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PROTOCOL

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Oral health effects of non-combustible nicotine products: protocol for a systematic review and network meta-analysis

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Abstract

Background Tobacco use is a global issue, and non-combustible nicotine products (NCNPs) like electronic nicotine delivery systems, nicotine pouches, snus, and nicotine replacement therapies offer potential risk/harm reduction for smokers unable or unwilling to quit. Although NCNPs are less harmful than tobacco smoking, their impact on oral health remains unclear. A systematic review and network meta-analysis will be conducted to answer the research question: What are the oral signs and symptoms associated with NCNPs as both monotherapies and combination therapies compared to each other, placebo, standard care, no drug treatment, and combustible cigarette smoking?

Methods We will search PubMed and Scopus databases, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 2024. This review will focus on randomized controlled trials (RCTs) with a minimum follow-up period of 1 month, comparing any NCNPs versus placebo, standard care, no drug treatment, combustible cigarette smoking or to each other in adult smokers. Our primary outcomes will be the number of participants reporting any oral side effect, aphthous ulcers, dry mouth and mouth irritation. Studies will be excluded if they involve: non-smokers, pregnant women, individuals with mental health or neurological disorders, participants consuming alcohol or other substances. Data will be analyzed using a network meta-analysis framework, estimating odds ratios with 95% confidence intervals. Risk of bias will be determined using the Cochrane risk of bias tool-version 2.0 for included RCTs and the Confidence In Network Meta-Analysis tool will be employed to assess the confidence of evidence contributing to each network estimate.

Discussion Our findings will provide critical insights into the oral health implications of NCNPs, informing clinical and public health decisions. Results are expected by May 2025 and will be disseminated through publications and presentations to guide tobacco harm reduction strategies.

Systematic review registration PROSPERO CRD42024565118.

Keywords Electronic nicotine delivery systems, Network meta-analysis, Nicotine replacement therapy, Non-combustible nicotine products, Oral health, Oral side effect

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Background

Tobacco consumption is a global health challenge, impacting millions of people worldwide [1]. For those unable to quit or unwilling to quit smoking, non-combustible nicotine products (NCNPs) offer a promising alternative to reduce health risks of tobacco cigarettes [2]. These products fall into several categories: electronic nicotine delivery systems (ENDS) such as e-cigarettes (e-cigs) and heated tobacco products (HTPS) [3, 4], nicotine pouches [5], smokeless tobacco products (STPs) including snus [6], and nicotine replacement therapies (NRTs) [7].

E-cigs are battery-operated devices that produce an aerosol containing nicotine and flavorings, which the user inhales [4]. Heated tobacco products also use batteries to heat tobacco sticks to a temperature below combustion, releasing nicotine in a vapor without producing the harmful chemicals found in tobacco smoke [8]. Nicotine pouches are small, thumbnail-sized sachets containing vegetable fibers infused with nicotine and flavorings, which are placed between the lip and gum, allowing nicotine to be absorbed through the oral mucous membrane. Since they contain no tobacco and require no combustion, their use avoids many of the risks associated with smoking [6, 9]. A wide variety of STPs are available globally, with significant differences in their preparation, usage methods, and toxicity [10]. Snus, a traditional oral tobacco product from Scandinavia, consists of ground tobacco leaves mixed with salt, water, and sometimes flavorings, placed under the upper lip. Snus use differs from cigarette use because it does not involve burning tobacco, thereby avoiding many smoking-related risks [6]. Gutka, another form of STPs, is primarily a mixture of powdered tobacco, areca nut (the fruit of the Areca catechu tree), and slaked lime (aqueous calcium hydroxide) [11]. NRTs, such as patches, gums, lozenges, and inhalers, provide a medically approved method to consume nicotine without tobacco, and are recognized by the World Health Organization as essential medicines [12, 13].

The oral cavity is the first area exposed to tobacco and NCNPs, making it particularly vulnerable to their effects. Tobacco cigarette use is associated with various oral health problems, including dry mouth, red and white lesions, premalignant lesions, oral cancer, gingival and periodontal diseases, and dental staining and mucosal pigmentation (smokers melanosis) [14–17]. However, the use of inhalable products such as e-cigarettes and HTPs also provide direct contact of the released aerosols with the oral epithelial cells for a considerable time span [18, 19]. Isolated reports of dry mouth and oral ulcers have been noted with the use of nicotine replacement therapies [20]. Despite the oral cavity being the first point of contact with NCNPs, research on their potential effects on oral health remains sparse and inconclusive. A recent network meta-analysis (NMA) [21] examined the relationship between different forms of NRTs and their oral side effects. The pooled estimates indicated that nicotine gum was significantly associated with an increased risk of aphthous ulcers. However, this analysis included a broad range of NRTs, such as nicotine skin patches and nasal sprays, which do not directly interact with the oral mucosa in the same way as NCNPs. Randomized clinical trials (RCTs) are available for individual products, including nicotine mouth spray [22], Swedish snus [23], and e-cigarettes [4], generally reporting good tolerability at the oral level. However, a comprehensive and systematic comparison of different NCNPs in terms of their specific effects on oral health is still lacking. Given the growing use of these products, it is necessary to assess their relative safety and potential risks through studies that compare multiple NCNPs within a single framework.

We aim to undertake the first systematic review and network meta-analysis to determine the oral health effects of non-combustible nicotine as both monotherapies and combination therapies in relation to each other, placebo, standard care, no drug treatment and combustible cigarette smoking. This analysis will provide valuable insights into the safety of NCNPs and guide clinical practice, public health policies, and decision-making for patients, physicians, and regulators regarding treatment options.

Methods

This systematic review with NMA will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24] for systematic review Protocols (PRISMA-P) [25, 26] and for Network Meta-Analyses (PRISMA-NMA) [27]. The protocol has been recorded in PROSPERO (CRD42024565118).

Research question

What are the oral signs and symptoms associated with NCNPs when used as monotherapies or combination therapies in current smokers, compared to each other, placebo, standard care, no drug treatment, and combustible cigarette smoking?

Selection criteria

Population

Inclusion criteria.

We will include all adult (≥ 18 years) smokers of either gender, and of any nationality and ethnicity.

Exclusion criteria.

Studies that recruited adults with mental health problems [28, 29], neurological disorders, alcohol or other

drugs/substances consumers, nonsmoking population, and pregnant women [30] will be excluded.

Interventions

Interventions will include non-combustible nicotine products: ENDS including e-cigs and HTPs; NRT in gum, mouth spray, inhalator, lozenge/sublingual tablet and mouth strip formulations; smokeless tobacco products (i.e., Swedish-style snus and gutka) and oral nicotine pouches will be included (Table 1). These interventions can be provided individually or in combination (i.e., e-cig + NRT). Primary, we will evaluate the oral health impact of product type, formulation, and mode of use (administered alone or in combination with other treatments) (Fig. 1).

Secondary, we will examine different nicotine treatment doses. Depending on the manufacturer and country regulations, the concentration of nicotine in ENDS and HTPs can be presented as low, medium or high, or expressed as mg/mL or as a percentage (% v/v). The concentrations range from 0 (0%, nicotine-free option) to ≥ 15 mg/mL (1.5%) per cartridge in most of the countries [31–33]. The nicotine concentration for nicotine inhalers varies from a standard dose (i.e., 10 mg) to a high dose (i.e., 15 mg) per cartridge, whilst for lozenge and chewing gum doses range from low dose (i.e., ≤ 2 mg) to high dose (i.e., 4 mg) [33].

To ensure the transitivity assumption (i.e., distributions of the potential effect modifiers, like study and patient-level covariates, are balanced across all pairwise comparisons), the NRT delivered as skin patches and nasal sprays or concurrent use of different NRT formulations different from those included, such as skin patch plus chewing gum [34] and pharmacotherapies including antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), clonidine, lobeline, dianicline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines, and silver acetate will be excluded [35]. Trial arms allowing patients to receive multiple undefined interventions will be also excluded. Moreover, studies examining the impact of NCNPs for smoking reduction involving the simultaneous use of cigarettes and NCNPs will also be excluded.

Control

Eligible comparators will be: other active interventions among those included, placebo, standard care, no drug treatment and combustible cigarette smoking [33]. "Placebo" includes placebo NRT, pouches or ENDS with non-nicotine liquid [33]. "Standard care" is defined as counseling with the possibility of using, as needed, any of the included interventions. "No drug treatment" will refer to participants were not given any medicine or placebo. "Combustible cigarette smoking" refers to subjects who continued to smoke their own brand of combustible cigarettes.

Outcomes

The primary outcomes will be any oral health effect defined as the number of participants reporting any oral signs or symptoms which may, in the trialists' opinion, be attributable to the intervention. These may include oral irritation/inflammation, dryness of the mouth/lip, sore mouth/lip/tongue, buccal erosions or ulcers, local

Table 1 Description of non-combustible nicotine products (NCNPs) products

Product	Description	Common formats	Nicotine content
E-cigarettes (e-cigs)	Battery-operated devices that produce an aerosol containing nicotine and flavorings	Portable devices, cartridges	Nicotine concentrations range from 0 (nicotine-free) to 50 mg/mL (5%) in nicotine salt formulations
Heated tobacco products (HTPs)	Devices that heat tobacco without combustion, releasing nicotine in vapor	Portable devices, tobacco sticks	Nicotine content varies, typically ranging from 0.5 to 14 mg per tobacco stick
Nicotine pouches	Small sachets containing nicotine and flavorings, placed between lip and gum	Small pouches or sachets	Nicotine content typically ranges from 1 to 20 mg per pouch
Snus (smokeless tobacco)	Ground tobacco leaves mixed with salt, water, and sometimes flavorings, placed under the lip	Loose or portioned pouches	Nicotine content varies, typically ranging from 4 to 20 mg per portion
Gutka (smokeless tobacco)	A mixture of powdered tobacco, areca nut, and slaked lime	Loose form or portioned pouches	Nicotine content varies widely, typically ranging from 6 to 20 mg per portion
Nicotine replacement therapies (NRTs)	Medically approved products providing nicotine without tobacco, available in different formulations	Patches, gums, lozenges, inhalers, mouth spray	Patches: 7–21 mg/patch Gum/lozenges: 2 to 4 mg. Inhalers: 10 to 15 mg per cartridge

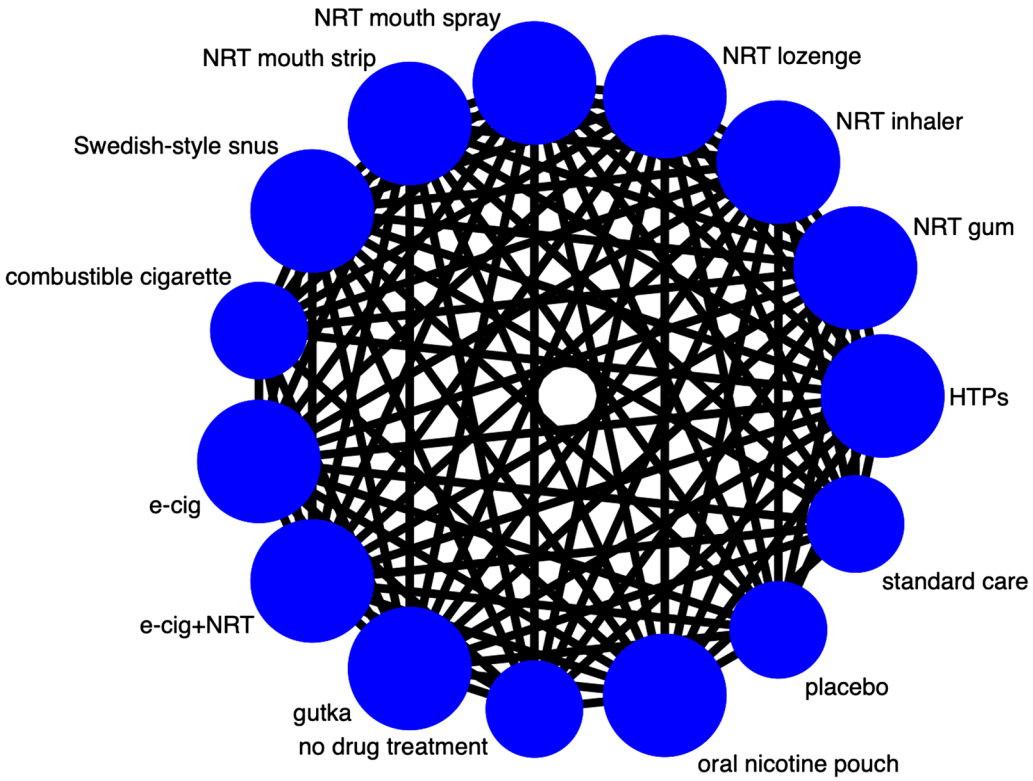

Fig. 1 This diagram shows the primary network of treatments, based on the impact of product type, formulation, and mode of use (administered alone or in combination). Direct comparisons among the devices are illustrated by edges sized proportionally to the number of studies included in the corresponding pairwise meta-analysis

reactions in the floor of the mouth like dryness, burning, parakeratosis or hyperkeratosis including leukoplakia, periodontal diseases such as gingivitis/gum bleeding, jaw ache from chewing, broken tooth, tooth or restoration pigmentation, mucosal pigmentation, and dental caries. Any other oral side effects reported will be included.

In addition, the number of patients with side effects categorized by type (i.e., aphthous ulcers, dry mouth, and mouth irritation) will be also evaluated.

Secondary outcomes will include dental issues, periodontal issues including gingivitis and gingival bleeding, jaw disorders, and any other oral side effects not included in the primary list; any oral serious side effect (defined as the number of participants experiencing events that resulted in death, were life-threatening, required hospitalization or resulted in significant disability [36]) and drop-outs due to oral adverse events.

Study design

Randomized controlled trials will be eligible. For cross-over studies, we plan to use the data from the first period only (i.e., before cross-over) to manage the risk of carry-over effects. Cluster RCTs, case reports, case series, non-randomized studies, reviews, meta-analyses, conference proceedings, policy papers, study protocols and expert opinions will be excluded.

Time frame

Acute (24/48 h) or subacute (< 1 month) studies will be excluded. No any other restriction on follow-up duration will be applied.

Search strategy

Electronic searches

We will search the following electronic databases from their inception to August, 2024: PubMed, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL). No language restrictions will be applied. We will apply a comprehensive search strategy using terms such as "e-cig*," "heated tobacco product*" "nicotine replacement therapy," "nicotine pouch*," "snus", "gutka", "oral nicotine" and "adverse event*". A specific filter for RCTs will be applied.

As an example, the search terms and full string for PubMed can be found below.

(((nicotine replacement therapy OR NRT) OR Nicotine (lozenges OR mouth spray* OR chewing gum OR gum OR inhalers OR sublingual tablet OR lozenge OR

mouth strip)) OR (e-cig* OR "electronic nicotine delivery system" OR HTPs OR "heated tobacco products") OR "Swedish-style snus" OR "smokeless tobacco" OR gutka OR "oral nicotine pouch") AND (smoking cessation OR tobacco control OR cigarettes) AND ("adverse effects" OR "side effects" OR "oral effects" OR "oral irritation" OR "oral inflammation" OR "sore mouth" OR "sore lip" OR "sore tongue" OR hyperkeratosis OR periodont* OR gingivitis OR jaw ache OR taste OR mouth ulcer* OR "dry mouth" OR ulcer* OR "mouth irritation" OR aphthous OR leukoplakia OR erythroplakia OR submucous fibrosis OR "nicotinic stomatitis" OR "oral dryness" OR xerostomia OR caries OR "broken tooth" OR "pigmentation") AND (randomizedcontrolledtrial[Filter]).

Secondary sources

References of the included articles and reviews papers will be further screened for other potentially relevant articles. Included studies will also be "citation chased" (i.e., snowball search) through Google Scholar.

Principal peer-reviewed scientific journals in dentistry and tobacco harm reduction journals (i.e., *Journal of Clinical Periodontology, Periodontology 2000, Journal of Periodontology, Journal of Dental Research, Journal of Periodontal Research, Journal of Dentistry, BMC Oral Health, Clinical Oral Investigations, Odontology, Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology, Nicotine & Tobacco Research, Tobacco Control, Addictive Behaviors, Tobacco Induced Diseases, Tobacco Use Insights*) will be also hand searched.

Additionally, a minimum of two medical experts will be consulted to identify relevant studies on the topic that may not have been found through previous methods.

A comprehensive gray literature search will be conducted on the websites of the most relevant oral health-related medical organizations (i.e., World Health Organization–Oral Health Program, International Association for Dental Research, American Dental Association, European Federation of Periodontology, World Dental Federation, and the Centers for Disease Control and Prevention–Division of Oral Health).

Selection of studies

Using Endnote v.21 software (Clarivate, London, UK), two independent reviewers, after undergoing training and calibration exercises, will autonomously screen titles and abstracts. Duplicates will be identified and deleted by applying the specific features of Endnote software. Any discrepancies will be resolved through consensus between the two reviewers. In cases where consensus cannot be reached, a discussion will be held with a senior author to resolve disagreements. Articles with any uncertainty regarding inclusion will proceed to the next stage. Subsequently, two reviewers will independently review the full texts of trials identified as potentially eligible. Discrepancies will be resolved through consensus between the two authors, with a senior author acting as an arbitrator if necessary. Data from multiple reports of the same study will be linked together. Missing data will be requested from authors via email where possible.

Data extraction

A pre-pilot data extraction form will be developed, and the following data will be extracted from each eligible study:

1. Publication details include the study citation, publication year, and the country where the study was undertaken.
2. General study characteristics encompassing the year (s) of the study, setting, number of centers involved, design (i.e., type of RCT), sample size, smoking status verification, and funding source (i.e., industry or academia).
3. Characteristics of study participants consisting of gender, mean and standard deviation (SD) or median and range of age, smoking history, the number randomized into each group with dropouts.
4. Details about interventions doses, formulation, duration, any add-on interventions, and whether the treatment was forced dose or optimized.
5. Time(s) of outcome measurement.
6. Number of patients reporting any oral side effects, as well as the number of patients with side effects categorized by type (aphthous ulcers, dry mouth, mouth irritation, periodontal issues, and the other oral side effects).
7. Number of patients reporting any serious oral event linked with the intervention.
8. Number of drop-outs due to adverse oral events.
9. Type of analysis, whether intention-to-treat or per protocol.

Risk of bias assessment

We will evaluate the risk of bias of the primary outcome from the included studies using the revised version of the Cochrane risk of bias tool, RoB 2 [37]. This tool comprises five domains that address various aspects of design, conduct, and reporting where bias could be introduced. Following the algorithm developed by a researchers group of the University of Bristol and adopted by Cochrane (https://www.riskofbias.info/welcome/rob-2-0-tool), we will assess the risk of bias associated with each domain

and the overall judgment. Judgments may indicate a risk of bias as "low", "high", or denote "some concerns".

Data analysis

Measure of treatment effect

Effect sizes will be estimated as odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous outcomes.

Statistical analysis

First, pairwise meta-analyses (intervention vs placebo, or intervention vs another active intervention) will be performed. The extent and impact of heterogeneity between the included studies will be assessed by forest plot inspection and calculation of I^2 statistics. If no substantial heterogeneity is detected ($p > 0.10$), results will be synthesized through a fixed-effects model; if the probability value is ≤ 0.10, a fixed- or random-effects model will be applied for $I^2 < 40\%$ or $\geq 40\%$, respectively [38]. We will report heterogeneity statistics unless only one study contributed data and heterogeneity would therefore not be applicable. Moreover, if a sufficient number of trials are incorporated ($n >= 10$) [39], analyses will be conducted to detect potential reporting biases by examining contour-enhanced funnel plots [40].

Second, network meta-analyses within a frequentist framework will be performed. We will assume equal heterogeneity parameter τ across all comparisons [41].

The body of evidence for each outcome will be presented in a network plot. Within each network, treatments will be visually depicted using nodes, with their sizes proportional to the sample size of patients receiving the same treatment within the network. For the primary network, the included interventions in different formulations will be treated as separate nodes, independently from nicotine doses. If there is a study with 3 or more arms, some of which have the same treatment but different doses (e.g., comparing A dose 1, A dose 2, control), the events and sample sizes in the arms with the same treatment will be summed for this network.

Additionally, whenever data is be available, we will perform a secondary analysis for the primary outcome splitting the nodes according to the nicotine dose.

Direct comparisons among the devices will be illustrated by edges sized proportionally to the number of studies included in the corresponding pairwise meta-analysis.

To assess the transitivity assumption, we will examine whether the effect modifiers, including sex, age, oral health status, and dose regimen, will be similarly distributed across the comparisons included in the network. We will visually inspect the distribution of these effect modifiers using box plots for continuous variables (e.g., mean age) and histograms for categorical variables. The incoherence between direct and indirect sources of evidence will be evaluated both at a global and local levels. Globally, we will use the design-by-treatment interaction test that estimates the incoherence of effect estimates between intervention comparisons. Locally, when applicable, we will use the loop-specific approach to evaluate the statistical agreement between direct and indirect evidence for a specific comparison [42]. Ranking probabilities for each intervention's possible rank will be estimated. The treatment hierarchy will then be summarized and presented as the surface under the cumulative ranking curve [43].

The CINeMA web application (CINeMA: Confidence in Network Meta-Analysis, University of Bern 2017, available from https://cinema.ispm.unibe.ch/) will be used to evaluate the confidence of evidence derived from the NMA. This tool considers the following six domains: within study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [44].

Data analysis will be performed using STATA/BE v.17 statistical package (StataCorp LT, College Station, TX, USA).

Management of missing data

In cases where relevant data are missing, authors will be contacted, and a second reminder will be sent after 14 days. If no response is obtained, the data will be excluded from the analysis or, if presented narratively, will be reported in the tables. No imputation methods will be applied to handle missing data and only available data or data provided by contacting authors will be analyzed.

For cross-over trials, when the pre-crossover data are absent in reports, we will reach out to the authors of the studies to obtain this information. If this data is not obtainable, we will exclude the study.

Additional analyses

To determine the potential influence of effect modifiers on the outcomes, we will conduct a subgroup analysis [45]. These factors will be: sex (i.e., male versus female), age (i.e., 18–45 years vs ≥46 years), oral status (i.e., healthy oral status vs pre-existing oral conditions), and regimen dose (i.e., forced dose treatment vs optimized). The robustness of the results will be assessed through sensitivity analyses, by excluding studies: (1) with a follow up less than 6 months, (2) financially supported, (3) at high risk of overall bias, and (4) dual users of different NCNPs (e.g., e-cig + NRT).

Timeline

The research on the databases and the studies selection was completed by September 2024. Data extraction, bias assessment, and analysis were concluded by March 2025,

and the final draft of the paper will be submitted by May 2025. In any case, the submission of the current protocol predates these stages, as it was completed and submitted for review in August 2024, prior to the subsequent phases of the bibliographic research, study selection, data extraction, bias assessment, and statistical analysis.

Discussion

Although the use of NCNPs represents a reduced risk to oral health compared to traditional cigarettes, they are not without risk. The oral cavity, in particular, being the area directly exposed during the use of these products, can experience various adverse effects related to both the mode of application and the substances released. Oral effects have been associated with the use of such devices, such as xerostomia [46], oral ulcers [47], gingival disease [48], or leukoplakia [49]. However, most of these studies are not free from bias, often being based on in vitro findings or data from non-randomized trials, which do not allow for the establishment of a causal relationship. Additionally, the decreased number of studies that report the oral side effects specifically, and the reduced sample size, often limit the level of the available evidence [34].

This is the first systematic review and network meta-analysis of randomized clinical trials that will enable a comparison of the most common adverse oral events associated with the use of these devices, both against a placebo/standard care/non-treatment group and among the different treatments themselves. Through a systematic approach and rigorous methodology, we will be able to provide updated and robust evidence capable of influencing health policy decisions and clinical recommendations.

In order to obtain results that are generalizable to the broader population, pregnant women and individuals with mental health or neurological disorders have been excluded, as the oral health of these populations could be affected differently by NCNPs. Pregnant women, for instance, might have increased susceptibility to oral manifestations due to hormonal fluctuations, while individuals with mental health or neurological conditions may have varying levels of treatment adherence, potentially influencing the occurrence of adverse effects [50, 51]. Furthermore, oral hygiene habits in these groups may differ from the general population, representing another possible confounder. While these groups were excluded to maintain consistency in our results, and also to meet the transitivity assumption in the situation of NMA, future research should focus on understanding the oral health effects of NCNPs in these populations.

We have chosen to include only locally delivered formulations, as these are presumed to have a direct effect on the oral cavity. However, we acknowledge that systemic formulations could also lead to oral manifestations, albeit less frequently—similar to certain medications associated with dry mouth. While these effects were not the primary focus of our review, future studies investigating both systemic formulations and other routes of administration will be valuable in providing a more comprehensive understanding of their potential impact on oral health.

Some effect modifiers have been considered in this study to account for potential differences in oral health outcomes associated with NCNPs. These include oral health status at baseline, age, sex, and treatment regimen.

The impact of NCNPs on oral health may vary depending on pre-existing conditions in the oral cavity. Individuals with periodontal disease could be more susceptible to worsening inflammation, while those with mucosal lesions might experience progression or enlargement of these lesions compared to healthy users. Similarly, age may influence susceptibility to oral adverse effects. Older individuals, due to reduced regenerative capacity and cumulative exposure to risk factors, may be at a higher risk of developing mucosal irritation, dry mouth, or periodontal disease compared to younger individuals [52, 53].

Sex-related differences may also play a role, as hormonal fluctuations in females, particularly those affecting vascularization and immune response, could influence the development of mucosal irritation or periodontal disease progression differently than in males [54, 55]. Additionally, behavioral variations in oral hygiene or smoking cessation patterns between sexes may contribute to differences in observed outcomes [56, 57].

The treatment regimen (i.e., forced dose vs. optimized) may also introduce variability in outcomes. A forced-dose approach, where participants receive a fixed dosage regimen, might not reflect real-world usage patterns and could lead to different exposure durations or intensities compared to an optimized regimen, where individuals adjust their intake based on personal needs [58]. Differences in exposure time and mode of use may influence oral health effects, making this an important factor to consider.

Smoking history was not included among the expected effect modifiers. Although smoking history is typically associated with variations in oral health outcomes, our study focuses specifically on smoking cessation. As confirmed by a preliminary assessment, participants in clinical trials on smoking cessation generally exhibit comparable smoking histories, typically having smoked for a minimum of 20 years with an average consumption of 20–25 cigarettes per day. Given this relative homogeneity, smoking history is unlikely to introduce significant variability in the study populations.

Project findings will be disseminated as original articles in peer-reviewed scientific journals and as oral presentations at national and international conferences focused on oral health and tobacco harm reduction. Additionally, the full dataset of the NMA will be made available online with open access in Mendeley Data, a secure online repository for research data.

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CINeMA	Confidence in Network Meta-Analysis
ENDS	Electronic nicotine delivery systems
HTPs	Heated tobacco products
NCNPs	Non-combustible nicotine products
NMA	Network meta-analysis
NRTs	Nicotine replacement therapies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Systematic Review Protocols
PRISMA-NMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RCTs	Randomized controlled trials
RoB	Risk of bias
STPs	Smokeless tobacco products

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Not applicable

Authors' contribution
The study was conceptualized and designed by GRMLR and RP. GRMLR developed the search strategy. CDG and SM were responsible for the methodology. GRMLR initially drafted the protocol, which was later revised by EP, IC, JK, and AA. All authors carefully reviewed the final protocol and provided their approval.

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Data availability
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
GRMLR was awarded a Scholarship Programme for 2024/25 by K•A•C Tobacco Harm Reduction. The scholarship is specifically intended to support the current project.
CDG, EP, JK, IC, SM, and AA have nothing to disclose.
RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. He has received grants from U-BIOPRED and AIR-PROM, Integral Rheumatology & Immunology Specialists Network (IRIS), Global Action to End Smoking (formerly known as Foundation for Smoke-Free World), Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl., Duska Therapeutics, Forest Laboratories, Ministero dell Universita' e della Ricerca (MUR) Bando PNRR 3277/2021 (CUP E63 C22000900006) and 341/2022 (CUP E63 C22002080006), funded by NextGenerationEU of the European Union (EU), and the ministerial grant PON REACT-EU 2021 GREEN- Bando 3411/2021 by Ministero dell Universita'e (MUR)–PNRR EU Community. He is founder of the Center for Tobacco Prevention and Treatment (CPCT) at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc., GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbooks royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for Lega Italiana Anti Fumo (LIAF) and the International Network of Nicotine Consumers Organizations (INNCO); and he is Chair of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). All other authors declare that they have no competing interests.

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