduce or quit smoking, good general health, acceptance not to take pharmaceutical nicotine products or any other non-protocol treatment to facilitate smoking cessation during the study period 62% F; av. age 44; av. CPD 27
Interventions	1. Snus: participants were provided with snus throughout the 48-wk study period. The snus was manufactured by Swedish Match AB according to the GothiaTék® standard. Participants could choose from 2 different sachet sizes (0.5 g and 1 g) and 2 different flavours (liquorice and eucalyptus). Whenever they felt an urge to smoke, participants were instructed to take a sachet of their allocated product. The number of sachets consumed each day was determined by the participants themselves. There was no prescribed tapering of product usage. Potential participants were invited to seminars on the health risks associated with smoking and available smoking cessation strategies. The physiological effects of nicotine were outlined, and an account given of the Swedish experience with snus including potential health risks associated with smokeless tobacco products. Participants were instructed to cut down on smoking as much as possible or quit smoking completely by replacing as many cigarettes as possible with their allocated study product. Those who managed to achieve the protocol definition of a substantial smoking reduction at the wk 24 visit or who had quit completely, continued in the trial up to 48 wks. During wks 25 - 48 they were actively instructed to quit smoking completely. Parti-

	<p>pants who did not meet the protocol criteria for smoking reduction at the wk-24 visit were counted as treatment failures in all efficacy analyses and were not actively followed after wk 24</p> <p>2. Placebo: As for group 1 but using placebo rather than snus product; they were almost identical to the snus products in physical appearance, mouth feel, pH, flavouring, and other sensory characteristics but they did not contain tobacco or nicotine</p>
Outcomes	<p>Consumption: salivary cotinine; exhaled CO; CPD reduction of 50%+ (verified by a reduced concentration of CO in exhaled air of at least 1 ppm), CPD reduction of 75%+</p> <p>Quitting: 7-day PP verified by exhaled CO of &lt; 10 ppm at 24 wks. We are only interested in data up to 24 wks as people were withdrawn after this if they had not reduced</p> <p>Health markers: BP (systolic and diastolic), body weight, BMI, pulmonary function (FEV 1.0, FVC, FEV%)</p> <p>Adverse effects: serious adverse events, adverse events, treatment-related adverse events and adverse events leading to discontinuation of treatment</p>
Notes	<p>Funding declaration: "The trial was officially sponsored by Swedish Match AB, Stockholm, Sweden. Sponsor provided funding, study products (snus and placebo snus), and study equipment. External contractors paid by the sponsor provided monitoring, data handling, and all statistical analyses (i3 Research, i3 Statprobe)."</p> <p>Conflicts of interest: "LER is an employee of Swedish Match AB. GJ, VST, RA, and RN received honoraria from Swedish Match AB for their work with this trial, but declare no other conflict of interest."</p>

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	With stratification by centre, and using a block size of 6, a predefined, central, computer-generated randomization sequence assigned participants in a 1:1 ratio to receive snus or matching placebo
Allocation concealment (selection bias)	Low risk	Randomization was done by consecutively associating each included participant's identifiers with a unique, computer-generated sequential number. Lists at the study sites linked these numbers to specific study products, i.e. snus or placebo. At the sites all study products were identified solely by identification numbers which ensured that both participants and investigators were blinded to treatment assignments
Blinding (performance bias and detection bias) All outcomes	Low risk	The placebo snus products were almost identical to the snus products in physical appearance, mouth feel, pH, flavouring, and other sensory characteristics but

		they did not contain tobacco or nicotine. All study products were identified solely by identification numbers which ensured that both participants and investigators were blinded to treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	This is judged low for the data extracted as we have only looked at outcomes to 24 wks (dropout 26/158 (16%) in snus and 23/161 (14%) in placebo). After this time point all participants who had not reduced by 50% or quit were withdrawn. If we had extracted past 24 weeks, risk of bias would have been judged as high

## Joseph 2008

Methods	Country: USA, Veterans Affairs Medical Centres Recruitment: Community volunteers and referrals and invited people with cardiovascular disorder Design: RCT Study dates: not stated
Participants	152 smokers (78 reduction group; 74 usual care), smoked $\geq 15$ CPD, unwilling or uninterested in setting quit date in next 30 days; 12% F, av. age 58, 27 CPD, av. 6 previous quit attempts
Interventions	1. Counselling to encourage reduction by $\geq 50$ CPD, at 1, 2 wks and 1, 2, 3, 4, 6, 12, 18m, additional visits after 4m if further interest. Encouraged to use up to 6 pieces of 4 mg nicotine gum, or patches if need for gum greater. (88% used some form of NRT) 2. Control (usual care): single brief session emphasizing importance of abstinence and encouragement to seek cessation assistance
Outcomes	Reduction > 50% in CPD at 18m, absolute reduction in CPD Abstinence at 18m (PP) Biomarkers: CO, urine cotinine, urine nicotine Other clinical markers: WBC count, NNAL, NNK. QoL, walk test Adverse events
Notes	5 in Control required urgent cardiac care at 6m vs 0 Intervention. No differences in any clinical or QoL outcomes. Error in control group denominator corrected for 2016 update (from 78 to 74) Funding declaration: "This study was supported by funding from the National Cancer Institute and National Institute Drug Abuse Grant DA13333-02." Conflicts of interest: "The authors do not have any conflicts of interest pertaining to this work."
<b><i>Risk of bias</i></b>	

**Joseph 2008** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, block size 10 by site
Allocation concealment (selection bias)	Low risk	Sealed envelope opened after enrolment
Blinding (performance bias and detection bias) All outcomes	High risk	Behavioural intervention meant blinding was not possible. Biochemical verification was used, but intervention group intervention received NRT and control did not
Incomplete outcome data (attrition bias) All outcomes	Low risk	64% - 68% followed at 18m, no significant differences between groups

**Kralikova 2009**

Methods	Country: Czech Republic, 2 medical centres Recruitment: community volunteers willing to control their smoking. Information but equal emphasis on cessation and reduction Design: double-blind placebo-controlled RCT; 2:1 active: placebo ratio Study dates: not stated
Participants	314 smokers (209 NRT; 105 placebo), smoking $\geq 15$ CPD, with at least 1 failed quit attempt, did not have to be motivated to quit. Excludes 11 enrolled who failed to attend baseline visit 58% F, av. age 46, av. CPD 25
Interventions	1. Choice of 4 mg nicotine gum (up to 24/day) or 10 mg nicotine inhaler (6 - 12 daily) for up to 6m with further 3m tapering 2. Choice of placebo gum or placebo inhaler Common components: brief behavioural cessation/reduction support at clinic visits (9 scheduled)
Outcomes	Sustained > 50% reduction in CPD from 6 - 12m (excluding sustained abstainers) Sustained abstinence from 6 - 12m (12m PP also reported) CVD risk factors assessed but not reported yet Validation: cessation: CO < 10ppm, reduction; any reduction in CO
Notes	Cessation was recommended but not mandatory for participation. Reduction was an alternative for participants unable to quit First included as 'Kralikova 2002' based on data from conference abstract and draft paper. PP replaced by 6 - 12m sustained abstinence in 2010 update Funding declaration: "This study was funded by McNeil AB, Helsingborg, Sweden. McNeil AB manufactures a range of nicotine replacement products, including nicotine gum and nicotine inhaler." Conflicts of interest: "Eva Kralikova and Jiri Kozak received funding from McNeil AB to perform this study (and have previously received payment from other pharmaceutical

**Kralikova 2009** (Continued)

	companies). Thomas Rasmussen and Gunnar Gustavsson are employees of McNeil AB. Jacques Le Houezec is a consultant in tobacco dependence for both the pharmaceutical industry and the public sector.”	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no other detail given. The placebo groups received matching treatment that did not contain nicotine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up rates at 12 months not provided.

**Mendes 2008**

Methods	<p>Country: USA, Clinical research centre and community</p> <p>Recruitment: Volunteers for a paid study of effects of different smoking devices, willing to switch from conventional cigarettes for an extended period</p> <p>Design: RCT</p> <p>Study dates: 2003</p>
Participants	<p>225 regular smokers randomised (77 full flavor group; 73 light group; 75 ultra light group), smoking 10 - 30 full-strength CPD (15 mg tar). 166 completed phase 1 of study and continued to phase 2</p> <p>24% F; av. age 35; av. CPD 20</p>
Interventions	<p>Test of switching to low-tar cigarettes: Participants continued smoking Marlboro Full Flavour cigarettes, or switched to Marlboro Lights (ML) or Marlboro Ultra Lights</p>
Outcomes	<p>Biomarkers of exposure and harm; urine nicotine equivalents, cotinine, NNAL, 1-OHP, urine mutagenicity, COHb, S-PMA, 3-PMA, Inter-Puff Interval. Longest follow-up 24 wks, measures taken daily for 8 days then 4-weekly</p>
Notes	<p>Funded declaration: “All test cigarettes used during the short- and long-term phases of the study were provided by Philip Morris USA.” No further information given</p> <p>Conflicts of interest: Study conduct and data analysis was carried out by MDS Pharma Services, Lincoln, Nebraska. No further information given</p>
<b><i>Risk of bias</i></b>	

**Mendes 2008** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded so at risk of performance bias; biomarkers of exposure were used
Incomplete outcome data (attrition bias) All outcomes	High risk	26% of those randomized to phase 1 study did not enter phase 2. Higher dropout from low-tar cigarette groups by end of study

**Nackaerts 2009**

Methods	Country: Belgium Recruitment: participants were electively hospitalized (smoking) adults, recruited from ENT, trauma, neurosurgery, pulmonology, gynaecology, vascular surgery and urology wards in 4 academic hospitals in Flanders, Belgium Design: parallel-group, placebo-controlled RCT Study dates: 2006-2008	
Participants	296 smokers (150 patch; 146 placebo). Inclusion criteria: > 18 years, smoking minimum of 15 CPD for 3 yrs and 10 CPD during the 7 days before admission to hospital, life expectancy of a minimum 1 year, conscious, able to read/sign consent form, hospitalization of at least 72 hours, agreement of treating physician and anaesthesiologist 67% F, av. age 50, av. CPD 20	
Interventions	1. Nicotine patch: Nicotine substitution provided for smoking whilst participants were in hospital. After randomization participants were offered nicotine patch (15 mg/16-hr) until discharge for a maximum of 7 days, alongside brief counselling after randomization (20 - 30 min session and a booklet (Belgian Foundation against Cancer) 2. Placebo patch: as for group 1 but with placebo rather than nicotine patch	
Outcomes	Quitting: self-reported smoking cessation to 6m follow-up (no more information reported on definition of abstinence; abstract and presentation slides only data source)	
Notes	A study of temporary abstinence during a period of hospitalization Funding declaration: Funded by the Research Foundation - Flanders (PWO), Korn Op Tegen Kanker, and McNeil AB, Sweden Conflicts of interest: not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement



**Nackaerts 2009** (Continued)

Random sequence generation (selection bias)	Unclear risk	“random”, no further information provided
Allocation concealment (selection bias)	Unclear risk	States “double blinded” but does not explain how blinding is achieved
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States “double blinded” but does not explain how blinding is achieved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Relatively low loss to follow-up, similar across both groups (138/150 followed up in intervention versus 130/146 followed up in control). However, participants were randomized (N = 359) and then 63 deemed ineligible, so the ITT population is reported as 296. We cannot tell whether ineligibility was matched between groups

**Rennard 2006**

Methods	Country: USA, 3 sites Recruitment: community volunteers Design: double-blind RCT Study dates: 1999-2001
Participants	429 smokers (215 NRT; 214 placebo), smoking $\geq 20$ CPD, interested in reducing cigarette consumption, excluded if planned to quit in next 4 wks, or 9 or 10 on Contemplation Ladder 55% F, av.age 45, av.CPD 30
Interventions	1. Nicotine inhalator 10 mg ad lib, recommended 6 - 12/day, for up to 12m. Cessation recommended from 6m 2. Placebo Common components: 9 clinic visits over 15m
Outcomes	Sustained reduction by > 50% from 4 wks to 15m PP abstinence at 15m CVD risk factors ,WBC, HDL, LDL, fibrinogen, C4RP at 4m reported for reducers + abstainers, not by condition Validation: CO for reduction
Notes	Some data from Pfizer internal report since only graph for reduction in published paper 15m outcomes used. 12m gives lower effect Funding declaration: Study carried out by Pfizer. Conflicts of interest: not stated
<b><i>Risk of bias</i></b>	

**Rennard 2006** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind. The matched placebo inhaler was identical to the active treatment with the nicotine excluded. No further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	41% of the active group and 30% of the placebo group completed the 15m study

**Riley 2002**

Methods	Country: USA Recruitment: community volunteers Design: RCT Study dates: not stated
Participants	93 smokers (44 computerized reduction; 49 self-help), smoking $\geq 15$ CPD, interested in reduction, 2 failures in planned quit attempts, not quit > 30 days in past yr 44% F, av. age 45, av. CPD 27, av. 5.6 previous attempts, av. 32m since last
Interventions	1. Computerized scheduled gradual reduction over 2 wks to 50% goal with programme covering computer operation, harm reduction, self-management and relapse prevention techniques 2. Self-help treatment guide instructing in gradual reduction using selective elimination of cigarettes
Outcomes	Reduction $\geq 50\%$ at 12m, (mean % reduction) PP abstinence at 12m Validation: CO < 10 ppm
Notes	Not shown in graphs 18.2% reduced (mean 38%) vs 18.4% (mean 35%) 5/44 (11.4%) vs 3/49 (6.1%) quit at 12m (NSS) Funding declaration: "This study was supported by a grant from the National Cancer Institute (R43CA83451)." Conflicts of interest: "Institution where work was carried out: Personal Improvement Computer Systems (PICS). All authors were employees of PICS, a commercial interest developing computerized smoking reduction products."
<b>Risk of bias</b>	

**Riley 2002** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Could not blind due to intervention design, so performance bias a risk. CO validation was used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The completion rate was 61% at 12m follow-up, but this is not reported by group allocation

**Roethig 2008**

Methods	Country: USA, clinical research centre and community Recruitment: Volunteers for a paid study of effects of different smoking devices, willing to switch from conventional cigarettes for an extended period Design: RCT Study dates: not stated	
Participants	97 regular smokers (64 EHCSS; 33 conventional cigs), smoking 10 - 40 low-tar (1 - 7 mg) cigarettes daily for at least 10 years, 25 - 65 years of age 54% F; av. age 42; av. CPD 24	
Interventions	Test of switching to 2nd generation electronically heated cigarette smoking system (EHCSS). Controls continued to smoke conventional cigs	
Outcomes	Biomarkers of exposure included plasma cotinine, carboxyhaemoglobin (COHb), urine nicotine and major metabolites, total NNAL, NNK, total 1-OHP, and urine mutagenicity Cardiovascular risk biomarkers included haemoglobin (Hb), hematocrit (Hct), red blood cell count, WBC, fibrinogen, HDL cholesterol, LDL cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP) Longest follow-up 12m, also assessed at 2 wks, 1, 2, 3, 4, 5, 6, 9m	
Notes	Funded declaration: “Financial support provided by Philip Morris USA.” Cigarettes provided free to participants by Phillip Morris Conflicts of interest: MDS Pharma Services were responsible for clinical conduct and bioanalytical and statistical analyses. No further information given	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

**Roethig 2008** (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded so at risk of performance bias; biomarkers of exposure were used
Incomplete outcome data (attrition bias) All outcomes	Low risk	50/64 using EHCSS completed last visit, 59/64 evaluable. 33/33 control evaluable

**Sarkar 2008**

Methods	Country: USA, clinical research centre and community Recruitment: Volunteers for a paid study of effects of different types of cigarette, willing to switch from their usual cigarettes for an extended period Design: RCT Study dates: not stated
Participants	97 regular smokers (45 6mg test cigarettes; 21 6mg conventional cigarettes; 16 11mg test cigarettes; 15 11mg test cigarettes), smoking 10 - 30 6 mg or 11 mg tar cigarettes daily; approximately 18 CPD at baseline
Interventions	2 substudies of switching to carbon-filtered cigarettes with 6 mg or 11 mg tar. Controls continued to smoke conventional cigs with same tar levels. Only interested in long-term studies
Outcomes	Biomarkers of exposure to gas phase: acrolein, 1,3-butadiene, benzene, measured by the 24-hr urinary excretion of metabolites. Biomarkers of exposure to particulate phase: nicotine, NNK, pyrene Biomarkers of cardiovascular risk: LDL cholesterol, HDL cholesterol, and triglycerides Longest follow-up 24 wks, also 4, 8, 12, 16, 20 wks
Notes	Funding declaration: "The research was funded by Philip Morris USA." The cigarettes were provided free to participants by Phillip Morris USA Conflicts of interest: "The authors have no additional competing interests to declare." The study, plus bioanalytical and statistical analyses were conducted by MDS Pharma Services

***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified

**Sarkar 2008** (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded so at risk of performance bias; biomarkers of exposure were used
Incomplete outcome data (attrition bias) All outcomes	High risk	2 studies are reported (LT-6 & LT-11) In LT-6, 45 took part in the intervention arm and 21 in the control arm. Of these 80% of the intervention group and 81% of the control group completed the study. In LT-11, 16 took part in the intervention arm and 15 in the control arm. Of these 94% of the intervention group and 53% of the control group completed the study. Therefore differential dropout was apparent between groups

**Wennike 2003**

Methods	Country: Denmark Recruitment: community volunteers for smoking reduction Design: placebo-controlled RCT Study dates: 1999-2001	
Participants	411 smokers (205 NRT; 206 placebo), smoking $\geq 15$ CPD, interested in reducing but unwilling/unable to give up 62% F, av. age 45, av. CPD 24	
Interventions	1. Nicotine gum, 2 mg if FTND = 5, 4 mg if 6 - 10, for up to 12m 2. Placebo gum Common components: brief individual information on smoking reduction, effects on health, suggestions on ways to reduce number of cigs, cessation recommended as ultimate goal	
Outcomes	Sustained (4, 12, 24m) and PP reduction of > 50% at 24m CPD,CO, cotinine and thiocyanate average % of baseline by treatment group in continuing participants at 24m. Also mean values by reducer categories PP abstinence at 24m Validation: CO < 10 ppm	
Notes	PP reduction gives a more conservative treatment effect Funding declaration: "This study was supported by a grant from Pharmacia AB, Sweden." Conflicts of interest: Not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement

**Wennike 2003** (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind. The placebo gum was similar in appearance and taste, but contained no nicotine. No further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	40% of the treatment group and 35% of the placebo group completed the study

av: average  
 BMI: body mass index  
 BP: blood pressure  
 C4RP: C4-reactive protein  
 CPD: cigarettes per day  
 CO: carbon monoxide  
 CVD: Cardiovascular disease  
 EHCSS: electrically heated cigarette smoking system  
 F: female  
 FTND: Fagerström Test for Nicotine Dependence  
 HDL: high-density lipoprotein  
 HMO: health maintenance organization  
 LDL: low-density lipoprotein  
 m: month(s)  
 NNAL:  
 NNK: nicotine-derived nitrosamine ketone  
 NRT: nicotine replacement therapy  
 NSS: not statistically significant  
 PP: point prevalence (abstinent during a limited defined period)  
 ppm: parts per million  
 SBP: systolic blood pressure  
 TQD: target quit date  
 WBC: white blood cells

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

Study	Reason for exclusion
<a href="#">Adriaens 2014</a>	All groups used electronic cigarettes. There was some variation between the experimental and control group (in the intensity of instructions), and follow-up points were not comparable

(Continued)

<a href="#">Applegate 2004</a>	Reported as a conference abstract. Insufficient data to include
<a href="#">Baker 2006</a>	Reduction was a secondary outcome in a trial of a cessation-focused intervention
<a href="#">Barrett 2011</a>	Did not provide follow-up of 6m or more
<a href="#">Benowitz 2005</a>	Short-term (3-wk) cross-over trial comparing conventional and 'light' cigarettes. Outcomes were biomarker exposures
<a href="#">Bloch 2010</a>	Did not provide follow-up of 6m or more
<a href="#">Borland 1999</a>	Intervention was intended to assist smokers in coping with workplace smoking bans by learning to cope with smoking behaviour. Smoking reduction was reported as change in CPD or any reduction. Use of intervention was low
<a href="#">Breland 2006</a>	Short-term cross-over trial comparing Advance, Eclipse, own-brand cigarettes, or no cigarettes. Outcomes were biomarker exposures
<a href="#">Caldwell 2010</a>	Short-term cross-over trial comparing snus, Zonnic and nicotine gum. Outcomes were urges to smoke, withdrawal symptoms and the sensory quality of the products
<a href="#">Chiou 2013</a>	Did not provide follow-up of 6m or more
<a href="#">Chisolm 2013</a>	Data on smoking behaviour was observational. Intervention was not testing tobacco harm reduction
<a href="#">Cunningham 2006</a>	Short-term (3m) follow-up. Trial compared a questionnaire containing tips on safer smoking with a control asking about harm reduction activities
<a href="#">Dautzenberg 2001</a>	Participants underwent a smoking cessation programme
<a href="#">Ebbert 2015</a>	Although participants were not willing or able to quit smoking within the next month they did need to be willing to reduce smoking and make a quit attempt within the next 3m at point of recruitment
<a href="#">Eliasson 2001</a>	Uncontrolled short-term study of reduction and cessation assisted by nicotine nasal spray
<a href="#">Etter 2003</a>	Outcome was effect of information about NRT and cigarette use on motivation to quit
<a href="#">Fagerström 1997</a>	Short-term (5-wk) follow-up. Test of NRT for smoking reduction. Participants tried out different types of NRT, then chose or were assigned a product in a cross-over design. No non-NRT control. No serious adverse effects reported
<a href="#">Fagerström 2000</a>	Short-term (6-wk) study. Compared a potentially reduced exposure product (Eclipse), nicotine inhaler or usual cigarettes
<a href="#">Fagerström 2002b</a>	Short-term (14 wk) follow-up. Participants enrolled in a previous study ( <a href="#">Fagerström 2000</a> ) self-selected a potentially reduced exposure product (Eclipse), nicotine inhaler or usual cigarettes

(Continued)

Fatemi 2005	Short-term (8 wk) cross-over study of bupropion or placebo for smoking reduction in people with schizophrenia
Fatemi 2013	Did not provide follow-up of 6m or more
Feng 2006	Short-term (8-day) study comparing biomarkers of exposure from conventional cigarettes, low tar, or electrically heated cigs
Frost 1995	Study to assess compensation when smoking low-tar brand
Frost-Pineda 2008	Short-term (12-wk) study comparing biomarkers in smokers of conventional cigarettes and smokers using an ECHSS
Gelkopf 2012	Did not provide follow-up of 6m or more
Glasgow 1983	No long-term follow-up of wait list control group. Smoking reduction was maintained at 6m follow-up in both treatment groups
Gray 2008	Laboratory study and short-term (20-day) study of toxicant exposure of different smokeless tobacco products
Hagen 2011	Both intervention groups had access to the tested intervention prior to the 1-year follow-up (the control group were also given the albendazole medication 2 weeks following their placebo medication)
Hatsukami 2004b	Short-term (6-wk) study comparing the effect on carcinogen exposure of switching from cigarette smoking to either the OMNI cigarette or a nicotine patch, and switching from smokeless tobacco to Swedish snus or a nicotine patch
Hatsukami 2005	Short-term (12-wk) study using NRT to reduce smoking with a target of 75% reduction. A wait list control delayed reduction for 6 wks. Outcomes were change in multiple biomarkers amongst successful reducers
Hatsukami 2007b	Short-term (12-wk) intervention for switching smokeless tobacco brands
Hatsukami 2008	Short-term (12-wk) intervention for reducing smokeless tobacco use
Hatsukami 2010	Short-term (6-wk) parallel study comparing effects of reduced nicotine cigarettes, very low-nicotine cigarettes or nicotine lozenges on compensatory smoking behaviour, biomarkers of exposure, tobacco dependence, tobacco withdrawal and abstinence rate
Hatsukami 2016	Although in the first instance the aim of the study was to get participants to switch from cigarettes to NRT or snus, the ultimate goal was to wean participants off NRT and snus. The aim of the study was cessation rather than harm reduction
Hughes 2004	Short-term (12-wk) cross-over study comparing the effect on smoking behaviour and toxin exposure of conventional cigarette smoking versus the Omni cigarette



(Continued)

<a href="#">Hurt 2000</a>	Uncontrolled study. Nicotine inhaler used to assist smoking reduction with follow-up at 24 wks
<a href="#">Hussain 2010</a>	Did not provide follow-up of 6m or more
<a href="#">Jimenez-Ruiz 2002</a>	Uncontrolled study. Nicotine gum used to assist smoking reduction with follow-up at 18m
<a href="#">Karem-Hage 2014</a>	Participants received a smoking cessation intervention
<a href="#">Kelly 2010</a>	In order to be eligible for inclusion smokers had to want to quit in the next 6m
<a href="#">Kotlyar 2007</a>	Short-term within-person cross-over study comparing nicotine concentrations, craving, withdrawal and product liking for 4 PREPs, moist snuff and medicinal nicotine
<a href="#">Lamb 2005</a>	Short-term study using financial incentives to reward reduced smoking
<a href="#">Lan 2007</a>	Some of the recruited participants were ready to quit at recruitment
<a href="#">Leelarungrayub 2010</a>	Did not provide follow-up of 6m or more
<a href="#">Lichtenstein 2008</a>	Outcomes were cessation and household smoking bans, not smoking reduction
<a href="#">Malchodi 2003</a>	Reduced smoking was a secondary outcome in a trial of a cessation intervention
<a href="#">McKinney 2014</a>	Did not provide follow-up of 6m or more
<a href="#">Mendoza-Baumgart 2007</a>	Short-term (5-wk) study comparing smokeless tobacco products to a nicotine lozenge for people stopping smoking
<a href="#">NCT01944423 2013</a>	The aim of the intervention was for smokers to quit completely (testing smoking cessation intervention)
<a href="#">Ostroff 2014</a>	The aim of the intervention was for smokers to quit completely (testing smoking cessation intervention)
<a href="#">Pisinger 2005</a>	Study was large population-based study. In the intervention arms those participants unwilling to quit were provided a different intervention to those willing to quit. However, the control group did not split participants according to their intention to quit. Therefore not eligible on the basis that some participants wanted to quit
<a href="#">Pollak 2013</a>	Did not provide follow-up of 6m or more
<a href="#">Prapavessis 2014</a>	Did not provide follow-up of 6m or more
<a href="#">Prikryl 2014</a>	Did not provide follow-up of 6m or more
<a href="#">Rennard 1990</a>	Uncontrolled study. Nicotine gum used to assist smoking reduction. Outcomes were measures of lower respiratory tract inflammation
<a href="#">Rennard 1994</a>	Insufficient data available from conference abstract.

(Continued)

<a href="#">Rennard 2002</a>	Short-term (8-wk) study of respiratory tract inflammation in smokers switching to potentially reduced exposure product (Eclipse)
<a href="#">Riggs 2001</a>	Short-term (7-wk) cross-over pilot study of 2 reduction strategies combined with nicotine gum
<a href="#">Robinson 1984</a>	Short-term (8-wk) trial comparing 'light' cigarettes to usual brand
<a href="#">Sarkar 2010</a>	Short-term (8-day) study comparing biomarker exposure from continuing smoking, reduction and ST use, ST use alone, and complete abstinence
<a href="#">Scherer 2006</a>	Short-term (2-wk) cross-over study comparing conventional and charcoal filter cigarettes
<a href="#">Shi 2013</a>	Did not provide follow-up of 6m or more
<a href="#">Shiffman 2009</a>	Trial of nicotine gum for reduction as a precursor to cessation, amongst smokers attempting to quit
<a href="#">Spain NNCG-008</a>	Only short-term (4m) outcomes available from Pfizer summary. There was a stratification error such that highly-dependent smokers received either nicotine 2 mg gum or placebo and the low-dependent smokers received either nicotine 4 mg gum or placebo. Results were consistent with other trials
<a href="#">Stein 2002</a>	Short-term (3m) study comparing homocysteine levels in continuing smokers, reducers and quitters
<a href="#">Strasser 2007</a>	Laboratory study comparing CO exposure from smoking reduced nicotine cigarettes
<a href="#">Sun 2009</a>	Trial of nicotine sublingual tablet for smoking cessation amongst people motivated to quit. Smoking reduction was a secondary outcome
<a href="#">Tang 2013</a>	Did not provide follow-up of 6m or more
<a href="#">Taylor 2014</a>	Did not provide follow-up of 6m or more
<a href="#">Tuten 2012</a>	Did not provide follow-up of 6m or more
<a href="#">Tønnesen 2005</a>	Primary analysis was based on smoking status at end of study, not by allocation to cessation, reduction or continued smoking category. NRT was used to assist quitting or reduction and quit rates at 4m were similar in cessation and reduction groups
<a href="#">Windsor 1999</a>	Secondary analysis of 4 trials of cessation interventions for pregnant smokers. Rates of significant reduction based on biochemical measures
<a href="#">Wu 2013</a>	The intervention tested was a cessation intervention

ECHSS: electrically-heated cigarette smoking system.

CPD: cigarettes per day

M: month(s)

NRT: nicotine replacement therapy

ST: smokeless tobacco

## Characteristics of ongoing studies *[ordered by study ID]*

### [Caponetto 2014](#)

Trial name or title	Smoking cessation and reduction in schizophrenia (SCARIS)
Methods	Randomized controlled 3-arm trial with 12m follow-up investigating the efficacy and safety of EC in schizophrenia patients Setting: psychiatric and smoking cessation centres, Italy Recruitment: local newspapers and radio/television advertisements
Participants	153 participants, schizophrenic in stable phase of illness, smoked at least 10 CPD over previous 5 years, aged 18 - 65, in good general health, not currently attempting to quit smoke or wishing to do so in next 6m Excluded if: use smokeless tobacco or NRT; pregnant or breastfeeding; current or recent (1 yr) history of drug or alcohol abuse; other significant comorbidities
Interventions	12-week supply of: 1. EC, high nicotine (24 mg) 2. EC, no nicotine (0 mg, with tobacco aroma) 3. Nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 weeks Outcome measures: Smoking cessation; smoking reduction ( $\geq 50\%$ from baseline); adverse events; quality of life; neurocognitive functioning; participant perceptions; satisfaction with products
Starting date	September 2014
Contact information	Pasquale Caponetto; p.caponetto@unict.it
Notes	

### [NCT02124187](#)

Trial name or title	Smoking cessation and reduction in depression (SCARID)
Methods	3-arm prospective 12m randomized controlled trial investigating efficacy and safety of ECs
Participants	129 participants Inclusion criteria: diagnosis of major depressive disorder (MDD) (according to DSM-5 criteria), smoke $\geq 10$ CPD (for at least the past 5 years), age 18 - 65 years, in good general health, unwilling to quit smoking in the next 30 days Exclusion criteria: use of smokeless tobacco or NRT or other smoking cessation therapies, pregnancy or breastfeeding, current or recent ( $< 1$ yr) past history of alcohol or drug abuse or both, active suicidal intention, other significant comorbidities according to the Investigator's clinical assessment (e.g. cancer, acute myocardial infarction, unstable angina, severe cardiac arrhythmia, recent cerebrovascular incident, or severe atherosclerosis)

Interventions	12-week supply of: 1. EC 24 mg nicotine 2. EC 0 mg nicotine 3. Nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 wks Outcome measures: Smoking cessation Smoking reduction ( $\geq 50\%$ from baseline) Adverse events Quality of life Neurocognitive functioning Participant perceptions and satisfactions with products
Starting date	February 2015
Contact information	Pasquale Caponnetto; <a href="mailto:p.caponnetto@unict.it">p.caponnetto@unict.it</a>
Notes	

**Taskila 2012**

Trial name or title	Nicotine-assisted reduction to stop in pharmacies - the redpharm study
Methods	2 × 2 randomized factorial trial of behavioural support versus no support and short versus standard length reduction programme
Participants	Pharmacists asked to recruit participants opportunistically as well as receiving referrals from GPs Estimated sample size of 160 participants recruited in 10 pharmacies Participants must be: 1. Aged 18 years or older. 2. Daily smokers with either a CO of at least 10 ppm at least 15 mins after last smoking or smoke at least 10 cigarettes or 8 g of loose tobacco as "roll up" cigarettes daily 3. Do not intend to stop in the next month, but are prepared to reduce their consumption with any of the programmes offered 4. Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study and consents to participate and be randomized to either arm 5. Have either a telephone or email for follow-up Participants presenting any of the following are excluded: 1. Currently using other NRT, bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture) that they are not willing to stop using 2. Unstable angina pectoris, myocardial infarction, acute coronary syndrome, or cerebrovascular accident during the last 3 weeks 3. Severe cardiac arrhythmia 4. Currently uncontrolled hyperthyroidism 5. Active pheochromocytoma 6. Pregnancy, lactation or intended pregnancy in the coming year

**Taskila 2012** (Continued)

	7. A severe acute or chronic medical or psychiatric condition or previously diagnosed clinically important renal or hepatic disease, that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the potential participant inappropriate for entry into this study
Interventions	<p>Trial arms:</p> <ol style="list-style-type: none"> <li>1. Short with behavioural support for smoking reduction (4 weeks)</li> <li>2. Standard with behavioural support for smoking reduction (34 weeks)</li> <li>3. Short with leaflet providing advice on smoking reduction (4 weeks)</li> <li>4. Standard with leaflet providing advice on smoking reduction (34 weeks)</li> </ol> <p>Use of NRT encouraged in all trial arms</p>
Outcomes	% of those who reduce and sustain their consumption to at least 50% of baseline value, the proportion of people who attain 4-week and 6m abstinence
Starting date	2010
Contact information	Paul Aveyard; paul.aveyard@phc.ox.ac.uk
Notes	

CPD: cigarettes a day

EC: electronic cigarette

NRT: nicotine replacement therapy

## DATA AND ANALYSES

### Comparison 1. Nicotine replacement therapy to assist smoking reduction versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in cigarettes/day of > 50% of baseline or cessation	8	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.44, 2.13]
1.1 Choice of NRT type versus placebo	2	848	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.11, 1.75]
1.2 Nicotine gum versus placebo	4	1404	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.57, 4.00]
1.3 Nicotine inhaler versus placebo	2	829	Risk Ratio (M-H, Fixed, 95% CI)	3.39 [1.70, 6.77]
2 Cessation at long-term follow-up (subgroups by type of NRT)	8	3081	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.43, 2.44]
2.1 Choice of NRT type versus placebo	2	848	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.04, 2.33]
2.2 Nicotine gum versus placebo	4	1404	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.46, 3.89]
2.3 Nicotine inhaler versus placebo	2	829	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.13, 3.20]
3 Other outcomes - consumption markers			Other data	No numeric data
4 Other outcomes - health markers			Other data	No numeric data

### Comparison 2. NRT combined with counselling to assist smoking reduction versus brief cessation advice

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in cigarettes/day of > 50% of baseline or cessation	2	1306	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.26, 2.43]
1.1 Nicotine gum, or patch, combined with counselling	2	1306	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.26, 2.43]
2 Cessation at long-term follow-up	2	1306	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.89, 2.50]
2.1 Nicotine gum, or patch, combined with counselling	2	1306	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.89, 2.50]
3 Other outcomes - consumption markers			Other data	No numeric data
4 Other outcomes - health markers			Other data	No numeric data

**Comparison 3. Nicotine patches versus placebo for temporary abstinence**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

**Comparison 4. Bupropion to assist smoking reduction versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Reduction in cigarettes/day of > 50% of baseline or cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Other outcomes - consumption markers			Other data	No numeric data

**Comparison 5. Varenicline to assist smoking reduction versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Other outcomes - consumption markers			Other data	No numeric data

**Comparison 6. Ecigarettes to assist smoking reduction versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Reduction in cigarettes/day of > 50% of baseline or cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2 Other outcomes - consumption markers	Other data	No numeric data
3 Other outcomes - health markers	Other data	No numeric data

#### Comparison 7. Snus to reduce and replace smoking versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Reduction in cigarettes/day of > 50% of baseline or cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Other outcomes - consumption markers			Other data	No numeric data
3 Other outcomes - health markers			Other data	No numeric data

#### Comparison 8. PREPs to assist smoking reduction versus smoking as usual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Other outcomes - consumption markers			Other data	No numeric data
2 Cessation at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Other outcomes - health markers			Other data	No numeric data

#### Comparison 9. Computerized programme to assist smoking reduction versus self-help reduction guide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Reduction in cigarettes/day of > 50% of baseline or cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Other outcomes - consumption markers			Other data	No numeric data



## Comparison 10. Behavioural reduction advice to assist smoking reduction versus health mailings

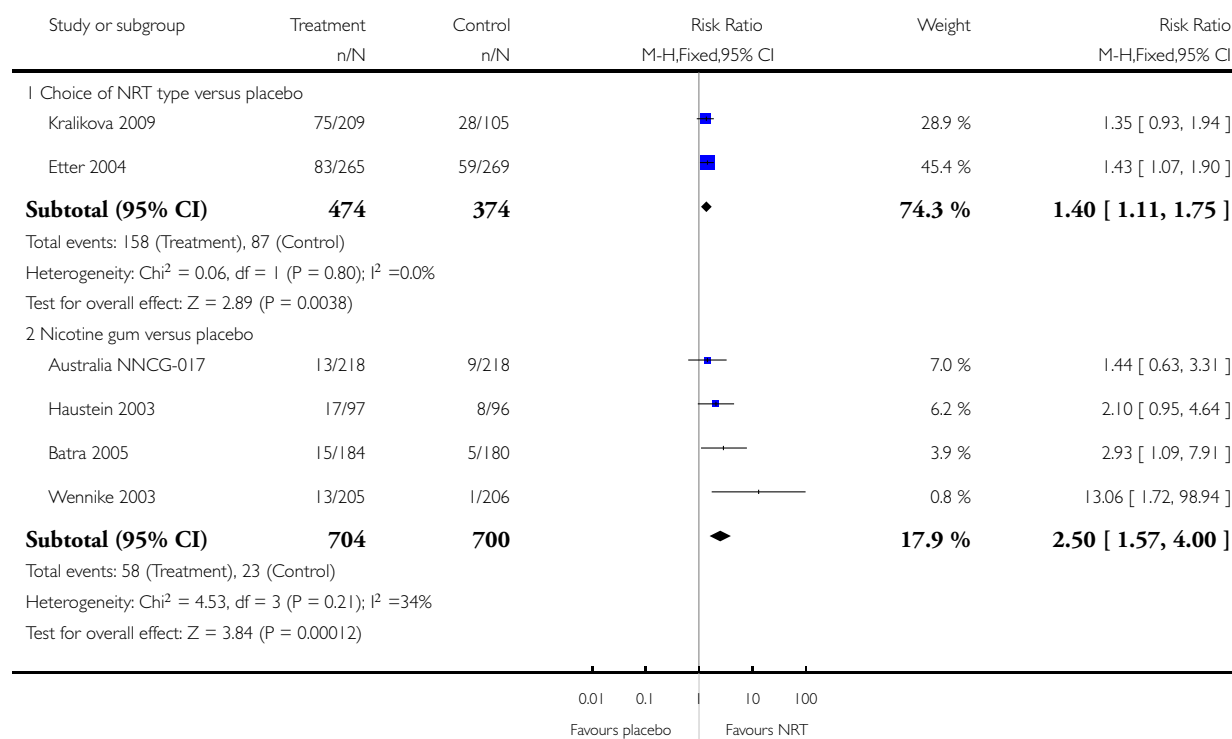
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcomes at long-term follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Reduction in cigarettes/day of > 50% of baseline or cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Other outcomes - consumption markers			Other data	No numeric data

### Analysis 1.1. Comparison 1 Nicotine replacement therapy to assist smoking reduction versus placebo, Outcome 1 Reduction in cigarettes/day of > 50% of baseline or cessation.

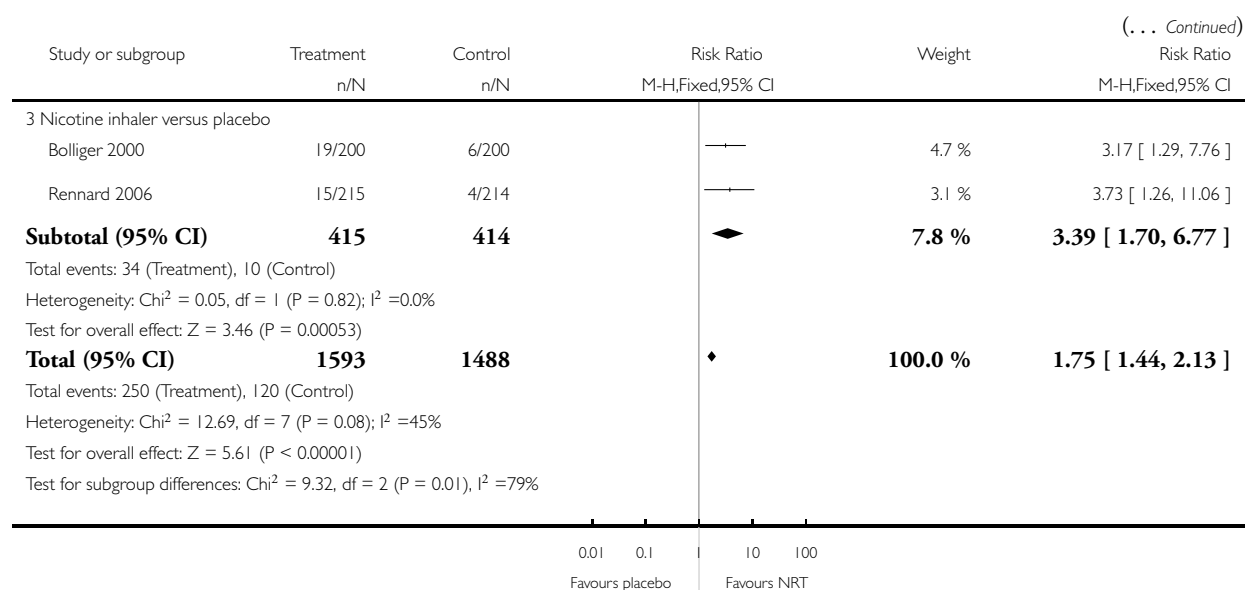
Review: Interventions to reduce harm from continued tobacco use

Comparison: 1 Nicotine replacement therapy to assist smoking reduction versus placebo

Outcome: 1 Reduction in cigarettes/day of > 50% of baseline or cessation



(Continued ...)

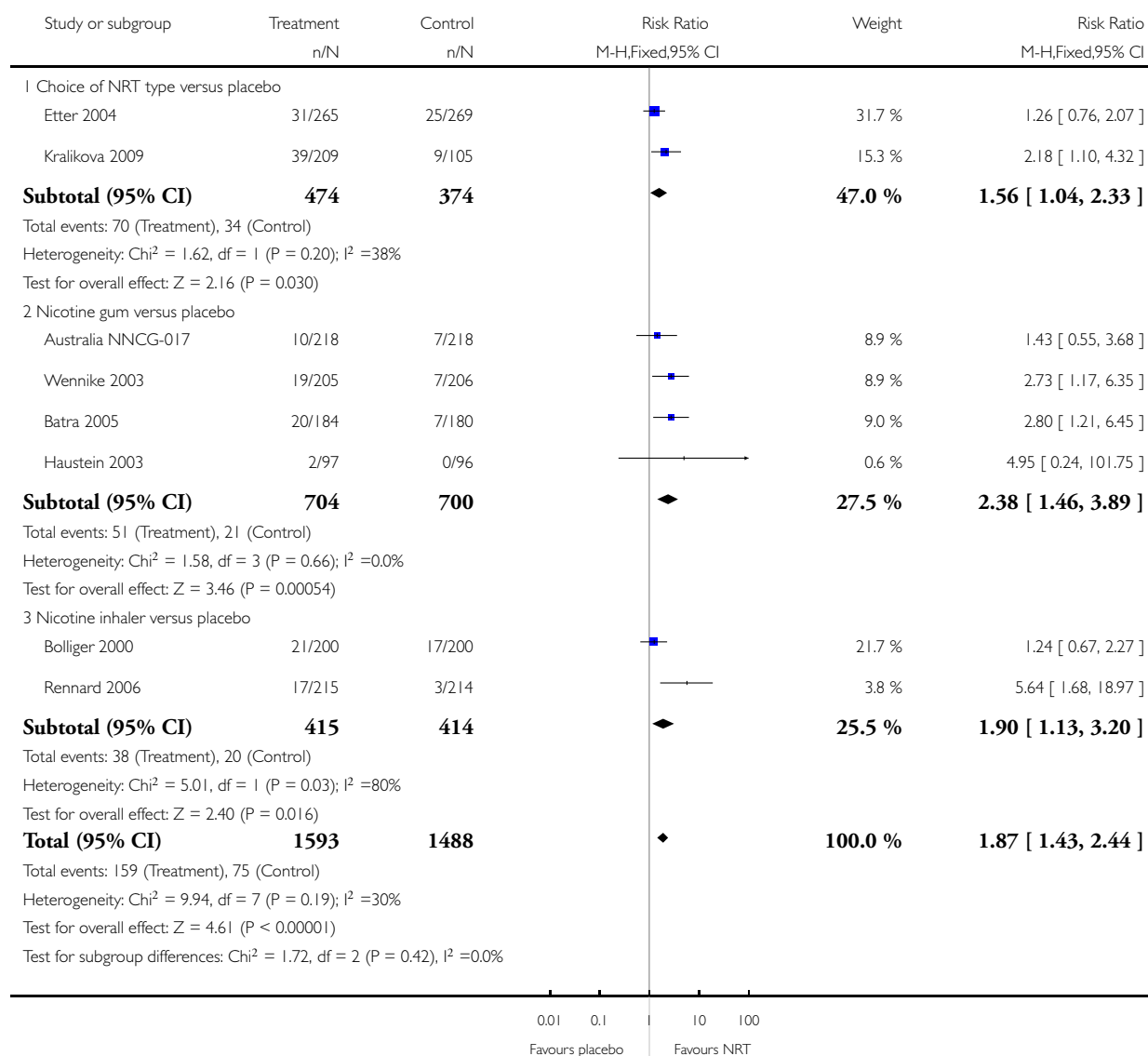


## Analysis 1.2. Comparison 1 Nicotine replacement therapy to assist smoking reduction versus placebo, Outcome 2 Cessation at long-term follow-up (subgroups by type of NRT).

Review: Interventions to reduce harm from continued tobacco use

Comparison: 1 Nicotine replacement therapy to assist smoking reduction versus placebo

Outcome: 2 Cessation at long-term follow-up (subgroups by type of NRT)



**Analysis 1.3. Comparison 1 Nicotine replacement therapy to assist smoking reduction versus placebo, Outcome 3 Other outcomes - consumption markers.**

**Other outcomes - consumption markers**

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Australia NNCG-017	Not reported	Not reported	At 12m reductions from baseline of > 50% as verified by reduction in CO Nicotine gum group 3/218 (1.4%) ; placebo group 2/218 (0.9%) (NS)	-
Batra 2005	At 13m % reductions from baseline for attenders including quitters: (n, mean, SD) CPD active 55, 64.0% (33.1%); placebo 39, 51.0% (33.9%) (NS)	As for CPD/CO based on attenders with data, including quitters Cotinine % reduction active n = 52, 31.8% (44.2%), placebo 36, 25.5% (40.0%) (P = 0.04) Thiocyanate active 46, 20.5% (30.5%), placebo 33, 16.7% (22.8%) (NS)	At 13m % reductions from baseline for attenders including quitters: (n, mean, SD) CO active 55, 43.1% (39.3%); placebo 39, 27.1% (40.5%) Sustained CO reduction > 20% at 13m; active 13.6%, placebo 5.6%	-
Bolliger 2000	As % of baseline value reported for participants still using inhalers every day at 18m: (n, mean, SD) Intervention 22, 36.2% (29.6%); placebo 8, 67.2% (27.8%) (P = 0.02) Among successful reducers (n = 25; 19 intervention, 6 control), mean (SD) CPD at 24m: 5.0 (6.4), entire placebo group 18.2 (11.2)	Among successful reducers (n = 25; 19 intervention, 6 control), mean (SD) cotinine (ng/ml) at 24m: 139 (167), entire placebo group 325 (163) (P < 0.05)	As % of baseline value reported for participants still using inhalers every day at 18m: (n, mean, SD) Intervention 22, 71.0% (58.8%); placebo 8, 81.7% (41.1%) (NS) Among successful reducers (n = 25; 19 intervention, 6 control), mean (SD) CO (ppm) at 24m: successful reducers 10.0 (8.5), entire placebo group 20.6 (11.2)	-
Etter 2004	After 26m the mean absolute reduction (ITT) in CPD was 9.8 for nicotine, 7.7 for placebo & control. Median reduction 7.5 vs 5.0. Amongst participants followed up	Not reported	Not reported	-

**Other outcomes - consumption markers** (Continued)

	at 60 months (excl quitters) the mean absolute reduction in CPD ranged from 6.3 to 7.9 (NS between groups). CPD as % of baseline was 74% NRT, 80% placebo & no treatment			
Hanson 2008	Mean CPD at baseline; end of treatment; 3m; 6m: Nicotine patch: 11.1; 5.0; 6.1; 8.9 Nicotine gum: 12.7; 6.0; 7.6; 9.3 Placebo: 11.6; 5.4; 4.6; 7.8 Reduction in all groups from baseline ( $P < 0.0001$ ) but difference between groups not statistically significant	Mean cotinine (ng/ml) at baseline; end of treatment; 3m; 6m: Nicotine patch: 3476; 3464; 3264; 4660 Nicotine gum: 3759; 3946; 2718; 4346 Placebo: 3072; 2505; 2734; 3949 Difference between groups not statistically significant	Mean CO (ppm) at baseline; end of treatment; 3m; 6m: Nicotine patch: 7.1; 5.2; 7.6; 8.7 Nicotine gum: 6.9; 6.7; 7.9; 9.1 Placebo: 5.7; 5.1; 5.4; 6.0 Significant interaction between treatment group and follow-up visit reported, with higher CO in nicotine gum than nicotine patch group in third week of follow-up ( $P = 0.05$ )	Mean total NNAL (pmol/mg) at baseline; end of treatment: Nicotine patch: 0.66; 0.65 Nicotine gum: 0.79; 0.87 Placebo: 0.54; 0.76 Difference between groups not statistically significant
Haustein 2003	CPD not reported as a continuous variable	Between-study group differences are not supplied. Comparisons were made between reducers (50%+ CPD) and non-reducers (< 50% CPD), and reducers had a significantly greater reduction in plasma cotinine and plasma thiocyanate between baseline and 12m follow-up reducers and non-reducers experienced a significant reduction in plasma cotinine, whereas only reducers experienced a significant reduction in plasma thiocyanate)	Between-study group differences are not supplied. Measures of CO reduction generally matched levels of CPD reduction i.e. those participants who reduced CPD by 50% - 74% reduced their CO by a mean of 51%, those who reduced CPD by 25% - 49% reduced their CO by a mean of 32.6% and those who reduced CPD by 0% - 24% reduced their CO by a mean of 25.4%	-
Kralikova 2009	Not reported	Significant reduction in plasma cotinine in ab-	Significant reduction in CO in	-

**Other outcomes - consumption markers** (Continued)

		stainers at 4m and 12m, and in reducers at 4m (mean at 12m: abstainers 40ng/mL, reducers 216, failures 271)	abstainers and reducers at 4m and 12m, and in failures at 12m, with larger reduction from baseline in abstainers and reducers (mean at 12m: abstainers 2.7 ppm, reducers 11.7, failures 17.2)	
Rennard 2006	Amongst successful reducers at 4m (reduction in daily smoking of at least 50% from baseline) the reduction in average CPD was 74% in both active (mean dropped from 29.1 to 7.6) and placebo (31.9 to 8.1) groups. In all participants, reduction in average CPD at 24m was 14.6% in active group and 12.2% in placebo group	Reduction from baseline in cotinine and thiocyanate in both active and placebo groups. Levels fell by more in $\geq 50\%$ reducers at 4 months than in non-reducers	Amongst sustained reducers at 15m, reducers of 50% to $< 75\%$ reduced their average CO by 8.3 ppm. Reducers of $> 75\%$ (incl quitters) reduced average CO by 25.2 ppm	No differences across treatment groups in any markers. Exploratory analyses of successful reducers at 4m showed significant change from baseline in HDL but no other markers
Wennike 2003	At 24m based on remaining participants no differences between active and placebo. CPD 54% vs 61% of baseline ( $P = 0.2$ ). At 4m effect size was similar (56% vs 67%) and statistically significant ( $P = 0.03$ )	At 24m based on remaining participants no differences between active and placebo. Cotinine 83% vs 93% of baseline ( $P = 0.1$ ), thiocyanate 74% vs 82% ( $P = 0.2$ ). At 4m differences were statistically significant, with the direction of the effect reversed for cotinine (cotinine 98% vs 86%, $P = 0.01$ ; thiocyanate 79% vs 89%, $P < 0.001$ )	At 24m based on remaining participants no differences between active and placebo. CO 63% vs 76% of baseline ( $P = 0.1$ ). At 4m effect size was similar (71% vs 84%) and statistically significant ( $P = 0.01$ )	-

**Analysis 1.4. Comparison 1 Nicotine replacement therapy to assist smoking reduction versus placebo, Outcome 4 Other outcomes - health markers.**

**Other outcomes - health markers**

Study	Lipoproteins	Haematological markers	Pulmonary function	Quality of life	Other health markers
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**Other outcomes - health markers** (Continued)

Batra 2005	Not reported	No statistically significant change in any cardiovascular risk markers (WBC, fibrinogen, CRP) between baseline and month 12 in the 20 successful sustained reducers/abstainers	Not reported	Not reported	Not reported
Bolliger 2000	Comparison between 25 (19 active, 6 placebo) sustained reducers and 285 non-reducers at 24m. Both groups had statistically significant reduction from baseline in total cholesterol/HDL ratio and LDL and increase from baseline in HDL. Placebo group also had statistically significant reduction in total cholesterol. Difference between groups statistically significant only for total cholesterol/HDL ratio, with greater reduction in reducers	Comparison between 25 (19 active, 6 placebo) sustained reducers and 285 non-reducers at 24m. Both groups had statistically significant reduction from baseline in haemoglobin and haematocrit. Placebo group also had statistically significant increase in fibrinogen and WBC. Difference between groups statistically significant only for haemoglobin, with greater reduction in reducers	Comparison between 25 (19 active, 6 placebo) sustained reducers and 285 non-reducers at 24m. Both groups had statistically significant reduction from baseline in FEV1 but not FVC. Difference between groups statistically significant only for FEV1, with greater reduction in reducers	Comparison between 25 (19 active, 6 placebo) sustained reducers and 285 non-reducers at 24m. Both groups had statistically significant increase from baseline in general health, physical functioning and emotional well-being. Placebo group additionally had statistically significant increase in energy. Difference between groups statistically significant only for general health, with greater increase in reducers	Comparison between 25 (19 active, 6 placebo) sustained reducers and 285 non-reducers at 24m. Both groups had statistically significant reduction from baseline for SBP but not pulse rate or DBP. Weight increased in female reducers and in both sexes in placebo group. Difference between groups statistically significant only for pulse rate (greater reduction in reducers) and female weight (greater increase in reducers)
Etter 2004	Not reported	Not reported	Not reported	Not reported	Average weight gain across all 3 groups over 60m was 2.4 kg (no significant difference between groups). Greater weight gain for successful quitters than for smokers was observed for men (mean 6 kg vs 2.2 kg) but not for

**Other outcomes - health markers** (Continued)

					women (mean 2.8 kg vs 2.1 kg)
Haustein 2003	In those participants who successfully reduced their smoking by 50% or more there was a 0.75% increase in HDL (-0.41 mg/dL change, N = 23), a 6.3% decrease in LDL (-8.30 mg/dL change, N = 22), a 4.2% decrease in cholesterol and a 28.2% increase in triglycerides between baseline and 12m follow-up. For the cholesterol and triglyceride measures a comparison was also made between reducers and non-reducers and there was no between-group significant differences in the changes found between baseline and 12m follow-up	In those participants who successfully reduced their smoking by 50% or more there was a 10.3% decrease in WBC (-0.85 $10^9/L$ change, N = 24), a 10.4% decrease in fibrinogen (-35.1 mg/dL change, N = 24) and 42.6% decrease in CRP (-0.26 mg/dL change, N = 24) between baseline and 12m follow-up. There was a 4.1% reduction in RBC, a 1.9% reduction in platelets, and a 4.5% decrease in haemoglobin. On these measures a comparison was made between reducers and non-reducers and there was no between-group significant differences in the changes found between baseline and 12m follow-up	Not reported	In those participants who had reduced their smoking by 50%+ at 12m significant improvements were observed in 10 of 14 QOL items on a rating scale (anxiety, cognitive function, emotional well-being, energy, general health, pain, physical functioning, self control, social interaction, worry)	After 12m the mean SBP, DBP and pulse rate were unchanged in both reducers and non-reducers compared to baseline. At 1 year the 24 successful reducers (50%+) had gained a mean of 3.49 kg compared to a mean weight gain of 1.14 kg in the non-reducers (P = 0.019)
Kralikova 2009	Not reported	No significant changes in WBC amongst reducers	Not reported	Not reported	Not reported
Rennard 2006	Reducers at 4m had a statistically significant increase from baseline in HDL (mean change 2.11 mg/dl, P = 0.003) and decrease in WBC (-0.34 $\times 10^9/L$ ,	Reducers at 4m had a statistically significant decrease from baseline in CRP (mean change -0.09 mg/dl, P = 0.04) and no significant change in fibrinogen (-18.6	Not reported	Greatest improvements in cough, phlegm, shortness of breath, and senses of smell and taste were observed in those who reduced consumption by $\geq 50\%$	Average weight gain among 20 participants who had quit smoking at 15m was 5.0 kg (P < 0.001) compared to those who did not quit, for whom there was



## Other outcomes - health markers (Continued)

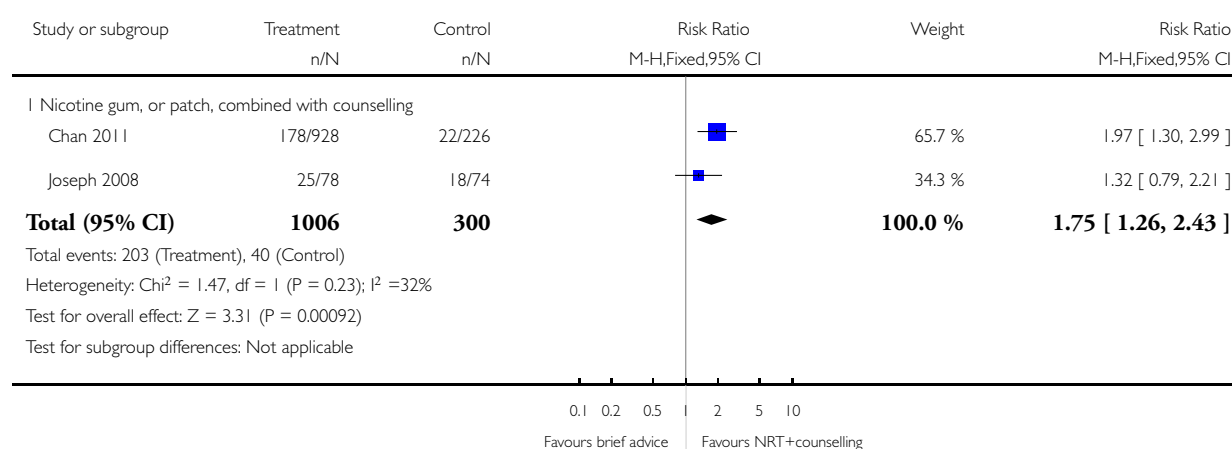
	P = 0.03). No significant change in LDL (-5.76 mg/dl, P = 0.23)	mg/dl, P = 0.15)		from baseline. These participants also reported significantly greater improvements in self-control (P < 0.001), with no difference in other quality of life outcomes	no significant weight change)
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## Analysis 2.1. Comparison 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice, Outcome 1 Reduction in cigarettes/day of > 50% of baseline or cessation.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice

Outcome: 1 Reduction in cigarettes/day of > 50% of baseline or cessation

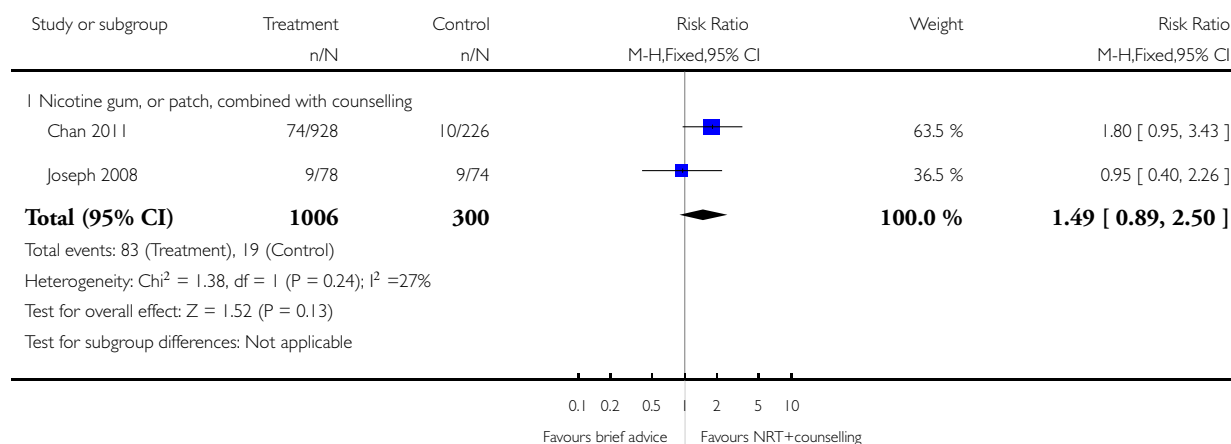


## Analysis 2.2. Comparison 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice, Outcome 2 Cessation at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice

Outcome: 2 Cessation at long-term follow-up



## Analysis 2.3. Comparison 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice, Outcome 3 Other outcomes - consumption markers.

### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Chan 2011	Among non-quiters, CPD at 6m was significantly lower in the combined intervention group (mean (SD) 9.5 (8.4)) than in the control group (13.1 (9.3)) ( $P < 0.001$ )	Urinary cotinine only reported as a validation measure for self-reported quitters	Difference in CO at 6m not statistically significant (mean (SD) 7.6 (9.3) in combined intervention group, 5.2 (10.7) in control group, $P = 0.30$ )	-
Joseph 2008	Reductions in CPD similar in both groups; decreasing from ~27 CPD at baseline to ~18 CPD at 18m, but with considerable variation between individuals	Urinary cotinine: no significant difference between groups in reduction from baseline	CO (ppm) reduction in both groups (Smoking reduction group mean 24 (baseline) to 16 (18m); Usual care group mean 25 (baseline) to 18 (18m)), no significant difference ( $P = 0.155$ )	Change from baseline in nicotine, total NNAL and 1-OHP was similar in both treatment groups

**Analysis 2.4. Comparison 2 NRT combined with counselling to assist smoking reduction versus brief cessation advice, Outcome 4 Other outcomes - health markers.**

**Other outcomes - health markers**

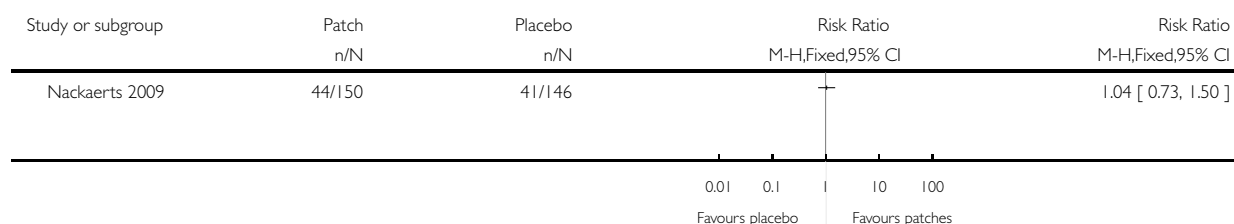
Study	Lipoproteins	Haematological markers	Pulmonary function	Quality of life	Other health markers
Joseph 2008	Not reported	Markers of inflammation and oxidation including WBC count, hs-CRP and F2-isoprostanes showed minimal change from baseline or between groups. Change from baseline in fibrinogen differed between groups (P = 0.019) but effect size was small (Smoking reduction group: mean 383 mg/dL at baseline, 367 at 18m; Usual care group: 384 at baseline, 352 at 18m)	Not reported	No differences between groups in quality of life at any time point	No differences between groups in frequency of angina at any time point

**Analysis 3.1. Comparison 3 Nicotine patches versus placebo for temporary abstinence, Outcome 1 Cessation at long-term follow-up.**

Review: Interventions to reduce harm from continued tobacco use

Comparison: 3 Nicotine patches versus placebo for temporary abstinence

Outcome: 1 Cessation at long-term follow-up

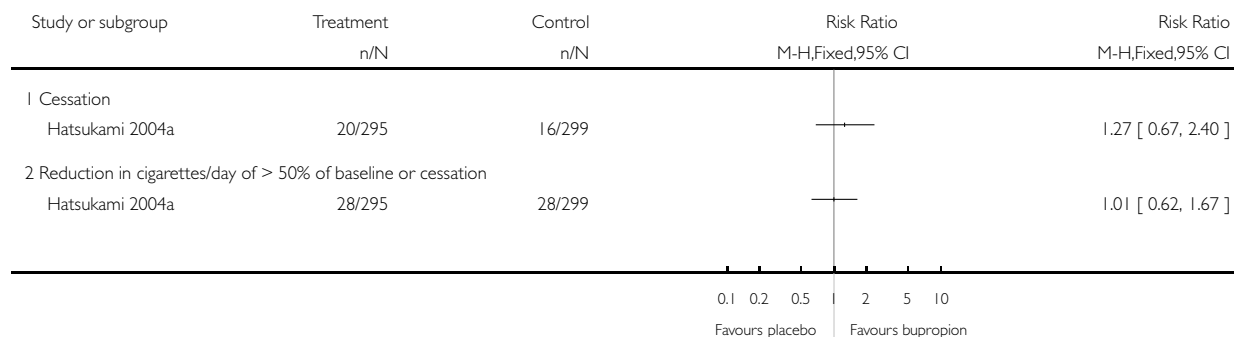


#### Analysis 4.1. Comparison 4 Bupropion to assist smoking reduction versus placebo, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 4 Bupropion to assist smoking reduction versus placebo

Outcome: 1 Outcomes at long-term follow-up



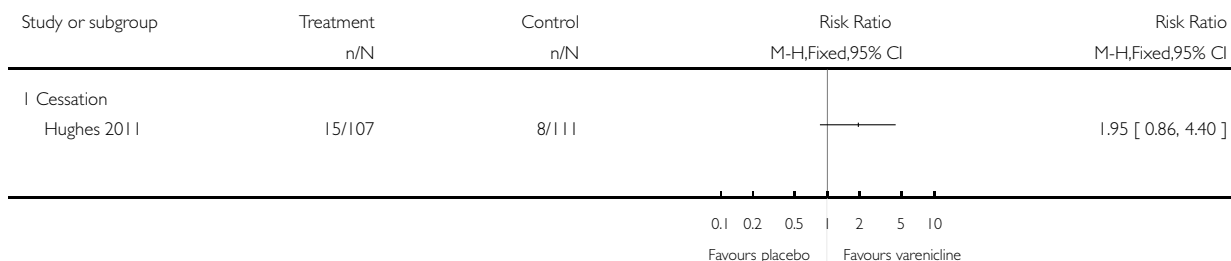
#### Analysis 4.2. Comparison 4 Bupropion to assist smoking reduction versus placebo, Outcome 2 Other outcomes - consumption markers.

##### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Hatsukami 2004a	Reduction in mean CPD from baseline to 3m: Bupropion group 6.5, placebo group 6.3. Proportion with 50% reduction in CPD from baseline statistically significant at 6m (16% vs 9%, P = 0.02) but not at 3m (28% vs 17%, P = 0.41) or 12m (5% vs 7%, P = 0.55)	In ITT analysis, mean urinary cotinine decrease from baseline greater in bupropion group than in placebo group (mean decrease approximately 340 ng/ml vs 130 ng/ml, P = 0.008) but difference at 12m not statistically significant (mean decrease 82 ng/mL vs 28 ng/ml, P = 0.25). Similar conclusion for % of participants achieving 50% reduction in urine cotinine	Not reported	-

### Analysis 5.1. Comparison 5 Varenicline to assist smoking reduction versus placebo, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use  
 Comparison: 5 Varenicline to assist smoking reduction versus placebo  
 Outcome: 1 Outcomes at long-term follow-up



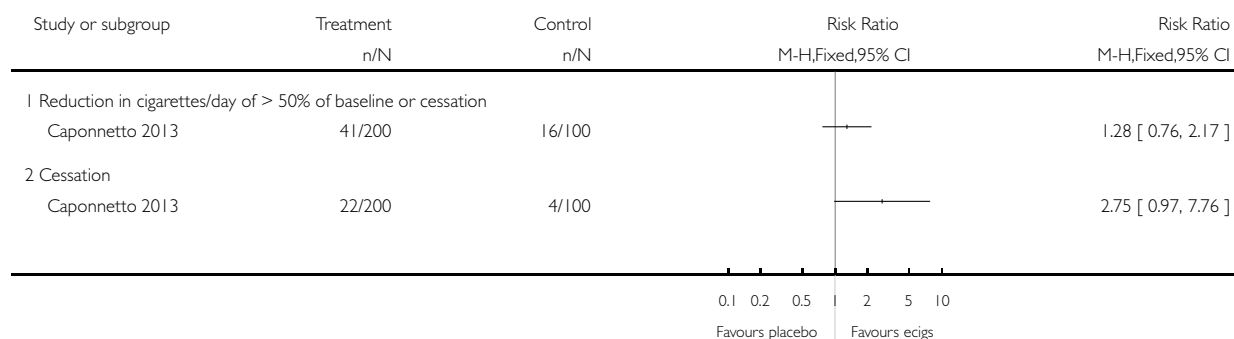
### Analysis 5.2. Comparison 5 Varenicline to assist smoking reduction versus placebo, Outcome 2 Other outcomes - consumption markers.

#### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Hughes 2011	Reduction in CPD was higher in varenicline group than in control group (reduction from baseline 5.8 (29%) vs 3.2 (17%), P = 0.003)	Not reported	Not reported	-

### Analysis 6.1. Comparison 6 Ecigarettes to assist smoking reduction versus placebo, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use  
 Comparison: 6 Ecigarettes to assist smoking reduction versus placebo  
 Outcome: 1 Outcomes at long-term follow-up



### Analysis 6.2. Comparison 6 Ecigarettes to assist smoking reduction versus placebo, Outcome 2 Other outcomes - consumption markers.

#### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Caponnetto 2013	Significant differences in CPD between groups (with higher CPD in the no-nicotine group) were reported at 2, 6 and 8 wks, but not at other intermediate time points, nor at the end of the study (52 wks, median CPD 12 - 14 in all groups)	Saliva cotinine levels at wk 6 and wk 12 were near zero in the no-nicotine group, and not significantly different between the other 2 study groups (median (ng/ml) 42.5 (wk 6) and 91.0 (wk 12) in the 7.2 mg nicotine group; 67.8 (wk 6) and 69.8 (wk 12) in the 5.4 mg nicotine group)	Significant difference in CO between groups was reported at wk 6 (P = 0.01) but at none of the other 7 time points during follow-up (at 52 wks, median CO was 15 - 17 ppm in all groups)	-

### Analysis 6.3. Comparison 6 Ecigarettes to assist smoking reduction versus placebo, Outcome 3 Other outcomes - health markers.

#### Other outcomes - health markers

Study	Lipoproteins	Haematological markers	Pulmonary function	Quality of life	Other health markers
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## Other outcomes - health markers (Continued)

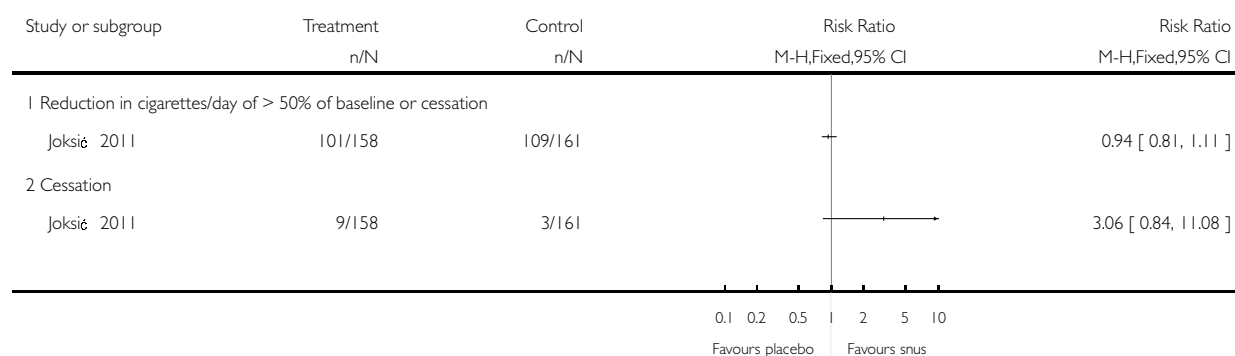
Caponnetto 2013	Not reported	Not reported	No significant changes in resting heart rate, SBP or DBP over time or between groups	Not reported	No significant changes in weight over time or between groups
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### Analysis 7.1. Comparison 7 Snus to reduce and replace smoking versus placebo, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 7 Snus to reduce and replace smoking versus placebo

Outcome: 1 Outcomes at long-term follow-up



### Analysis 7.2. Comparison 7 Snus to reduce and replace smoking versus placebo, Outcome 2 Other outcomes - consumption markers.

#### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Joksić 2011	At 48 wks, CPD had decreased to around ¼ of baseline in each group (mean 7.6 (snus group), 8.6 (placebo group)), difference between groups not statistically significant	Reduction from baseline in plasma cotinine was similar in both groups (snus group: mean 98.9 ng/ml (baseline), 66.1 (48 wks); placebo group: 101.2 (baseline), 69.1 (48 wks))	Reduction from baseline in exhaled CO was similar in both groups (snus group: mean 23.5 ppm (baseline), 11.5 (48 wks); placebo group: 23.5 (baseline), 12.1 (48 wks))	-

**Analysis 7.3. Comparison 7 Snus to reduce and replace smoking versus placebo, Outcome 3 Other outcomes - health markers.**

**Other outcomes - health markers**

Study	Lipoproteins	Haematological markers	Pulmonary function	Quality of life	Other health markers
Joksić 2011	No changes in total, LDL or HDL cholesterol over time or differences between groups	No changes in WBC, CRP or fibrinogen over time or differences between groups	No changes in FEV1, 0, FVC or FEV% over time or differences between groups	Not reported	No changes in SBP, DBP, weight or BMI over time or differences between groups

**Analysis 8.1. Comparison 8 PREPs to assist smoking reduction versus smoking as usual, Outcome 1 Other outcomes - consumption markers.**

**Other outcomes - consumption markers**

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Benowitz 2012	Small but statistically significant differences between control and reduced-nicotine groups in change in CPD from baseline to 26 wks, and from 14 wks to 26 wks (mean CPD: control 19 (baseline), 21 (14 wks), 22 (26 wks); reduced-nicotine 22 (baseline), 24 (14 wks), 20 (26 wks))	For plasma cotinine, larger reductions from baseline to 14 wks and 26 wks follow-up in reduced-nicotine group (mean (ng/ml) 256 (baseline), 240 (26 wks)) than in control group (mean 256 (baseline), 113 (26 wks)) (P < 0.001), with greatest decline in the reduced-nicotine group occurring between 6 and 18 wks	No differences between groups at any time point (mean CO (ppm): control 20 (baseline), 24 (14 wks), 20 (26 wks); reduced-nicotine 21 (baseline), 25 (14 wks), 23 (26 wks))	Pattern of plasma nicotine was similar to that seen for cotinine (greater decline in reduced-nicotine group than in control group). Significantly greater reduction between 14 wks and 26 wks in reduced-nicotine group than in control group. No difference between groups in sum of phens, 2-naphthol, sum of fluors or 1-hydroxypyrene
Mendes 2008	Mean CPD at baseline; short-term phase; long-term phase: MFF group: 19.7; "between 19.1 and 19.7"; 26.3 ML group: 20.3; "between 20.0 and 20.5"; 26.8 MUL group: 19.8; "between 18.6 and 19.8"; 30.3	Statistically significantly lower during the short-term phase in MUL group (mean 230 ng/mL) than in MFF group. No difference between ML group and MFF group	Not reported	Mean urine nicotine equivalents over the whole study was lower in MUL group (mean 13.1 mg/24 hrs) in MFF group (16.8) (P = 0.02) but similar between MFF group and ML group (15.4) (P = 0.76). A similar pattern was observed in the short-term phase (first 8 days), when levels were slightly higher in all groups. Overall urine total NNAL was lower in MUL group than in MFF



**Other outcomes - consumption markers** (Continued)

				group in the short-term phase ( $P = 0.05$ ); differences in long-term phase not significant. Urine total 1-OHP lower in MUL group than in MFF group during both phases. Urine mutagenicity: differences between groups not significant. COHb tended to be lowest in MUL group and highest in ML group. Some evidence that urine S-PMA was lower in MUL group than MFF group in long-term phase ( $P = 0.05$ ). 3-HPMA decreased from baseline in all groups. Mean values of the Fagerström Test for Nicotine Dependence “were between 5.4 and 5.8 on a scale of 0-9 and did not change during the study”
Roethig 2008	Mean CPD increased from 24.3 (baseline) to 63.4 (52 wks) in EHCSS group (a 95% increase) and from 23.3 (baseline) to 36.6 in CC group (a 27% increase) ( $P < 0.001$ for difference between groups)	Over 12m, mean plasma cotinine decreased by 16% in EHCSS group and increased by 5% in CC group ( $P = 0.018$ )	Not reported	Over 12m, urine nicotine equivalents decreased by 18% in EHCSS group and increased by 0.1% in CC group ( $P = 0.014$ ). Also greater and statistically significant reductions in the EHCSS group than in the CC group in total NNAL, total 1-OHP, urine mutagenicity, 4-ABP Hb adducts, COHb AUC (7 - 23 hrs) and 3-HPMA (all $P < 0.001$ )
Sarkar 2008	In different study groups, mean CPD was between 17.5 and 19.1 at baseline and increased to between 24.6 and 35.1 at 24 wks (differences between groups not statistically significant)	Not reported	Not reported	For most time points in both short- and long-term follow-up, MHBMA, 3-HPMA and S-PMA were all statistically significantly lower in the test cigarette groups than in the conventional cigarette groups. At most follow-up times, dif-

## Other outcomes - consumption markers (Continued)

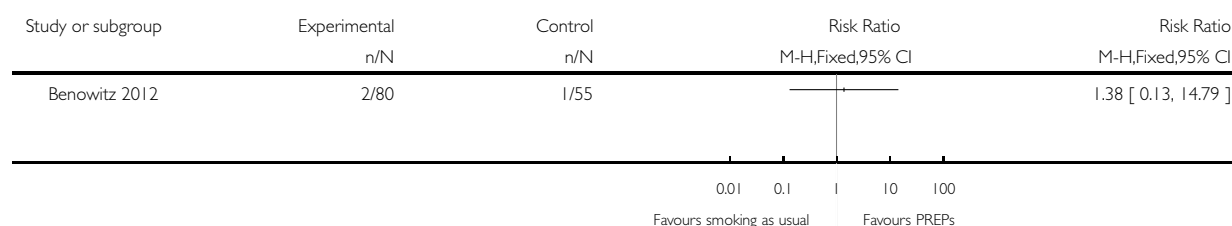
				ferences between groups in nicotine equivalents, total NNAL, total 1-OHP were not statistically significant
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### Analysis 8.2. Comparison 8 PREPs to assist smoking reduction versus smoking as usual, Outcome 2 Cessation at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 8 PREPs to assist smoking reduction versus smoking as usual

Outcome: 2 Cessation at long-term follow-up



### Analysis 8.3. Comparison 8 PREPs to assist smoking reduction versus smoking as usual, Outcome 3 Other outcomes - health markers.

#### Other outcomes - health markers

Study	Lipoproteins	Haematological markers	Pulmonary function	Quality of life	Other health markers
Benowitz 2012	No significant changes in any group for HDL cholesterol	No significant changes in any group for WBC, haemoglobin or fibrinogen	Not reported	Not reported	Average weight gain among compliant smokers in the reduced nicotine group was 2 kg (statistically significant), but no difference between control and reduced-nicotine group overall. No significant changes in any group for blood pressure or heart rate

**Other outcomes - health markers** (Continued)

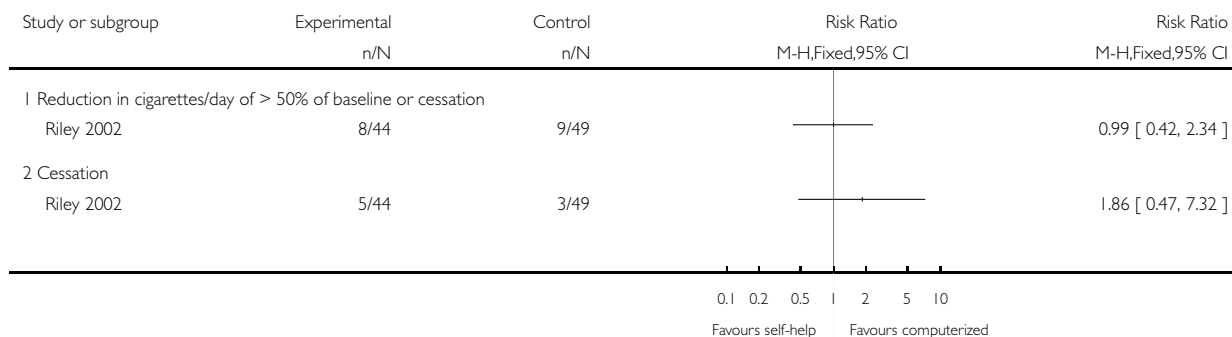
Roethig 2008	Greater % increase for HDL cholesterol in EHCSS group than in CC group (P = 0.008), Differences between groups in LDL cholesterol not statistically significant	% reduction from baseline to 12m was greater in EHCSS group than in CC group for haemoglobin, haematocrit, RBC, WBC, neutrophils, lymphocytes and urine 11-dehydrothromboxane B <sub>2</sub> (P < 0.02 in each case). Differences between groups in CRP, fibrinogen and urine 8-epi-prostaglandin F <sub>2α</sub> not statistically significant	Not reported	Not reported	Not reported
Sarkar 2008	Differences between groups in HDL cholesterol, LDL cholesterol and triglycerides not statistically significant	Differences between groups in urine microalbumin, 11-dehydrothromboxane B <sub>2</sub> , 8-epi-prostaglandin F <sub>2α</sub> , fibrinogen, von Willebrand factor and CRP not statistically significant, with the exception of urine microalbumin in a single group	Not reported	Not reported	Not reported

### Analysis 9.1. Comparison 9 Computerized programme to assist smoking reduction versus self-help reduction guide, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 9 Computerized programme to assist smoking reduction versus self-help reduction guide

Outcome: 1 Outcomes at long-term follow-up



### Analysis 9.2. Comparison 9 Computerized programme to assist smoking reduction versus self-help reduction guide, Outcome 2 Other outcomes - consumption markers.

#### Other outcomes - consumption markers

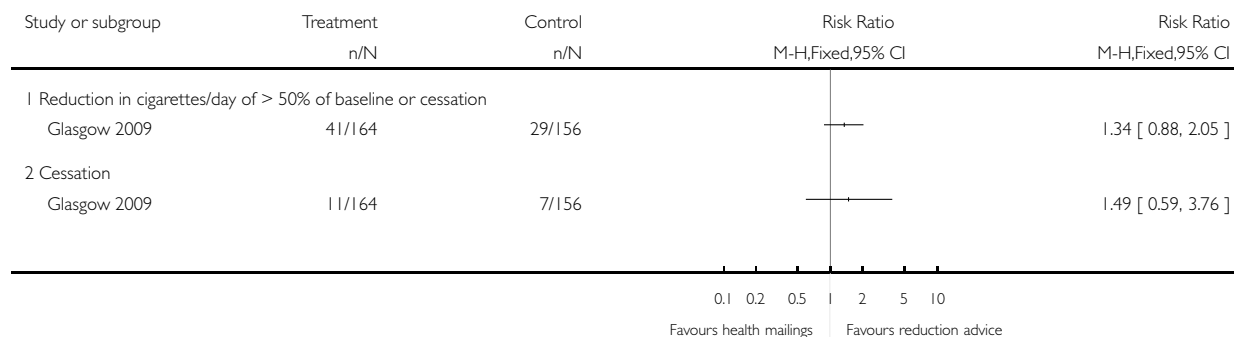
Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Riley 2002	A mean reduction of approximately 10 CPD between pretreatment to post-treatment in both groups, which was essentially maintained over 1 year. Differences in % reduction from pre-treatment to 6m (N = 60; 32% for CSGR; 25% for SER) and to 12m (N = 57; 38% for CSGR; 35% for SER) were not significant	Not reported	Overall reduction in mean CO from 22.6 to 19.6 ppm (P < 0.01) from pre- to post-treatment, but no significant effect of treatment	

### Analysis 10.1. Comparison 10 Behavioural reduction advice to assist smoking reduction versus health mailings, Outcome 1 Outcomes at long-term follow-up.

Review: Interventions to reduce harm from continued tobacco use

Comparison: 10 Behavioural reduction advice to assist smoking reduction versus health mailings

Outcome: 1 Outcomes at long-term follow-up



### Analysis 10.2. Comparison 10 Behavioural reduction advice to assist smoking reduction versus health mailings, Outcome 2 Other outcomes - consumption markers.

#### Other outcomes - consumption markers

Study	CPD	Cotinine/Thiocyanate	CO	Other consumption markers
Glasgow 2009	No difference between groups in CPD at 3m (Intervention mean (SD) 17.2 (9.6); Control 17.3 (8.7)) or at 12m (15.8 (10.3); 15.3 (9.2)), but both groups had showed "modest change from baseline" (21.2 (9.4); 20.1 (8.9))	Not reported	Mean (SD) CO levels At baseline: Intervention (n = 164) 29.8 (13.9); Control (n = 156) 29.8 (14.5) At 12m: Intervention (n = 164) 24.9 (14.0); Control (n = 156) 24.3 (13.8). No significant between-group difference in the change from baseline	-

## APPENDICES

### Appendix I. Cochrane Register of Studies (CRS) search strategy

#1 MeSH DESCRIPTOR Harm Reduction  
 #2 Harm Reduction:MH  
 #3 Harm Reduction:TI,AB,EMT,KY,XKY,KW  
 #4 MeSH DESCRIPTOR Risk Reduction Behavior  
 #5 Risk Reduction Behavior:MH  
 #6 Risk Reduction:TI,AB,EMT,KY,XKY,KW  
 #7 smoking reduction:TI,AB,MH,EMT,KY,XKY,KW  
 #8 (reduce\* smoking):TI,AB,MH,EMT,KY,XKY,KW  
 #9 (tobacco harm):TI,AB,MH,EMT,KY,XKY,KW  
 #10 (cigarette ADJ2 (reduction or reduce\*)):TI,AB,MH,EMT,KY,XKY,KW  
 #11 (controlled smoking):TI,AB,MH,EMT,KY,XKY,KW  
 #12 MeSH DESCRIPTOR Risk Assessment  
 #13 Risk Assessment:MH  
 #14 (electronic nicotine delivery system\*):TI,AB  
 #15 (Potential reduced exposure products OR PREP OR PREPs):TI,AB  
 #16 (electronic cigar\* OR e-cig\* OR ecig\*):TI,AB  
 #17 (temporary and (abstinence or abstain\*)):TI,AB,MH,EMT,KY,XKY,KW  
 #18 dual use\*:TI,AB,MH,EMT,KY,XKY,KW  
 #19 smokeless ADJ tobacco:TI,AB,MH,EMT,KY,XKY,KW  
 #20 (swap or substitut\*):TI,AB,MH,EMT,KY,XKY,KW  
 #21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

## WHAT'S NEW

Date	Event	Description
7 December 2016	Amended	Correction: Citation reference changed from Ranstrom 2014 to Ramstrom 2014 in 'Additional references' section

## HISTORY

Date	Event	Description
13 October 2016	New search has been performed	Updated with 6 new studies added. Some data points updated to ensure reductions over 50% also included participants who had quit in all cases. We now exclude 1 previously included study ( <a href="#">Pisinger 2005</a> ). The study was previously borderline include and results were not meta-analysed. This was because the study was not conducted or reported so that participants willing to quit could be

(Continued)

		separated from those unwilling to quit in the control arm
13 October 2016	New citation required and conclusions have changed	New interventions added with new associated conclusions at this update
24 June 2010	New search has been performed	Updated with six new studies and published data for one previously included study. Outcome summaries changed from odds ratio to risk ratio. No substantial change to conclusions
28 October 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

Conception of review: KH, LS, TL (original authors of the protocol for this review).

Study eligibility decisions: AF, JHB, NLH, RB

Data extraction: AF, JHB, NLH, RB

Statistical support & drafting of review tables for secondary outcomes: TRF

Drafting of review: NLH

Review of draft: AF, JHB, RB, TL, TRF

## DECLARATIONS OF INTEREST

AF has received personal consultancy fees from the Annals of Internal Medicine to write an independent review of a commissioned article.

JHB has no known conflicts of interest.

NLH is a co-applicant on a completed trial investigating nicotine patch preloading for smoking cessation (not a harm reduction approach). The nicotine patches were provided free of charge by GlaxoSmithKline; however the trial was funded by the NIHR HTA (09/110/01), and the running and the reporting of the trial were carried out independently to the funder and treatment provider.

RB has no known conflicts of interest.

TL has no known conflicts of interest.

TRF has no known conflicts of interest.

## SOURCES OF SUPPORT

### Internal sources

- Nuffield Department of Primary Care Health Sciences, University of Oxford, UK.  
Provides infrastructure for NLH, JHB, RB, TRF, TL, and salary for RB
- Public Health, Epidemiology & Biostatistics, University of Birmingham, UK.  
Salary and infrastructure support for AF

### External sources

- National Institute for Health Research, UK.  
Salary support for JHB & NLH and infrastructure for the Cochrane Tobacco Addiction Group

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes for the 2016 update:

1. Specification that rates of reduction of 50% of baseline CPD or more include those participants who have stopped smoking completely (this is deemed to be a reduction of 100%);
2. Clearly specified that participants must not be intending to quit at enrolment;
3. Extended the search strategy to include terms relating to outcomes and products more recently adopted as harm reduction aids, such as temporary abstinence and electronic cigarettes.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Tobacco Use Cessation Products; Biomarkers [blood]; Bupropion [therapeutic use]; Carbon Monoxide [blood]; Cotinine [blood]; Electronic Cigarettes; Nicotine [therapeutic use]; Nicotinic Agonists [therapeutic use]; Randomized Controlled Trials as Topic; Smoking [adverse effects; blood; \*prevention & control]; Smoking Cessation [methods]; Tobacco Use Disorder [\*therapy]

### MeSH check words

Humans