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[Intervention Review]

Oral nicotine pouches for cessation or reduction of use of other tobacco or nicotine products

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ABSTRACT

Rationale

Oral nicotine pouches (ONP) emerged in the late 2000s, but have gained popularity since their introduction to the global market in 2016, with claims about their harm reduction potential.

Objectives

Primary objectives

• To evaluate the benefits and harms of ONP when used to help people transition away from combustible tobacco use (smoking).

• To evaluate the impact of ONP on the prevalence of combustible tobacco use.

Secondary objectives

• To evaluate the benefits and harms of ONP when used to help people transition away from other non-combustible tobacco/commercial nicotine product use.

• To evaluate the impact of ONP on the prevalence of use of other non-combustible tobacco/commercial nicotine products.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO from 2000 to 13 January 2025. We also covered ClinicalTrials.gov and the WHO ICTRP through our search of CENTRAL.

Eligibility criteria

We included randomised controlled trials (RCTs) of ONP in people using tobacco or other non-combustible tobacco/non-pharmaceutical nicotine products. RCTs must have reported tobacco/nicotine use at 4+ weeks or biomarkers or adverse events at 1+ weeks. We also sought interrupted/multiple time-series studies of ONP's population-level effects on the prevalence of use of other tobacco/nicotine products.

Outcomes

Our critical outcomes were: smoking abstinence at 4+ weeks; number of people reporting serious adverse events (SAEs) at 1+ weeks; and change in the prevalence of smoking. Important outcomes included tobacco-specific nitrosamines (TSNAs), carboxyhaemoglobin (COHb), metals, and inflammatory markers detected in human biosamples.

Risk of bias

We used the Cochrane RoB 1 tool to assess risk of bias.

Synthesis methods

We synthesised results using random-effects meta-analysis where possible. We used I^2 to quantify statistical heterogeneity. Where meta-analysis was not possible, we graphically plotted available data in forest plots. We used risk ratios (RR) for dichotomous outcomes and mean differences (MD) or standardised mean differences (SMD) for continuous outcomes, with 95% confidence intervals (CI). We assessed the certainty of evidence using GRADE.

Included studies

We included four small studies (n < 150 for each, total n = 284; 3 independent, 1 industry-funded; 3 at high risk of bias and 1 at unclear risk of bias). All were RCTs in people who smoked combustible cigarettes at baseline. Three were conducted in the USA, and one in New Zealand. Two compared higher- versus lower-nicotine dose ONP. Two compared ONP to instructions to continue smoking as usual. One each compared ONP to electronic cigarettes (e-cigarettes), snus, and pharmaceutical nicotine replacement therapy (NRT).

Synthesis of results

Smoking abstinence

Smoking abstinence may be slightly higher in people randomised to ONP compared to no intervention at eight-week follow-up (RR 1.58, 95% CI 0.07 to 35.32; 1 study, 27 participants; very low-certainty evidence (risk of bias and imprecision; CI incorporated possibility of no difference)), but the evidence is very uncertain. Low-certainty evidence (serious imprecision; CI incorporated possibility of no difference) suggests there may be lower abstinence rates in those randomised to ONP compared to e-cigarettes (RR 0.25, 95% CI 0.03 to 2.02; 1 study, 36 participants). Evidence from one study (n = 30) comparing higher- versus lower-dose ONP found a higher quit rate in the higher-dose arm, but again with wide CI encompassing the possibility of no difference and of higher quit rates in the lower-dose arm (RR 5.00, 95% CI 0.26 to 96.13; evidence certainty not assessed).

Serious adverse events

No SAEs occurred in the three studies reporting this outcome. Data were available for the comparisons ONP versus minimal control (2 studies, 124 participants; very low-certainty evidence (risk of bias and serious imprecision)) and ONP versus e-cigarettes (1 study, 26 participants; low-certainty evidence (serious imprecision)).

TSNA

One study reported on a TSNA (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)) comparing ONP with instructions to continue smoking. There may be lower levels with ONP (MD −265.30 ng/g creatinine, 95% CI −350.64 to −179.96; 53 participants; very low-certainty evidence (risk of bias and imprecision)), but the evidence is very uncertain. Data from two studies suggested no difference in NNAL levels between higher- and lower-dose ONP (SMD −0.16, 95% CI −1.87 to 1.56; I^2 = 0%; 77 participants; evidence certainty not assessed).

COHb

Based on one study, there may be lower levels of COHb with ONP compared to instructions to continue smoking (MD −6.7%, 95% CI −8.33 to −5.07; 53 participants; very low-certainty evidence (risk of bias and imprecision)), but the evidence is very uncertain. When comparing higher- versus lower-dose ONP, the same study found very slightly lower levels in the higher-dose group, with the 95% CI incorporating the possibility of no difference (MD −0.40%, 95% CI −1.19 to 0.39; evidence certainty not assessed).

No studies reported on prevalence, inflammatory markers, metals, or use of tobacco/nicotine products other than cigarettes.

Authors' conclusions

There is limited evidence on the use of ONP for cessation or reduction of cigarette use. There is no evidence on the use of ONP for cessation or reduction of other tobacco or nicotine products or on the effects of ONP on prevalence of tobacco use/nicotine vaping. Low-certainty

evidence suggests that people randomised to ONP may be slightly less likely to quit smoking than those randomised to e-cigarettes, but data were from one small study and therefore imprecise. Limited, short-term data did not identify any serious health harms from ONP when used to help people transition away from tobacco smoking.

More research on the effects of ONP for cessation or reduction of use of other tobacco or non-pharmaceutical nicotine products is urgently needed. Future trials should prioritise comparing ONP to other active interventions (e.g. NRT and e-cigarettes).

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Registration

Registration: Cochrane, via protocol available via DOI:10.1002/14651858.CD016220.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of oral nicotine pouches when used to help people stop smoking, vaping nicotine, or using other forms of tobacco?

Key messages

- Limited evidence from three small studies found no short-term serious health harms of oral nicotine pouches in people who smoke.
- We are uncertain if oral nicotine pouches help people quit smoking compared to instructions to continue smoking as usual or no support to quit.
- Future research is needed, in particular comparing oral nicotine pouches to other active treatments (e.g. nicotine replacement therapy and e-cigarettes).

What are oral nicotine pouches?

Oral nicotine pouches are preportioned pouches containing nicotine, sold in various flavours and nicotine strengths. They are similar in appearance and use to snus. Snus is a form of smokeless tobacco placed between the gum and lip that is popular in Nordic countries, but whose sale is banned in the UK and European Union countries excluding Sweden. Unlike snus, nicotine pouches do not contain tobacco leaf. Like nicotine e-cigarettes and pharmaceutical forms of nicotine replacement therapy (such as nicotine patches and gums), oral nicotine pouches may be able to help people transition away from harmful forms of tobacco/nicotine product use by replacing them with a product that does not contain tobacco leaf and which, unlike e-cigarettes, does not involve inhaling vapour into the lungs.

Common brand names of oral nicotine pouches include Zyn, Velo, and Nordic Spirit.

What did we want to find out?

We wanted to find out if oral nicotine pouches can help people transition away from smoking, nicotine vaping, or other forms of tobacco use. We also wanted to know if oral nicotine pouches caused any unwanted effects when used for this purpose.

What did we do?

We searched for studies where people who smoked, vaped, or used other tobacco products were given oral nicotine pouches as a way to quit. We included studies if they tracked tobacco use or vaping for at least four weeks or looked at unwanted effects or chemical changes in the blood, breath, or urine for at least one week.

What did we find?

We found four studies including a total of 284 people who were smokers at study start. The studies were conducted between 2006 and 2023, and in those that reported race or ethnicity, were conducted in majority white populations. The average age across studies ranged from 34 to 50 years. The average number of cigarettes smoked by participants at study start was between 14 and 23 per day. The longest study ran for eight weeks. Three studies were independently funded, and one was funded by a tobacco manufacturer.

Based on two small studies, it was not clear whether using nicotine pouches helped more people to quit smoking compared to instructions to continue smoking as usual or no support to quit, and there may be lower quit rates in those using nicotine pouches compared to those using a nicotine e-cigarette (vaping).

No serious health harms occurred in any group in the three studies that reported this information, so it is unclear if using nicotine pouches affects the chances of experiencing a serious health harm.

We also looked at certain chemicals measured in blood, breath, or urine that can signal exposures to harmful substances. Tobacco use exposes the body to cancer-causing chemicals. NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a chemical formed when these cancer-causing chemicals enter the body, measures exposure to harmful ingredients in tobacco smoke. One small study reported lower levels of NNAL in people using oral nicotine pouches compared to those given no specific treatment to stop smoking. Combined evidence from two studies suggested no difference in NNAL levels between people receiving higher- versus lower-dose nicotine pouches. Carbon monoxide is a poisonous gas present in tobacco smoke. When carbon monoxide binds with blood haemoglobin, it forms a substance called carboxyhaemoglobin. Carboxyhaemoglobin measures how much carbon monoxide a person has been exposed to in their blood. One study found lower levels of carboxyhaemoglobin in people using oral nicotine pouches compared to those who continued smoking. When comparing higher- versus lower-dose nicotine pouches, the same study found very slightly lower carboxyhaemoglobin levels in the higher-dose group.

What are the limitations of the evidence?

We have little to very low confidence in the evidence because the studies were relatively small, and there are not enough studies to be certain about the results. Also, some studies had issues with the way they were designed that could have affected their results. Many studies are currently underway, and we plan to update this review when their findings become available.

How up-to-date is this evidence?

The evidence is current to January 2025.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table - Oral nicotine pouches compared to minimal control (advice to continue smoking as usual) for smoking cessation in adults

Oral nicotine pouches compared to minimal control (advice to continue smoking as usual) for smoking cessation in adults

Patient or population: smoking cessation in adults
Setting: Community and laboratory
Intervention: oral nicotine pouches
Comparison: minimal control (advice to continue smoking as usual)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with minimal control (advice to continue smoking as usual)	Risk with oral nicotine pouches				
Smoking abstinence assessed with: Biochemical validation follow-up: mean 8 weeks	11 per 1000	**18 per 1000** (1 to 392)	**RR 1.58** (0.07 to 35.32)	27 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	
Serious adverse events (SAEs) assessed with: Self-report follow-up: range 1 weeks to 8 weeks	Not pooled	Not pooled	Not pooled	124 (2 RCTs)	⊕⊖⊖⊖ Very low[c,d]	0 participants across the 2 studies contributing data (total n = 124) reported any SAEs
NNAL follow-up: mean 1 weeks	The mean NNAL was **330** ng/g creatinine	MD **265.3 ng/g creatinine lower** (350.64 lower to 179.95 lower)	-	53 (1 RCT)	⊕⊖⊖⊖ Very low[a,e]	RR for 1 study: −265.30 ng/g creatinine, 95% CI −350.64 to −179.96
Carboxyhaemoglobin (COHb) assessed with: % saturation (blood) follow-up: mean 1 weeks	The mean Carboxyhaemoglobin was **11.3** %	MD **6.7 % lower** (8.33 lower to 5.07 lower)	-	53 (1 RCT)	⊕⊖⊖⊖ Very low[a,e]	RR for 1 study −6.70%, MD −8.33 to −5.07
Metals - not measured	-	-	-	-	-	
Inflammatory markers - not measured	-	-	-	-	-	

*__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; **MD:** mean difference; **RR:** risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_456803033811046639.

[a] Downgraded two levels due to risk of bias; only study contributing data judged to be at high risk of bias
[b] Downgraded two levels due to imprecision; one small study contributed data, with only 1 event overall
[c] Downgraded two levels due to risk of bias; both studies judged to be at high risk of bias in at least one domain
[d] Downgraded two levels due to imprecision; no events occurred in any arms
[e] Downgraded one level due to imprecision; one relatively small study contributed data, but CI excludes possibility of no difference

Summary of findings 2. Summary of findings table - Oral nicotine pouches compared to nicotine replacement therapy for smoking cessation in adults

Oral nicotine pouches compared to nicotine replacement therapy for smoking cessation in adults

Patient or population: smoking cessation in adults
Setting: community
Intervention: oral nicotine pouches
Comparison: nicotine replacement therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with nicotine replacement therapy	Risk with oral nicotine pouches				
Smoking cessation - not measured	-	-	-	-	-	
Serious adverse events - not measured	-	-	-	-	-	
NNAL - not measured	-	-	-	-	-	
Carboxyhaemoglobin - not measured	-	-	-	-	-	
Metals - not measured	-	-	-	-	-	

Inflammatory markers - not measured	-	-	-	-	-

*__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

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_456869932904911653.

Summary of findings 3. Summary of findings table - Oral nicotine pouches compared to e-cigarettes for smoking cessation in adults

Oral nicotine pouches compared to e-cigarettes for smoking cessation in adults

Patient or population: smoking cessation in adults
Setting: Community
Intervention: oral nicotine pouches
Comparison: e-cigarettes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with e-cigarettes	Risk with oral nicotine pouches				
Smoking cessation assessed with: Biochemical validation follow-up: mean 8 weeks	222 per 1000	**56 per 1000** (7 to 449)	**RR 0.25** (0.03 to 2.02)	36 (1 RCT)	⊕⊕⊖⊖ Low[a]	Note: we did not downgrade due to risk of bias, as although the study was unblinded, this comparison is between 2 equally intensive interventions
Serious adverse events (SAEs) assessed with: self-report follow-up: mean 8 weeks	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	26 (1 RCT)	⊕⊕⊖⊖ Low[b]	0 events reported in either study arm. Note: we did not downgrade due to risk of bias, as although the study was un-

						blinded, this comparison is between 2 equally intensive interventions
NNAL - not measured	-	-	-	-	-	
Carboxyhaemoglobin - not measured	-	-	-	-	-	
Metals - not measured	-	-	-	-	-	
Inflammatory markers - not measured	-	-	-	-	-	

*__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

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_456870008006811447.

[a] Downgraded two levels due to serious imprecision; one small study contributed data with 5 events overall, 95% CI wide and encompasses possibility of both benefit and harm
[b] Downgraded two levels due to serious imprecision; one small study contributed data with 0 events overall

BACKGROUND

Description of the condition

Combustible tobacco use (i.e. smoking) is the leading preventable cause of disease and death worldwide [1]. Other commercial, non-pharmaceutical products containing tobacco leaf, or synthetic or naturally derived nicotine, vary in popularity and harm profiles. Nicotine e-cigarettes are defined as handheld electronic vaping devices that produce an aerosol for inhalation formed by heating an e-liquid containing nicotine, flavourings, and humectants [2]. They are considered to represent some risk to the user, particularly people who do not have a history of combustible tobacco use, but have also been proven to help people who smoke transition away from smoking. They are considerably less harmful than traditional cigarettes [2]. Heated tobacco products (HTPs) are designed to heat specially treated tobacco to a high enough temperature to release an aerosol, without burning it or producing smoke. They differ from electronic cigarettes (e-cigarettes) because they heat tobacco leaf/sheet rather than a liquid. Companies who make HTPs claim they produce fewer harmful chemicals than conventional cigarettes, but independent data on their harm profiles and impacts on combustible tobacco use remain inconclusive [3]. Smokeless tobacco products include snus (a pouch of powdered tobacco leaves placed under the lip) and chewing tobacco, which are products used orally that contain tobacco leaf. Because combustion is the cause of most of the deadly toxins users are exposed to through smoking, oral tobacco products, though still posing varying risks to users, are also considered less harmful than smoking [4, 5, 6, 7].

Smoking is addictive and deadly. Most adults who smoke want to stop, but many find it difficult to do so, even with evidence-based support [8, 9]. There remains an urgent need to identify new alternatives to support people in transitioning away from combustible tobacco use.

Description of the intervention and how it might work

Oral nicotine pouches (ONP) are preportioned pouches sold in various flavours and nicotine strengths. They are similar in appearance and use to snus. Snus is a form of smokeless tobacco placed between the gum and lip, which is popular in Nordic countries, but whose sale is banned in the UK and European Union countries excluding Sweden. However, unlike snus, nicotine pouches do not contain tobacco leaf. As a result, they are often marketed as being 'tobacco-free' [10]. Given that ONP do not contain tobacco leaf, and as their use does not involve inhalation into the lungs, they are expected to carry a lower toxicant burden and have fewer respiratory health effects than combustible cigarettes; evidence to date is consistent with this [10]. Like nicotine e-cigarettes and pharmaceutical forms of nicotine replacement therapy (NRT), ONP may have the potential to help people transition away from more harmful forms of tobacco/nicotine product use [2, 11].

Since their introduction to the market in 2016, ONP have grown in popularity [12, 13, 14, 15, 16, 17]. Claims have been made regarding their potential to reduce harm in people who use other forms of tobacco/non-pharmaceutical nicotine, and they are being marketed as a possible form of 'tobacco harm reduction' by manufacturers.

Regulation and availability of ONPs vary worldwide. As the studies in this current version of this review come from the USA and New Zealand, we have focused here on regulations in place in those two jurisdictions at the time of writing. The US Food & Drug Administration (FDA) classifies and regulates ONP as a "tobacco product" under the Family Smoking Prevention and Tobacco Control Act of 2019. As of January 2025, the FDA has authorised the marketing of 20 ONP products (all manufactured by ZYN) through the premarket tobacco product application pathway (PMTA). Companies that submitted PMTAs before August 2024 that are still pending review are allowed to market their products temporarily, as long as they have not received a denial [18]. Some US states, such as California, prohibit the sale of flavoured tobacco products, which includes bans on the sale of flavoured versions of ONP [19]. Meanwhile, New Zealand classifies ONP as "oral nicotine products" and bans their commercial import or sale unless they have been approved as medicines. Importation of ONP for personal recreational use is also not allowed; the product must be intended as a medicine by the manufacturer or supplier and be used personally for a therapeutic purpose [20].

Why it is important to do this review

Due to the immense harm caused by smoking combustible tobacco cigarettes, there remains interest in products that might reduce the burden of tobacco-related disease as well as, more recently, interest in products that might facilitate reductions in nicotine vaping. ONP also have the potential to replace oral tobacco products such as snus, potentially exposing users to fewer harmful chemicals given the absence of tobacco leaf. Simultaneously, there are concerns regarding potential unwanted effects of ONP, including on health, and on tobacco and nicotine use, with some people worrying that ONP may perpetuate, rather than lessen, addictions to other tobacco and non-pharmaceutical nicotine products. There is a high degree of uncertainty in the existing evidence base. Whereas there is a substantial amount of epidemiological evidence relating to tobacco pouches (i.e. snus) and their toxicant profiles, there is very little on ONP without tobacco leaf. Though existing evidence suggests that ONP may expose users to lower levels of toxicants than forms of inhaled or oral tobacco, many of the studies contributing to this evidence are funded by industries that produce ONP, with independent studies having more equivocal findings [10]. There is also some evidence to suggest that the different characteristics of ONP, including their flavours and nicotine content, may impact their effects [10]. ONP are relatively new to the market and are an increasing focus for independent researchers and policymakers, meaning independent research in this area is likely to evolve quickly over the coming years. People who use tobacco, health professionals, and policymakers have all highlighted ONP as a research priority.

OBJECTIVES

Primary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from combustible tobacco use (smoking).
- To evaluate the impact of oral nicotine pouches on the prevalence of combustible tobacco use.

Secondary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from other non-combustible tobacco/commercial nicotine product use.
- To evaluate the impact of oral nicotine pouches on the prevalence of use of other non-combustible tobacco/commercial nicotine products.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review [21], and PRISMA 2020 for reporting [22].

Criteria for considering studies for this review

We used different criteria for different objectives, following the approach taken in the Cochrane review of heated tobacco products [3], and delineated as follows.

- Benefits and harms: objectives relating to transitioning away from tobacco/other nicotine product use.
- Prevalence: objectives relating to prevalence of tobacco/other nicotine product use.

Types of studies

We considered different study types for different objectives, following the approach taken in the Cochrane review of heated tobacco products [3]. We included studies regardless of setting, language, or publication status. We restricted our searches to articles published from 2000 onwards, as ONP were not available or in development before then.

Benefits and harms

For those objectives relating to transitioning away from tobacco/other nicotine product use (here on referred to as 'benefits and harms studies'), we restricted inclusion to individual-level and cluster-randomised controlled trials (RCTs) and randomised cross-over trials. We did not include quasi-randomised studies.

Prevalence

For objectives relating to the prevalence of tobacco/other nicotine product use (here on referred to as 'prevalence studies'), we considered interrupted and multiple time-series studies examining the population-level effect of ONP on the prevalence of use of other tobacco/commercial nicotine products. Individual-level interventions involving ONP may not be representative of the way most people use ONP, which is without support from a researcher or trained specialist. Moreover, even if ONP encourage switching away from tobacco/other commercial nicotine products, their impact on prevalence also depends on how they affect initiation of these products. We planned to use time-series studies to assess how changes in ONP prevalence are associated with changes in prevalence (or sales) of tobacco or other commercial nicotine products, acknowledging the limitation that associations might not reflect causal effects. However, we found no studies of prevalence that met our inclusion criteria.

Types of participants

Benefits and harms

We included people currently using any kind of tobacco product or non-pharmaceutical nicotine product at baseline other than exclusively using ONP.

Had we found studies where only a subset of participants met this criterion, but where all other criteria were met, we planned to include the study if information on the eligible subset was available either in the manuscript or via contact with study authors to obtain data on the subset of interest. If this information was not available, we would include the study if more than 50% of participants met our eligibility criteria, and note this as a limitation and conduct sensitivity analyses removing these studies. However, this did not arise in this version of the review.

Prevalence

For studies evaluating the impact of ONP on the prevalence of use of other tobacco/nicotine products, we would consider any population, regardless of tobacco/nicotine product use status at baseline.

We did not exclude studies based on participants' demographic factors.

Types of interventions

Our intervention of interest is ONP (preportioned pouches similar in appearance to snus, but not containing tobacco leaf).

Benefits and harms

We considered any intervention in which a person who used another tobacco or nicotine product was instructed to use ONP to help them reduce or quit their other tobacco/non-pharmaceutical nicotine product use. We considered studies comparing ONP-based interventions with the following comparator groups.

- Interventions providing another commercial tobacco or nicotine product, e.g. snus, non-snus oral tobacco, heated tobacco products, or e-cigarettes.
- Another ONP intervention, e.g. different product, duration, dose, or instructions for use.
- Interventions providing pharmacotherapies designed to facilitate smoking cessation, including but not limited to medicinal nicotine replacement therapy (NRT), bupropion, cytisine, and varenicline.
- 'Placebo' ONP; in other words, pouches designed to mimic ONP, but which do not contain nicotine.
- Experimental cigarettes with altered characteristics, e.g. very low nicotine content cigarettes.
- Minimal control (no or minimal intervention), or a co-intervention also delivered to the intervention group (e.g. if both groups receive the same behavioural support, and the intervention group is also randomised to an ONP intervention).

Prevalence

For studies evaluating the impact of ONP on the prevalence of use of other tobacco/nicotine products, we considered the introduction of ONP to the market or the time point where ONP began gaining popularity as the intervention of interest. For multiple time-series

studies, we planned to consider the extent to which changes in the prevalence of ONP use were associated with changes in the prevalence of use of other tobacco/commercial nicotine products (or sales of these products as a proxy), after adjusting for other influences that could affect changes in the prevalence of use of these products at the population level. For these studies, the comparisons of interest included the following.

- Earlier versus later time periods
- Cross-jurisdictional comparisons
- Synthetic control groups
- Any combination of the above

We found no studies of prevalence.

Outcome measures

Studies must have reported measuring at least one of the critical or important outcomes listed below to be eligible for inclusion.

Critical outcomes

- Benefits: smoking abstinence at the longest follow-up point available, at four-week follow-up or longer. Had studies provided multiple definitions of abstinence, we would prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We used intention-to-treat analyses, assuming participants with missing data at follow-up were non-abstainers.
- Harms: number of people reporting serious adverse events (SAEs) at one week or longer. Where multiple follow-up periods were reported, we used data for the one closest to the end of the intervention. We defined SAEs as medical incidents that are potentially life-threatening, require hospitalisation, result in disability or death, or a combination of these.
- Prevalence: change in the prevalence of smoking, measured as the proportion of people in a given locality that report smoking, over a defined time period. Where multiple time periods were provided, we would use the outcome at the longest follow-up. If relevant, we would include sales as a proxy for prevalence, but this should be considered as an indirect measure of prevalence, because people can reduce their tobacco consumption without quitting.

Important outcomes

Benefits and harms

- Biomarkers of toxicant and carcinogen exposure at one week or longer (including measures of exposure to tobacco-specific N-nitrosamines, polycyclic aromatic hydrocarbons, volatile organic compounds, and carbon monoxide). We extracted all biomarkers fitting this definition. Each biomarker was its own outcome (i.e. biomarkers were not combined in composite measures). If multiple follow-up periods were reported, we would use data from the one closest to the end of the intervention.
- Biomarkers of harm at one week or longer (including lung function, blood pressure, heart rate, heart rate variability, blood oxygen saturation, and markers of oxidative stress and inflammation). If multiple follow-up periods were reported, we would use data from the one closest to the end of the intervention.
- Number of people reporting adverse events (AEs) at one week or longer. If multiple follow-up periods were reported, we used data from the one closest to the end of the intervention. We defined AEs as medical problems (e.g. cough, headache, dry mouth) that did not fulfil the above criteria to be considered serious.
- Change in tobacco or commercial nicotine product use from baseline, at the longest follow-up point available, at four-week follow-up or longer (e.g. change in cigarettes per day). This would be grouped by product class, including: combustible tobacco; heated tobacco products; e-cigarettes; non-combustible products containing tobacco leaf (e.g. snus, chewing tobacco). We would use intention-to-treat analyses, assuming participants with missing data at follow-up had not changed their use from baseline.
- Other tobacco or commercial nicotine product abstinence at the longest follow-up point available, at four-week follow-up or longer. This would be grouped by product class, including: heated tobacco products; e-cigarettes; non-heated/non-combustible products containing tobacco leaf (e.g. snus, chewing tobacco). Should studies provide multiple definitions of abstinence, we would prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We would use intention-to-treat analyses, assuming participants with missing data at follow-up were non-abstainers.
- Abstinence from all commercial (non-pharmaceutical) tobacco/nicotine products at the longest follow-up point available, at four-week follow-up or longer. Should studies provide multiple definitions of abstinence, we would prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We would use intention-to-treat analyses, assuming participants with missing data at follow-up were non-abstainers.
- Abstinence from all nicotine products (including pharmaceutical NRT products) at the longest follow-up point available, at four-week follow-up or longer. Should studies provide multiple definitions of abstinence, we would prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We would use intention-to-treat analyses, assuming participants with missing data at follow-up were non-abstainers.

Prevalence

- Change in the prevalence of other forms of tobacco/commercial nicotine use, measured as the proportion of people in a given locality that report use of these products, over a defined time period. Should multiple time periods be provided, we planned to use the outcome at the longest follow-up. If relevant, we planned to include sales as a proxy for prevalence, considered as an indirect measure of prevalence because people can reduce their tobacco consumption without quitting.

Search methods for identification of studies

Electronic searches

We searched the following databases from 2000 to 13 January 2025 for relevant studies:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2025, Issue 1) via the Cochrane Register of Studies (crsweb.cochrane.org);

- MEDLINE (via Ovid);
- Embase (via Ovid);
- PsycINFO (via Ovid).

Through our search of CENTRAL, we also covered two online trial registries to identify unpublished studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch).

We did not limit any of our searches by language or publication format. We limited searches from 2000 onwards, as ONP were not available before then. Search terms can be found in Supplementary material 1.

Searching other resources

To help identify unpublished research and studies that may have been missed by our electronic searches, we contacted other experts in the field and checked the reference lists of included studies for potentially relevant literature.

We searched for post-publication amendments and examined any relevant retraction statements and errata for included studies (e.g. through PubMed and the Retraction Watch Database (retractionwatch.com/retraction-watch-database-user-guide/)), as errata could reveal important limitations or even serious flaws in the included trials [23]. We are confident that our search strategy would have caught any post-publication amendments currently published, including expressions of concern, errata, corrigenda, and retractions. For future updates of this review, we will check each included study manually for any such additional records.

Data collection and analysis

No review authors had direct involvement in any of the primary studies. Should this arise in the future, any review authors who have direct involvement in the conduct, analysis, or publication of a study that could be included in the review will not make study eligibility decisions about, extract data from, or carry out risk of bias or GRADE assessments for that study.

Selection of studies

We adhered to the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* [24].

We de-duplicated and screened search results in Covidence [25]. Where multiple publications reported a single study, we combined them, paying particular attention to post-publication amendments, including expressions of concern, errata, corrigenda, and retractions.

Two review authors (of JHB, HTB, ADW, and NL) independently checked the titles and abstracts for relevance against the eligibility criteria. Any disagreements were resolved through discussion with a third review author (of JHB, ADW, or NL). We obtained the full-text versions of papers considered to be potentially relevant, and two review authors (of JHB, HTB, ADW, and HJ) independently assessed the full-text reports for inclusion in the review. Any disagreements were resolved through discussion with a third review author (of JHB, NL, or JLB). We contacted study investigators for further information to aid our decision-making as needed. We recorded and reported reasons for excluding studies at the full-text stage.

We screened and included studies reported in any language. All studies were published in English, but in the future, we will arrange for the translation of non-English language papers if necessary, first via software, or, if that proves insufficient, via help from a person fluent in the language. Where multiple citations related to the same study, we grouped them into one study record with a single study ID.

Data extraction and management

For each included study, two review authors (of JHB, NL, or JLB) independently extracted data to be used in analyses (including covariates) and for risk of bias assessment. Study characteristics were extracted by a single review author (NL or JLB). We piloted our data extraction form, extracting data from two studies and involving everyone responsible for data extraction, before extracting data from all eligible studies. We extracted data on the following variables.

- Methods (study design, study dates, recruitment methods, location, setting)
- Participants (n per group, age, sex/gender, race/ethnicity, tobacco/nicotine use history, inclusion/exclusion criteria)
- Interventions (product, nicotine content, flavouring, brand, any instructions regarding duration or frequency of use, behavioural support including any instructions for switching or ceasing use of tobacco/nicotine product(s))
- Comparators (as per interventions, but also with the possibility of no intervention/treatment)
- Outcomes (details on which eligible outcomes were reported and outcome data for each, details on how each outcome was measured, including whether analyses were conducted per-protocol or intention-to-treat or both, in how many participants, over what period of time, and by whom)
- Funding sources and author conflicts of interest (extracted verbatim from manuscripts)

We cross-checked dual extraction, with any disagreements between review authors resolved through discussion. Where necessary, we contacted study authors to obtain additional information.

If necessary in the future, we will arrange for the translation of non-English language papers, first via Google Translate [26], and if that proves insufficient, via help from a person fluent in the language. We will then extract this information following the above process.

Risk of bias assessment in included studies

We assessed risk of bias based on our critical outcomes only. For all studies, two review authors (of JHB, JLB, and NL) independently assessed the risk of bias, with any discrepancies resolved via discussion or referral to another review author.

Benefits and harms

We followed Cochrane guidance for assessing risk of bias [27, 28]. As per the Cochrane review of heated tobacco products [3], and the Cochrane Tobacco Addiction Group guidance on assessing risk of bias [29], we used the Cochrane RoB 1 tool. We assessed the following risk of bias domains.

- Selection bias (via random sequence generation and allocation concealment)
- Performance bias
- Detection bias
- Attrition bias
- Selective reporting bias
- Other risk of bias

For each study, we made an overall judgement to summarise the risk of bias across domains. Following the guidance from the Cochrane Tobacco Addiction Group on assessing risk of bias [29], we considered a study at high risk of bias overall if at least one domain was judged to be at high risk, at low risk of bias overall if all domains were judged to be at low risk, and at unclear risk of bias overall for all other scenarios.

Prevalence

Should studies report prevalence outcomes in the future, we will take the following approach.

We will use ROBINS-I to assess risk of bias in non-randomised studies that report the critical outcome of smoking prevalence, following the approach taken in the Cochrane Review of heated tobacco products [3]. We will use the most recent version available at the time of assessment and will assess the following domains, judging each as low, moderate, serious, or critical risk.

- Bias due to confounding (considering important confounders to be: tobacco/nicotine use prevalence at study start, if comparisons are being made between groups; other tobacco control interventions or developments)
- Bias in the selection of participants into the study
- Bias in the classification of the intervention (here we will consider definitions and measurements of ONP use)
- Bias due to missing outcome data
- Bias in measurement of the outcome (here we will consider definitions and measurement of smoking)
- Bias in selection of the reported result (which will be informed by whether or not authors have preregistered their analysis plans, and whether these have been followed)

We will not assess 'bias due to deviations from intended interventions', as our non-randomised studies of interest are not testing interventions as they are typically defined.

We will assess overall risk of bias in the same way as the RCTs, but with the judgement categories aligning to those of ROBINS-I, namely: low; moderate; serious; critical. In other words, to be judged at low risk of bias overall using ROBINS-I, all domains for a given study would have to be judged at low risk. Studies with at least one domain judged as critical would be judged to be at overall critical risk of bias. Studies where no domains were judged at critical risk, but at least one domain was judged at serious risk, would be judged to be at serious risk overall. Studies where no domains were judged at critical or serious risk, but where at least one domain was judged to be at moderate risk, would be judged to be at moderate risk overall.

Measures of treatment effect

Benefits and harms

We calculated risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes.

For continuous data, we calculated mean differences on the raw (MD) or log-transformed (LMD) scale and corresponding 95% CIs between the ONP and control groups at follow-up. If studies reported geometric means, we planned to convert these onto the (natural) log scale, and if studies being pooled reported mixtures of geometric and arithmetic means, we planned to convert them all onto the log scale, using Method 1 described in Higgins 2008 where appropriate [30].

We used the longest follow-up data reported for outcomes assessing potential benefits. For outcomes assessing potential harms, we used data at the closest follow-up after the end of treatment. Where possible, we calculated treatment effects on an intention-to-treat basis.

Prevalence

We did not include any prevalence studies. If we do so in the future, we plan to take the following approach. For interrupted time-series studies, the treatment effect could be reflected by the step change and change in trends in prevalence or sales following the introduction of ONP to the market (or the time point where they started gaining popularity) in the relevant locality, after adjusting for confounding variables.

For multiple time-series studies, the treatment effect of interest will be the association between ONP prevalence and prevalence or sales of the other tobacco/nicotine product in question, after adjusting for confounding variables. Where variables are log-transformed, the resulting coefficient describes the percentage change in other product prevalence associated with a 1% change in ONP prevalence.

Unit of analysis issues

Effectiveness and safety

For RCTs with more than two intervention arms, we planned to combine data from all relevant intervention conditions where ONP were offered, where possible. Where this was not possible, we used the intervention arm representing the most intensive intervention (e.g. longest duration of treatment, highest dose of nicotine, etc). For RCTs with more than two control arms, we planned to either combine data from each arm, or choose the most appropriate comparator. If pooling intervention arms was considered inappropriate, we would split the control arm to act as a comparator to each separate intervention arm; however, this was not necessary for this version of the review. Had we identified cluster-RCTs, we would have attempted to extract an estimate of the effect accounting for the cluster design of the study (the intraclass correlation coefficient; ICC) and adjusted for this. If this was not reported, we would attempt to identify an ICC from a similar study to use in our adjusted analysis. If an ICC could not be identified, we would not adjust for clustering, but would remove the study in a sensitivity analysis.

Dealing with missing data

Benefits

For studies measuring other forms of tobacco/commercial nicotine product use as an outcome, we would assume that people with missing data at follow-up had not achieved abstinence, as is common in the field [31]. (No studies reported on this outcome.)

Harms

When assessing SAEs and AEs, we calculated the proportion of those available at follow-up who experienced an event (when relevant data were available), rather than the proportion of people who were randomised. When assessing biomarkers, we removed participants with missing follow-up data from the analysis (complete case).

Prevalence

We did not expect issues with missing data in time-series studies.

Reporting bias assessment

We planned to assess reporting bias using funnel plots if a meta-analysis contained 10 or more studies; the greater the asymmetry in the plots, the higher the risk of reporting bias. However, none of our analyses included 10 or more studies.

We emailed study authors for missing information relevant to our review; where this was provided, it is noted in the study record.

Synthesis methods

We only pooled data where studies fell into the same comparator group, reported the same outcome, and where synthesis would provide clinically meaningful results. We listed studies alphabetically by study ID. For studies where data could not be statistically synthesised, we followed Synthesis Without Meta-analysis (SWiM) guidelines [32]. In particular, we planned to create effect direction plots, grouped by comparison and outcome. We conducted meta-analyses in RevMan [33]. We used the I^2 statistic to quantify statistical heterogeneity [34], considering I^2 values > 50% as indicating potentially substantial statistical heterogeneity. When interpreting heterogeneity, we planned to consider both the direction and magnitude of the effects; however, this did not arise. Had studies varied in effect direction, and I^2 was > 75%, we would not have presented pooled results.

Benefits and harms

For dichotomous data, following the standard methods of the Cochrane Tobacco Addiction Group, we planned to combine RRs and 95% CIs from individual studies using a Mantel-Haenszel random-effects model, to calculate pooled overall RRs with 95% CIs; however, this was precluded by insufficient data.

For continuous safety outcomes (biomarkers), we pooled MDs or LMDs and measures of variance for individual studies using a generic inverse-variance random-effects model.

Prevalence

Had we found prevalence studies, we would have aimed to calculate pooled estimates and their standard errors using a random-effects model for each of three coefficients, when reported: step change in prevalence or sales following the introduction of ONP (date as defined by study authors); change in these trends after the introduction; and changes associated with changes in prevalence or sale of ONP. We would not pool time-series studies with notably different time periods (e.g. weekly versus annual).

Investigation of heterogeneity and subgroup analysis

Our planned subgroup analyses were precluded by insufficient studies. If sufficient studies are identified in the future (i.e. 10 in a given meta-analysis), we will undertake the following subgroup analyses.

- Intensity of behavioural support provided for tobacco/other commercial nicotine product use outcomes, as this could be an effect modifier. This will be grouped as: no behavioural support; one-off behavioural support or written support only; multiple sessions of in-person behavioural support.
- For biomarker outcomes, we will undertake additional subgroup analyses to investigate differences by whether analyses were per-protocol or intention-to-treat, as we might expect effects to be more pronounced in per-protocol analyses. We define per-protocol analyses as those that only included participants who exclusively (or almost exclusively) used the product they were assigned, whereas intention-to-treat analyses include all participants regardless of actual product use.
- For continuous outcomes, whether data measure change from baseline (preferred) or absolute value at follow-up.
- For benefits and harms, ONP characteristics including flavour and nicotine dose.
- For prevalence, whether the outcome or exposure is actual prevalence of use, or sales data as a proxy measure.

All of the above are study-level variables. We will compare subgroup differences using the Chi^2 and I^2 statistics for subgroup differences, considering $P < 0.05$ or $I^2 > 50\%$ as indicating potentially significant subgroup differences for each test, respectively. We note that lack of a 'significant' moderation effect could simply be due to low statistical power.

Equity-related assessment

We did not investigate health inequity in this review, as based on our scoping searches there are not currently sufficient data to investigate using this lens.

Sensitivity analysis

Had sufficient data been available, we planned to carry out sensitivity analyses removing studies with the following characteristics.

- Judged to be at high risk of bias for at least one domain (according to RoB 1), or having serious concerns (according to ROBINS-I)
- With a minimum length of follow-up of less than four weeks (safety outcomes only)
- Funded by (or authors have received funding from) the tobacco or commercial nicotine industry
- Only classifying participants as ONP users if they use their product daily (prevalence only)
- Not all participants met our inclusion criteria, and data for the relevant subgroup were not provided

- Cluster-RCTs where adjustment for clustering could not be carried out
- Only used lower-nicotine dose ONP (i.e. less than 4 mg)
- Did not collect data beyond four weeks (biomarker outcomes only)

We will consider whether the point estimates in the sensitivity analyses are consistent in interpretation with those of the main analyses, as well as the extent to which CIs overlap between both analyses.

Certainty of the evidence assessment

We created summary of findings tables using GRADEpro GDT for all critical outcomes, for biomarkers of exposure (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), carboxyhaemoglobin (COHb), and metals), and for inflammatory markers, following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* [35, 36, 37]. We used the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each of these outcomes.

We focused on the following comparisons for studies of benefits and harms.

- ONP versus minimal control (no or minimal intervention)
- ONP versus NRT
- ONP versus e-cigarettes

Two review authors (JHB and NL) independently assessed the certainty of evidence, with any disagreements resolved via discussion or referral to a third review author (involving JHB, NL, JLB, or CM).

Consumer involvement

This review has been commissioned as a part of the Center for the Assessment of Tobacco Regulation (CAsToR) 3.0, a National Institutes of Health (NIH)-FDA Tobacco Center of Regulatory Science (TCORS). All members of the CAsToR 3.0 steering committee, which includes diverse stakeholders, had the opportunity to provide input on the scope and design of this review via an online meeting and by commenting on a proposal. They also provided input into dissemination plans. They are not able to dictate whether the review is published, or what it finds.

In addition to the CAsToR steering committee (predominantly based in the USA), two members of the public (patient and public involvement, PPI, based in the UK) with experience of tobacco and nicotine products commented on the review, paying particular attention to the Plain language summary. We took this approach such that our PPI is not confined to a single country.

We met with the CAsToR steering committee and with our PPI representatives after completion of analyses, but before write-up, to discuss the implications of our results and the best routes for dissemination.

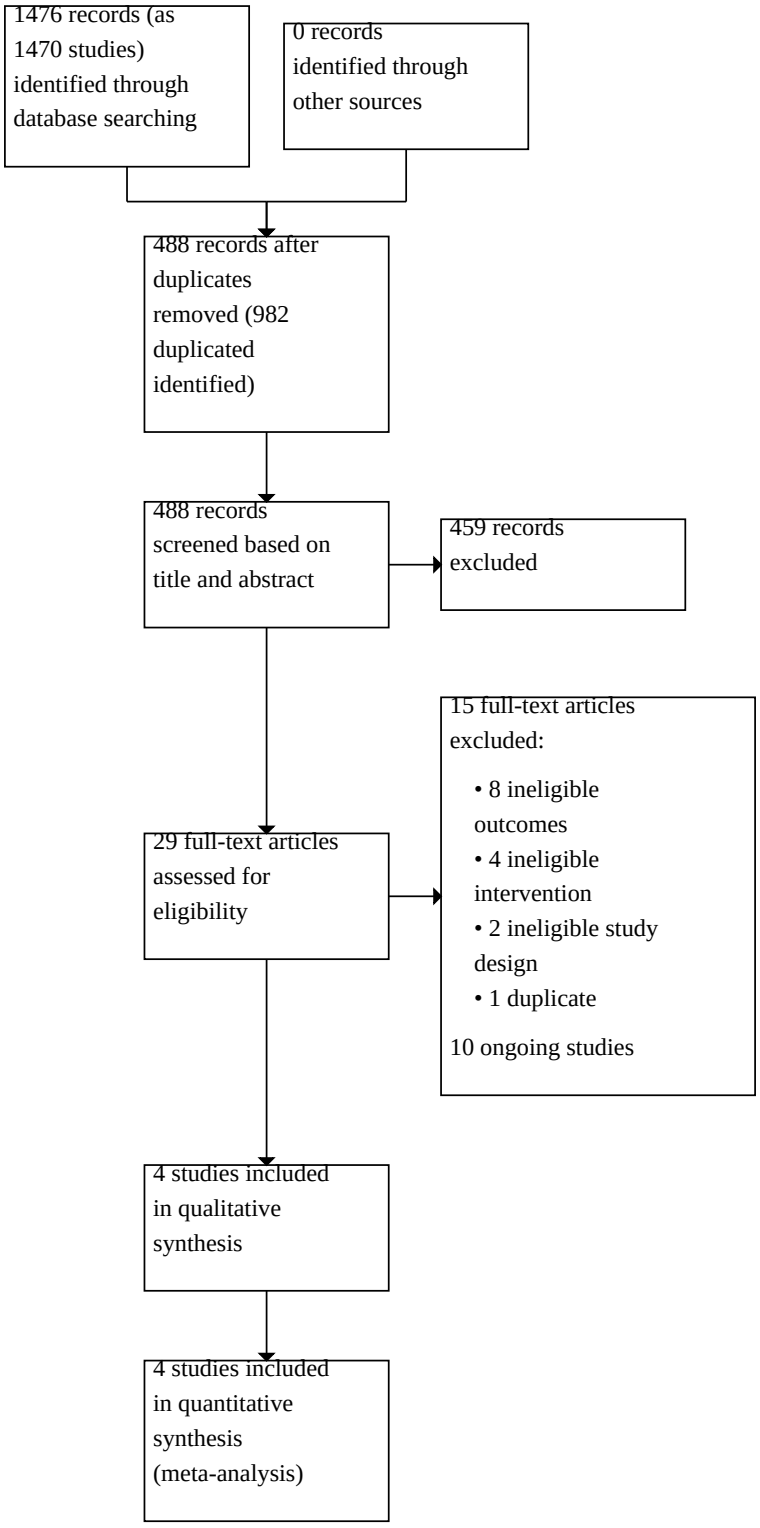
RESULTS

Description of studies

Results of the search

Our initial database searches identified 1476 records (representing 1470 studies), leaving a total of 488 unique records after de-duplication (see Figure 1). After screening records based on title and abstract, we identified and retrieved the full-text reports for 29 potentially relevant articles, of which 15 studies were excluded, 10 studies are ongoing, and 4 studies (14 records) were included in the review (Avila 2024 [38, 39]; Caldwell 2010 [40, 41]; NCT04250727 [42]; Rensch 2023 [43, 44, 45]). See 'Characteristics of ongoing studies' table in Supplementary material 4. We approached the authors of two included studies for additional information; both authors responded (Avila 2024; NCT04250727).

Figure 1. Study flow diagram.



Included studies

A summary of the key features of the four included studies is provided below; for further details, see the 'Characteristics of included studies' table in Supplementary material 2; this information is summarised in Table 1. Three of the four included studies were published in academic journals at the time of writing; the fourth had data available via a clinical trials registry, and we extracted information from there (NCT04250727).

Study types

All four studies were RCTs. One study (Caldwell 2010) was a randomised cross-over trial in which all the participants received all products under study.

Participants

Overall, the four included studies represent a total of 284 participants. Study size ranged from 30 to 146 participants. Three of the four studies were conducted in the USA, while the fourth was conducted in New Zealand. In three of the studies, participants were all over the age of 21; the fourth study included only adults, but it is unclear what age cut-off was used for participant eligibility. All four studies were conducted in people who reported current use of cigarettes, though the studies varied in the extent to which participants were interested in quitting. Three of the studies included participants who were not motivated and not actively planning to quit smoking. One of the studies reported that some, but not all, of their participants were strongly interested in quitting or reducing smoking (Caldwell 2010). ONP use at baseline was unlikely in at least three studies, since people with a recent use of tobacco or nicotine products other than combustible cigarettes (including ONP) were excluded.

Interventions and comparators

The included studies investigated the following products: nicotine pouches in varying concentrations (2 mg, 3 mg, 4 mg, 6 mg, 8 mg) in original, mint, and other flavours; e-cigarettes (5% nicotine e-liquid pods) in tobacco or menthol flavours; snus (8 mg) in general, cassis, and eucalyptus flavours; and pharmaceutical nicotine gum (4 mg) in mint and fruit flavours. In two of the studies, participants were instructed to use the study product when they wanted to smoke a cigarette, though they were not explicitly asked to quit smoking. One study explicitly told participants to stop smoking their usual brand of cigarettes (Rensch 2023). One of the studies included minimal behavioural support (i.e. a weekly phone check-in for safety monitoring) (NCT04250727).

One study compared ONP with e-cigarettes and a minimal control condition (Avila 2024). The products were provided to participants for four weeks, and participants could choose their preferred flavour for the study. One study, a randomised cross-over trial, compared ONP, snus, and nicotine gum (Caldwell 2010). All participants were provided with the three products in random order. One study compared higher- versus lower-dose ONP provided for four weeks at eight cans per week (NCT04250727). The remaining study compared varying doses of ONP in three product study groups with a "no tobacco" group that was not allowed access to any tobacco products and a minimal "continue smoking" control condition group (Rensch 2023). Except for the "no tobacco" and "continue smoking" groups, the remaining participants in this study were provided with ONP ad libitum, except for at three specific test product use opportunities during the study day.

Across the four studies, the length of participant follow-up ranged from seven days to eight weeks.

Outcomes

Of the critical outcomes

Two studies (Avila 2024; NCT04250727) reported smoking abstinence or cessation at four weeks or longer. Two studies (Avila 2024; Rensch 2023) reported on SAEs at one week or longer.

Of the important outcomes

Three studies reported biomarkers of exposure at one week or longer, though one of these (Avila 2024) was limited to change in carbon monoxide (CO), while other biomarker outcomes in the trial registry were not reported in the final results. All studies reported AEs at one week or longer, with seven days being the shortest time frame. Regarding changes in tobacco or commercial nicotine product use at four weeks or longer, two studies reported on smoking reduction (cigarettes per day, percentage of smoke-free days). None of the studies reported on abstinence of other tobacco or commercial nicotine product at four weeks or longer.

Funding

One study was funded by the manufacturer or provider of the intervention (tobacco industry) (Rensch 2023). The remaining three studies were funded by philanthropic, academic, or governmental organisations.

Excluded studies

We excluded 15 studies at the full-text stage for the following reasons:

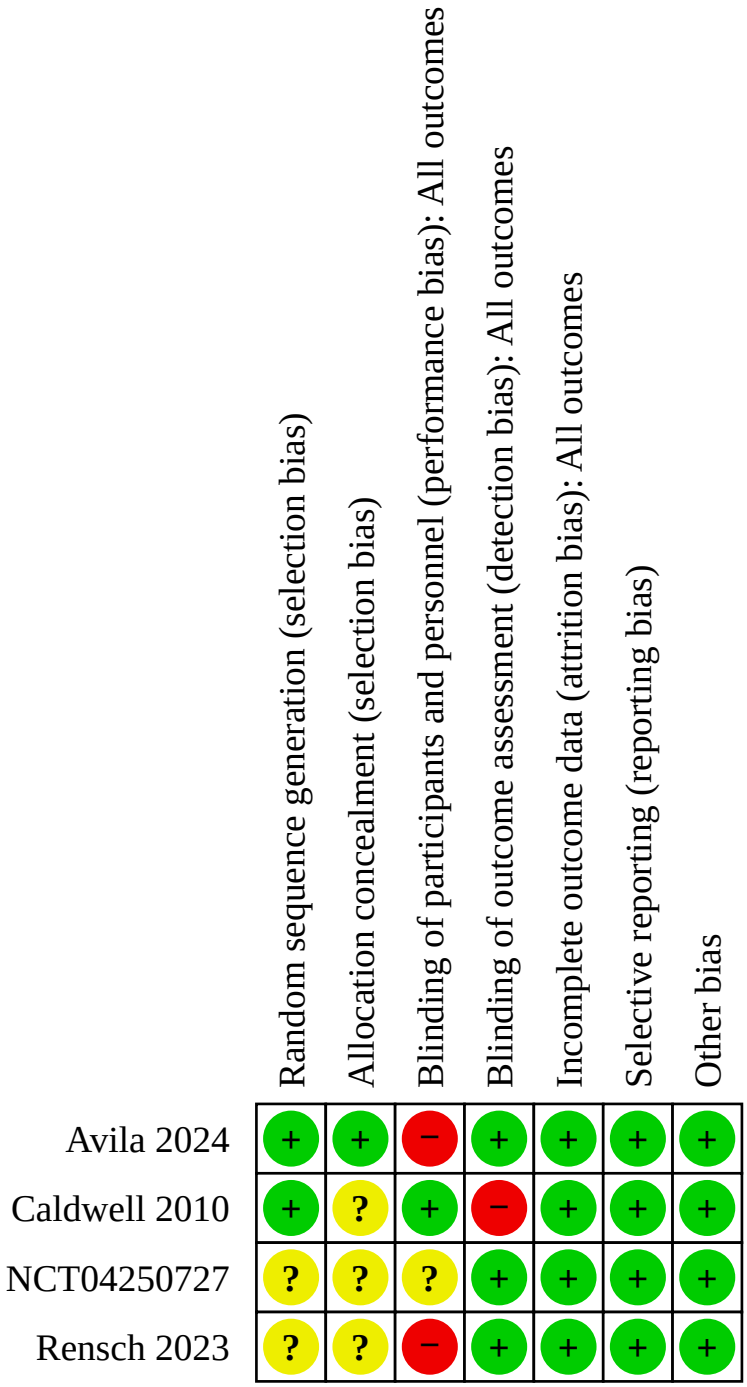
- ineligible outcomes (8 studies);
- ineligible intervention (4 studies);
- ineligible study design (1 study);
- a duplicate record (1 study);
- an observational study that did not analyse the association between ONP and other tobacco/nicotine product use at the population level (1 study).

These reasons are also represented in the PRISMA diagram (Figure 1). Characteristics of the excluded studies (not including the duplicate) are provided in Supplementary material 3.

Risk of bias in included studies

In our risk of bias assessment, none of the studies was judged to be at low risk of bias overall (Figure 2). We assessed one study (NCT04250727) as at unclear risk of bias overall; this was the unpublished study for which limited data were available. We assessed the remaining three studies as at high risk of bias overall (Avila 2024; Caldwell 2010; Rensch 2023).

Figure 2. The figure summarises the risk of bias in the included studies from the section Risk of bias in included studies and in Supplementary material 2.



Selection bias

We judged one study (Avila 2024) to be at low risk of selection bias, and the remaining three studies (Caldwell 2010; NCT04250727; Rensch 2023) as at unclear risk of bias due to limited reporting on methods of randomisation or allocation concealment, or both.

Performance bias

We judged Caldwell 2010 to be at low risk of performance bias. We judged Avila 2024 and Rensch 2023 to be at high risk of bias, as participants were unblinded and received different levels of interventions. We judged NCT04250727 as at unclear risk of bias due to insufficient data to permit a judgement, as this was an NCT record only.

Detection bias

We judged Avila 2024, Rensch 2023, and NCT04250727 to be at low risk of detection bias as biochemical validation was used for key outcomes. We judged Caldwell 2010 to be at high risk of bias due to a lack of objective outcome measures relevant to this review.

Incomplete outcome data and selective reporting

We judged all studies to be at low risk of bias across these domains. Follow-up was above our prespecified threshold, and all expected outcomes were reported. Though Avila 2024 originally planned to analyse additional biomarkers, they were unable to do so due to lack of adequate funding, and we do not consider this a risk of bias.

Other risk of bias

We detected no other risk of bias in the included studies, and therefore judged all studies as at low risk of bias for this domain.

For details on the risk of bias judgements for each domain for each of the four studies, see the 'Characteristics of included studies' table in Supplementary material 2.

Synthesis of results

Findings are summarised by comparison below and in Summary of findings 1; Summary of findings 2; Summary of findings 3.

ONP versus minimal control (continued smoking)

Smoking behaviour

One study (Avila 2024, high risk of bias) reported smoking cessation at eight-week follow-up; the comparator arm was given no intervention. One of 18 participants in the ONP arm had quit smoking, compared to none (of 9) in the control arm (RR 1.58, 95% CI 0.07 to 35.32; n = 27; Analysis 1.1). We judged the evidence to be of very low certainty due to serious imprecision and risk of bias (Summary of findings 1).

Avila 2024 also reported cigarettes per day (cpd) among people who continued to smoke; at eight-week follow-up, participants randomised to the ONP arm had slightly lower cpd than those randomised to minimal control, but CIs were wide and incorporated the possibility of no difference as well as large positive and negative differences (MD −1.07 cpd, 95% CI −12.72 to 10.58; n = 19 (complete-case only); Analysis 1.2).

Adverse events

Two studies (Avila 2024 and Rensch 2023, both at high risk of bias) reported no SAEs across all study arms when comparing ONP to minimal control (RR and 95% CI not estimable; n = 124; Analysis 1.3). In Rensch 2023, the minimal control arm was instructed to continue smoking as usual. Again, this evidence was judged to be of very low certainty due to serious imprecision and risk of bias (Summary of findings 1).

Neither study reported AE data that could permit meta-analysis. Avila 2024 noted that cough and shortness of breath were more common in ONP participants in the first week of the study than in the continued-smoking group, and Rensch 2023 noted four events considered related to ONP use (two headaches, one instance of nausea, and one instance of mouth irritation). For further details, see Table 2.

Biomarkers

Avila 2024 and Rensch 2023 (both high risk of bias) both reported on CO-related outcomes, measured in different ways. In Avila 2024 (n = 19), exhaled CO was lower in those assigned to ONP than those randomised to minimal control, but the CI was wide and incorporated no difference (Analysis 1.4). Rensch 2023 (n = 53 for this comparison) measured blood COHb (% saturation) and found very low-certainty (due to imprecision and risk of bias) evidence of lower levels in the ONP arm, with the CI excluding no difference (Analysis 1.5) (Summary of findings 1). Rensch 2023 measured an additional 16 biomarkers of exposure; all point estimates favoured the ONP arm, and the 95% CI excluded no difference (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) (Analysis 1.6), 2-aminoadipic acid (2-AN) (Analysis 1.7), 4-aminobiphenyl (4-ABP) (Analysis 1.8), 2-hydroxyethyl mercapturic acid (HEMA) (Analysis 1.9), cyanoethyl mercapturic acid (CEMA) (Analysis 1.10), S-phenylmercapturic acid (S-PMA) (Analysis 1.11), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) (Analysis 1.12), 3-hydroxypropyl mercapturic acid (3-HPMA) (Analysis 1.13), 2-hydroxypropyl mercapturic acid (2-HPMA) (Analysis 1.14), N-acetyl-S-(2-carbamoylethyl)-cysteine (AAMA) (Analysis 1.15), N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine (GAMA) (Analysis 1.16), 2-hydroxybutene-1-yl mercapturic acid (2-MHBMA) (Analysis 1.17); 2-hydroxyfluorene (2-OH-Flu) (Analysis 1.18), 2-hydroxynaphthalene (2-OH-Nap) (Analysis 1.19), 1-hydroxyphenanthrene (1-OH-Phe) (Analysis 1.20), 3-hydroxybenzo[a]pyrene (3-OH-BaP) (Analysis 1.21), 1-hydroxypyrene (1-OH-Pyr) (Analysis 1.22)).

None of our other prespecified outcomes were reported for this comparison.

ONP versus no tobacco or nicotine product use

Only Rensch 2023 (high risk of bias, n = 46 for this comparison) contributed data to this comparison. No smoking outcomes were reported.

Adverse events

No SAEs occurred in either study arm (Analysis 2.1). As noted in Table 2, Rensch 2023 did not break down AEs by study arm, but as noted above, did report four non-serious AEs considered to be related to ONP use.

Biomarkers

Of the 18 biomarkers measured, none showed clear evidence of a difference. Eight showed a point estimate favouring ONP, but with CI incorporating no difference (NNAL, Analysis 2.2; 4-ABP, Analysis 2.4; HMPMA, Analysis 2.8; 3-HPMA, Analysis 2.9; 2-MHBMA, Analysis 2.13; 2-OH-Nap, Analysis 2.15; 1-OH-Phe, Analysis 2.16; 3-OH-BaP, Analysis 2.17); nine showed a point estimate favouring no tobacco or nicotine product use but with CI incorporating no difference (2-AN, Analysis 2.3; HEMA, Analysis 2.5; CEMA, Analysis 2.6; S-PMA, Analysis 2.7; 2-HPMA, Analysis 2.10; AAMA, Analysis 2.11; GAMA, Analysis 2.12; 2-OH-Flu, Analysis 2.14; blood COHb, Analysis 2.19); and one had a point estimate indicating no difference and 95% CI that spanned the possibility of benefit and harm (MD 0) (1-OH-PyR, Analysis 2.18).

None of our other prespecified outcomes were reported for this comparison.

ONP versus e-cigarettes

Smoking behaviour

One study (Avila 2024, high risk of bias) reported smoking cessation at eight-week follow-up. One of 18 participants in the ONP arm had quit smoking, compared to four of 18 in the e-cigarette arm (RR 0.25, 95% CI 0.03 to 2.02; n = 36; Analysis 3.1). We judged this evidence to be of low certainty due to serious imprecision, as the CI included the possibility of large positive and negative differences (Summary of findings 3).

Avila 2024 also reported cpd: at eight-week follow-up, participants randomised to the ONP arm had higher cpd than those randomised to e-cigarettes, but CIs were wide and incorporated the possibility of no difference (MD 5.32 cpd, 95% CI −2.16 to 12.80; n = 26 (complete-case only); Analysis 3.2).

Adverse events

No SAEs occurred in either study arm in Avila 2024 (Analysis 3.3, low-certainty evidence of no difference, limited by serious imprecision) (Summary of findings 3). The study authors did not report the number of participants experiencing AEs, but did report that participants in the ONP group were more likely to report having a cough throughout the day and shortness of breath when exercising or walking up the stairs in the first week of the intervention period (n = 5 for cough and n = 6 for shortness of breath) than those in the e-cigarette group (n = 3 for cough and n = 1 for shortness of breath). They reported that the frequency of cough and shortness of breath decreased and became similar across groups by week 4. For further details, see Table 2.

Biomarkers

Exhaled CO levels were higher in the ONP than the e-cigarette arm at eight-week follow-up, though the 95% CI incorporated the possibility of no difference (Analysis 3.4).

None of our other prespecified outcomes were reported for this comparison.

ONP versus snus

Only one study, Caldwell 2010 (randomised cross-over trial judged to be at high risk of bias, n = 63) reported data for this comparison, and the only outcome for which data were reported was AEs. The study authors reported that side effects were "uncommon". ONP use was associated with fewer reports of "bad taste" than snus and similar levels of "gastrointestinal side effects". One participant receiving ONP and one participant receiving snus reported discontinuing use due to gastrointestinal symptoms. For further details, see Table 2.

ONP versus nicotine replacement therapy

Caldwell 2010 was the only study to report data for this comparison; as noted above, they only reported on AEs. ONP use was associated with fewer reports of "bad taste" or "gastrointestinal side effects" than NRT. One participant reported discontinuing ONP use due to gastrointestinal symptoms, compared to two participants who discontinued gum use due to gastrointestinal symptoms. For further details, see Table 2. None of our other prespecified outcomes were reported for this comparison (Summary of findings 2).

ONP at different nicotine content doses

Smoking behaviour

One study (NCT04250727, unclear risk of bias, comparing 6 mg versus 3 mg dose) reported cessation at four-week follow-up; more participants quit in the higher-dose group (2 of 15 participants) compared to the lower-dose group (0 of 15 participants), but the CI incorporated the possibility of no difference as well as very large positive and negative differences (RR 5.00, 95% CI 0.26 to 96.13; n = 30; Analysis 4.1). Log-transformed mean cpd was lower in the higher-dose arm than the lower-dose arm at four weeks, with the CI excluding no difference (MD −0.20, 95% CI −0.27 to −0.13; n = 30; Analysis 4.2).

Adverse events

Two studies provided data on SAEs when comparing higher- versus lower-dose ONP (NCT04250727, unclear risk of bias, and Rensch 2023, high risk of bias). No SAEs occurred in either study group (n = 77; Analysis 4.3). NCT04250727 (n = 30) also reported the number of participants experiencing AEs; the number was the same in both groups (13 of 15), with the CI incorporating the possibility of either direction of effect (RR 1.00, 95% CI 0.76 to 1.32; n = 15; Analysis 4.4). NCT04250727 noted that 2 (of 15) participants in the 6-milligram group reported nicotine toxicity symptoms, involving dual use of cigarettes and pouches; one participant temporarily reduced smoking and pouch use, then resumed pouch use after symptoms resolved, while the other stopped pouch use and withdrew. Details on other types of AEs experienced in NCT04250727 can be found in Table 2. Rensch 2023 (n = 146) reported no evidence of a difference in the numbers of participants reporting moderate AEs due to study product use between higher- and lower-dose arms (again, see Table 2 for further details).

Biomarkers

NCT04250727 (unclear risk of bias) and Rensch 2023 (high risk of bias) both reported NNAL for this comparison. CI for NNAL included both positive and negative differences, and the point estimate was lower in the higher-dose group (SMD −0.16, 95% CI −1.87 to 1.56; I^2 = 0%; n = 77; Analysis 4.5). Results were not sensitive to the exclusion of the one study (Rensch 2023) at high risk of bias, which was also industry-funded. A further 17 biomarkers were measured and reported by Rensch 2023 (n = 47). Of these, point estimates for nine favoured the lower-dose product, but the CI

incorporated the possibility of no difference (2-AN, Analysis 4.6; 4-ABP, Analysis 4.7; CEMA, Analysis 4.9; S-PMA, Analysis 4.10; 3-HPMA, Analysis 4.12; 2-HPMA, Analysis 4.13; 2-MHBMA, Analysis 4.16; 2-OH-Flu, Analysis 4.17; 3-OH-BaP, Analysis 4.20). Point estimates for four biomarkers favoured the higher-dose product, but the CI incorporated no difference (HMPMA, Analysis 4.11; 2-OH-Nap, Analysis 4.18; 1-OH-Phe, Analysis 4.19; blood COHb, Analysis 4.22). For three biomarkers, the point estimate favoured the lower-dose product, and the 95% CI excluded the possibility of no difference (HEMA, Analysis 4.8; AAMA, Analysis 4.14; GAMA, Analysis 4.15). For the final biomarker, there were wide CIs and no difference between groups, with a point estimate of 0 (1-Oh-Pyr, Analysis 4.21).

None of our other prespecified outcomes were reported for this comparison.

Reporting biases

We found too few studies to conduct a formal assessment of publication bias.

DISCUSSION

Summary of main results

The evidence base regarding ONP use in people who smoke or use other non-combustible nicotine products is at present sparse, but is set to grow in the coming years (as evidenced by the 10 ongoing studies identified). The four trials contributing data to this review focused only on people who smoked tobacco. No SAEs were reported in any study arms. All included studies were fairly small and shorter-term (longest follow-up: 8 weeks).

We found low-certainty evidence of higher quit rates in people randomised to e-cigarettes than to ONP (Summary of findings 3), though CIs incorporated the possibility of no difference and effects in either direction. Evidence on quit rates in people randomised to ONP compared to minimal control was of very low certainty; CIs were wide and incorporated large effects in either direction, and as this was an unblinded study with a non-intensity matched comparison, we judged this to be at risk of bias (Summary of findings 1). There was also evidence from one study of higher quit rates in those randomised to higher (6 mg) compared to lower (3 mg) nicotine dose pouches (evidence certainty was not assessed, as this was not a prespecified comparison for a summary of findings table). Biomarker data were also sparse, but there was very low-certainty evidence that switching from smoking to ONP use may lead to reductions in some biomarkers of exposure (Summary of findings 1).

Limitations of the evidence included in the review

The main limitation of this evidence base is the lack of completed studies, reflecting the recency of ONP to the market and to the research world. This led to serious imprecision for every outcome in our review, as at a maximum, only two studies contributed to each analysis, with most outcomes having one or no studies contributing data.

Additionally, we judged three studies to be at high risk of bias in at least one domain (the fourth study was based on a clinical trial record and hence was assessed as at unclear risk of bias due to insufficient information to permit a judgement). One study was funded by the tobacco industry, but it did not contribute any data on smoking cessation, and its findings were consistent with non-industry-funded studies.

We found no studies looking at prevalence of smoking or other tobacco/nicotine product use. We also found no studies reporting the use of tobacco/nicotine products overall, or use of specific, non-cigarette products (the latter reflecting in part the fact that all included studies were conducted in people who smoked at baseline).

Limitations of the review processes

We followed best practice for conducting Cochrane reviews, with screening, extraction, and appraisal done in duplicate, grey literature searched, and a full database search strategy developed by a search specialist (JLB). However, it is still possible that eligible studies may have been missed, either because they were not indexed properly, or because the terms they used to describe pouches were not used in our search (we tried to use as expansive a list as possible).

We used intention-to-treat analyses, assuming that anyone missing was non-abstinent, in our tobacco use outcomes analyses. This is the standard approach used in the field and the most conservative; it could underestimate absolute quit rates. For our other outcomes, we relied on complete-case data, as it was the only type available that could be consistently synthesised. Studies did not report that methods of imputation changed overall conclusions, but these were often small studies with imprecise findings, and methods of accounting (or not) for lack of follow-up could in the future affect pooled estimates.

We did not include any industry publications such as shareholder reports in the search strategy, which may have had informal population-level analyses on impact of ONP use, so it is possible we have missed these.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews with similar objectives as ours as of yet. Reviews of pharmaceutical nicotine replacement therapies and of nicotine cigarettes both provide high-certainty evidence that providing people who smoke with alternate forms of nicotine helps them achieve smoking abstinence [8].

Outside of clinical trial evidence, a 2024 scoping review investigating the potential impact of ONP on public health included a range of study designs, incorporating data from chemical composition studies as well as those in humans [10]. The authors concluded that ONP appear to be less toxic than cigarettes and deliver comparable nicotine, but that data from independent research are critically needed.

AUTHORS' CONCLUSIONS

Implications for practice

There is limited available evidence on the use of oral nicotine pouches (ONP) for cessation or reduction of cigarette use in people who smoke. There is no evidence on the use of ONP for cessation or reduction of other tobacco or non-pharmaceutical nicotine products.

The three studies that reported data for serious adverse events found that none were experienced.

Low-certainty evidence suggests that people randomised to ONP may be slightly less likely to quit smoking than those randomised to nicotine electronic cigarettes (e-cigarettes), but these data were from one small study, leading to serious imprecision.

There were no data on whether ONP use affected prevalence of use of other tobacco/non-pharmaceutical nicotine products. Evidence for all other comparisons and other outcomes was either entirely absent, or, in the case of biomarkers and non-serious adverse events, was of very low certainty, meaning we are not able to draw conclusions.

Ten further studies of ONP for cessation or reduction of other tobacco or nicotine products are currently underway.

Implications for research

More research on the effects of ONP for cessation or reduction of use of other tobacco or nicotine products is urgently needed. Future trials should prioritise comparing ONP to other active interventions, for example nicotine replacement therapy or nicotine e-cigarettes, or both. They should aim to measure abstinence and serious adverse events for as long as possible. Abstinence data at six months or longer would be particularly welcome.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016220.pub2.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of ongoing studies

Supplementary material 5 Analyses

Supplementary material 6 Data package

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

Cochrane Tobacco Addiction supported the authors in the development of this Cochrane review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Tari Turner, Cochrane Australia; Cochrane Editorial Board;
- Managing Editor (provided editorial guidance to authors, edited the article): Luisa Fernandez Mauleffinch, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments, and supported the editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Dr Abdul Shakoor (patient and public review); Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review); and Jo Platt, Central Editorial Information Specialist (search review). One additional peer reviewer provided clinical peer review but chose not to be publicly acknowledged.

Contributions of authors

JHB: conception of the review; funding acquisition; project administration; supervision; screening; data extraction; critical appraisal; analysis; rating of certainty; writing – original draft

HTB: methodology; screening; writing – review and editing

JB: methodology; writing – review and editing

LS: methodology; writing – review and editing

MLG: methodology; writing – review and editing

CLM: screening; writing – original draft

ADW: methodology; screening; writing – review and editing

NT: methodology; screening; writing – review and editing

HJ: conception of the review; funding acquisition; writing – review and editing

JLB: conception of the review; funding acquisition; screening; data extraction; critical appraisal; analysis; rating of certainty; writing – original draft

NL: conception of the review; funding acquisition; screening; data extraction; critical appraisal; rating of certainty; writing – review and editing

Declarations of interest

JHB is an editor for Cochrane. She was not involved in the editorial process of the review. She has received payments from the Truth Initiative and the US Food & Drug Administration for tobacco-related work. She has received grant funding (to her institution) from the National Institutes of Health, US Food & Drug Administration, World Health Organization, British Heart Foundation, Cancer Research UK, University of Oxford, and the British National Institute for Health Research. None of these are deemed conflicts of interest.

HTB has no conflicts of interest.

JB is an unpaid member of the scientific advisory board for the SmokeFree app. JB is employed by University College London. JB is

a sign-off editor for Cochrane. He was not involved in the editorial process of the review.

LS has received honoraria for talks, an unrestricted research grant and travel expenses to attend meetings and workshops from Pfizer, and an honorarium to sit on an advisory panel from Johnson & Johnson, both of which are pharmaceutical companies that make smoking cessation products. He has acted as paid reviewer for grant-awarding bodies and as a paid consultant for healthcare companies. Other research has been funded by the UK Department of Health, UKRI, a community-interested company (National Centre for Smoking Cessation) and charitable sources (Cancer Research UK, Yorkshire Cancer Research). He has never received personal fees or research funding of any kind from alcohol, electronic cigarette, or tobacco companies.

MLG received a research grant from Pfizer and served as a member of the Scientific Advisory Board to Johnson & Johnson; he has also consulted with the US Food & Drug Administration, World Health Organization, Medical Research Agency of Poland, and Campaign for Tobacco-Free Kids on the toxicity of tobacco products and tobacco control policies. MLG is also a Member of the IASLC Tobacco Control and Smoking Cessation Committee and AACR Tobacco Product and Cancer Subcommittee.

CLM has no conflicts of interest.

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JLB is an editor for Cochrane. He was not involved in the editorial process of the review. He has no conflicts.

NL has received payment for lectures on systematic review methodology (Oxford University Hospitals NHS Foundation Trust) and has been an applicant and principal investigator on project funding to carry out research in the area of tobacco control from the NIHR, Cancer Research UK (charity), Clarion Futures (charity), Oxfordshire County Council, the NIHR Oxfordshire and Thames Valley ARC, Greater Manchester NHS Integrated Care, the NIH and Reading Borough Council. None of this is deemed a conflict of interest.

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Registration and protocol

Registration: Cochrane, via protocol available via DOI: 10.1002/14651858.CD016220.

Data, code and other materials

As part of the published Cochrane review, the following is made available for users of the Cochrane Library: our search strategies Supplementary material 1 full citations for all included studies, all ongoing studies, relevant excluded studies, and studies awaiting classification in the reference section of the review; study data, including study information, study arms and risk of bias assessments in our characteristics of studies tables (Supplementary material 2; Supplementary material 3; Supplementary material 4); analysis data, including overall estimates, subgroup estimates, and individual data rows (all the rows in all the analyses) is in the main review and in Supplementary material 5. Data supporting the results of this systematic review are from published information and are available in the review. All analyses have been conducted within RevMan, for details of the computational methods see https://documentation.cochrane.org/revman-kb/statistical-methods-210600101.html. Analyses were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. Data was extracted in Excel and are available from the authors on reasonable request. The data are shared within the published review directly from RevMan Supplementary material 6.

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ADDITIONAL TABLES

Table 1. Overview of syntheses and included studies table

Study ID	Country	Study arms	Outcomes	**Overall risk of bias judgement**
Avila 2024	USA	• ONP • E-cigarette • No intervention	• Cigarette abstinence at week 8 • Serious adverse events • Change in cpd • Change in cigarette dependence • Change in CO • E-cigarette/ONP use • Trial registry also lists change in cotinine, change in NNAL, change in 8-isoprostane, but these results are not reported	High
Caldwell 2010	New Zealand	• ONP • Snus • Nicotine gum	• Adverse events	High
NCT04250727	USA	• Zyn; 3 mg nicotine • Zyn; 6 mg nicotine	• Data collection time points: up to week 4 • Cessation at week 4, validated with CO (< 5 ppm verifying no smoking) • Adverse events • Number of cigarettes smoked per day • Percentage of smoke-free days • Level of biomarker (NNAL) among smokers • Willingness to continue ONP use	Unclear

Rensch 2023	USA	• On!, 2 mg nicotine
		• On!, 4 mg nicotine
		• On!, 8 mg nicotine
		• Stop using all tobacco products
			• Adverse events, in narrative report not broken down by study group
			• Urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)
			• An additional 19 biomarkers of exposure:
			  ○ nicotine equivalents,
			  ○ 2-aminonaphthalene,
			  ○ 4-aminobiphenyl,
			  ○ 2-hydroxyethylmercapturic acid,
			  ○ 2-cyanoethylmercapturic acid (CEMA),
			  ○ S-phenyl mercapturic acid,
			  ○ 3-hydroxy-1-methylpropylmercapturic acid,
			  ○ 3-hydroxypropylmercapturic acid,
			  ○ 2-hydroxypropyl-mercapturic acid,
			  ○ N-acetyl-S-(2-carbamoylethyl)-l-cysteine,
			  ○ N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-l-cysteine,
			  ○ 2-hydroxybutenyl-mercapturic acid,
			  ○ 2-OH-fluorene,
			  ○ 2-naphthol (2-OH-Nap),
			  ○ 1-OH-phenanthrene,
			  ○ 3-hydroxybenzo[a]pyrene,
			  ○ urinemutagenicity,
			  ○ 1-hydroxypyrene in urine,
			  ○ carboxyhemoglobin (COHb) in blood
			• Product use behaviour on Day 7
				High

cpd: cigarettes per day; CO: carbon monoxide; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; ONP: oral nicotine pouches; ppm: parts per million

Table 2. Adverse event reporting

Study	Reporting	Total participants	Type of adverse event
Avila 2024	Reported serious adverse events. Respiratory symptoms measured with the American Thoracic Society Questionnaire (ATSQ).	45 (18 in EC, 18 in ONP, 9 in combustible cigarette)	"Participants in the nicotine pouch group were more likely to report having a cough throughout the day and shortness of breath when exercising or walking up the stairs every day in the first week of the intervention period (N = 5 for cough and N = 6 for shortness of breath) than those in the EC group (N = 3 for cough and N = 1 for shortness of breath). The frequency of cough and shortness of breath decreased and became similar across groups by week 4."
Caldwell 2010	The following side effects were rated on an ad hoc 5-point Likert scale from 1 = not at all to 5 = extremely: indigestion, heartburn, acid reflux, hiccup, burp, hurt mouth, and bad taste. Dizziness and nausea is reported as part of the Cigarette Evaluation Scale.	63 (all participants received ONP, snus, gum)	Dizziness (score out of 5): mean 1.61 (ONP), 1.65 (Snus), 1.75 (Gum). Nausea (score out of 5): mean 2.07 (ONP), 1.86 (Snus), 1.74 (Gum). "Side effects were uncommon for all three products [ONP, Snus, gum]. Seventy-five percent of subjects gave scores of less than 3 for all side effects except "tasted bad," for which snus had the worst median score of 4, followed by gum 3, and Zonnic 2. Gum had a statistically significant ($p < .05$) higher median total gastrointestinal side-effects score of 7 compared with 5 for snus and Zonnic". The following side effects were rated on an ad hoc 5-point Likert scale from 1 = not at all to 5 = extremely: indigestion, heartburn, acid reflux, hiccup, burp, hurt mouth, and bad taste. Gastrointestinal symptoms was one of the reasons given for discontinuing product use (1 ONP, 2 gum, and 1 snus).
NCT04250727	Not clear - NCT record only	30 (15 in 3 mg, 15 in 6 mg)	3 mg - 13 people experienced AEs, 15 followed up. 6 mg - 13 experienced AEs, 15 followed up. **"**Two 6mg group participants reported nicotine toxicity symptoms, both involving dual use of cigarettes and pouches. One temporarily reduced smoking and pouch use, then resumed pouch use after symptoms resolved. The other stopped pouch use and withdrew.**"** Chest pain: 1 (3mg), 1 (6mg) Rapid heartbeat: 1(3mg), 3(6mg) Vision problems: 1(3mg), 1(6mg) Abdominal pain: 4(3mg), 1(6mg) Appetite changes: 3(3mg), 4(6mg) Diarrhaea: 0(3mg), 1(6mg) Nausea: 4(3mg), 6(5mg) Vomiting: 1(3mg), 1(6mg) Fatigue: 3(3mg), 6(6mg) Fever: 1(3mg), 1(6mg)

Table 2. Adverse event reporting *(Continued)*

			Other: 6(3mg), 8(6mg) Sore throat: 5(3mg), 2(6mg) Weight loss: 1(3mg), 1(5mg) Dizziness: 0(3mg), 2(6mg) Fainting 0(3mg), 0(6mg) Headache: 7(3mg), 6(6mg) Vivid dreams: 2(3mg), 3(6mg) Difficulty sleeping: 4(3mg), 3(6mg) Shortness of breath: 5(3mg), 3(6mg) Coughing: 5(3mg), 5(6mg) Itching/rash: 1(3mg), 0(6mg) Sweating: 1(3mg), 4(6mg)
Rensch 2023	Narrative report not broken down by study group.	146 (28 to 30 in each of 4 study arms + control)	"Among the 146 randomized participants, 56 (38%) experienced a total of 86 AEs; the majority of AEs (76) were mild inseverity, and 10 were moderate. Headache was the most frequently reported event, experienced by a total of 23 participants (16%); all remaining AEs were experienced by 5 or fewer participants (≤3.4%) each. Of the AEs that were reported as moderate in severity in the test product groups, the investigator considered 4 events (2 of headache in the 4 mg group; 1 each of mouth irritation and nausea in the 8 mg group) to be related to the study products."

AE: adverse event; EC: electronic cigarette; ONP: oral nicotine pouches