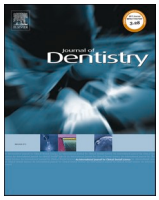
Journal of Dentistry 160 (2025) 105910

Contents lists available at ScienceDirect

Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent



Review article

Oral health effects of non-combustible nicotine products: a systematic review and network meta-analysis of randomized controlled trials

Giusy Rita Maria La Rosa [a,*], Cinzia Del Giovane [b,c,1], Silvia Minozzi [d,1], Jan Kowalski [e], Iain Chapple [f], Amaliya Amaliya [g], Konstantinos Farsalinos [h], Riccardo Polosa [a,i]

[a] Department of Clinical and Experimental Medicine, University of Catania, Via Santa Sofia, 89, Catania 95123, Italy
[b] Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, Modena, Italy
[c] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[d] Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
[e] Department of Periodontology, Medical University of Warsaw, Warsaw, Poland
[f] Periodontal Research Group, Institute of Clinical Sciences, College of Medical & Dental Sciences, The University of Birmingham, Birmingham Community Healthcare NHS Foundation Trust, Birmingham, UK
[g] Department of Periodontology, Faculty of Dentistry, Universitas Padjadjaran, West Java, Indonesia
[h] Department of Public and Community Health, School of Public Health, University of West Attica, Athens, Greece
[i] Center for the Acceleration of Harm Reduction, University of Catania, Catania, Italy

ARTICLE INFO

Keywords:
Adverse effects
Aphthous ulcers
Dry mouth
Mouth irritation
Non-combustible nicotine products
Oral health
Smoking cessation

ABSTRACT

Objectives: To evaluate the oral adverse effects of non-combustible nicotine products (NCNPs) compared with each other, placebo, standard of care, no treatment and combustible cigarettes through a systematic review and network meta-analysis.

Data sources and study selection: Randomized controlled trials involving adult smokers and reporting oral adverse events (e.g., mouth irritation, dry mouth, aphthous ulcers) were included. PubMed, Scopus, and Cochrane CENTRAL were searched up to August 2024. Risk of bias was assessed using RoB 2, and evidence certainty with CINeMA.

Results: Thirty-six trials were included, with 21 contributing to the network meta-analysis. Most comparisons with placebo showed no significant differences across four primary outcomes. The odds of developing aphthous ulcers were significantly higher in the nicotine replacement therapy (NRT) gum group compared with standard of care (OR = 2.36; 95 % CI: 1.05–5.30). Higher odds of mouth irritation were also observed for e-cig (OR = 4.06; 95 % CI: 1.67–9.85), NRT mouth spray (OR = 4.36; 95 % CI: 1.14–16.63), NRT gum (OR = 4.25; 95 % CI: 1.51–11.94) and snus (OR = 13.56; 95 % CI: 1.07–171.52) when compared with standard of care. Sensitivity analyses confirmed the main findings. Secondary outcomes revealed isolated associations but were based on limited data. Evidence certainty was low to very low due mainly to imprecision and risk of bias.

Conclusions: NCNPs appear to be generally well tolerated. Most placebo comparisons showed no increased risk, although some products exhibited higher odds of aphthous ulcers and mouth irritation compared with standard of care. Better reporting of oral adverse events in RCTs is needed.

Clinical significance: Given the current limitations of the evidence base, dental professionals should play an active role in tobacco harm reduction strategies by monitoring oral health during NCNP use and supporting product choice based on safety, tolerability, and individual patient needs.

1. Introduction

Tobacco use remains a significant global health concern, affecting millions of individuals worldwide [1]. Non-combustible nicotine products (NCNPs) represent a promising option both for smoking cessation and as a harm reduction strategy for smokers who are either unable or unwilling to quit [2]. These alternatives include various categories, including electronic nicotine delivery systems (ENDS) such as

* Corresponding author.
E-mail address: giusy.larosa@unict.it (G.R.M. La Rosa).
[1] These authors contributed equally as second authors.

https://doi.org/10.1016/j.jdent.2025.105910
Received 20 May 2025; Received in revised form 10 June 2025; Accepted 12 June 2025
Available online 13 June 2025

e-cigarettes (e-cigs) and heated tobacco products (HTPs) [3–5], nicotine pouches [6], smokeless tobacco products (STPs) like snus [7], and nicotine replacement therapies (NRTs) [8].

E-cigs are battery-powered devices that generate an aerosol containing nicotine and flavorings, and which users inhale [9]. Similarly, HTPs operate by heating tobacco sticks to a temperature below combustion, releasing nicotine in vapor form without producing the harmful byproducts of tobacco smoke [10]. Another alternative that has recently gained popularity is nicotine pouches - small, tobacco-free sachets containing nicotine and flavorings, which are placed between the gum and lip for absorption through the oral mucosa [6,11,12]. Unlike e-cigs and HTPs, which involve inhalation, nicotine pouches provide nicotine through oral absorption, eliminating any exposure to aerosolized compounds.

Smokeless tobacco products also represent a diverse category with significant regional variations in composition, usage, and health risks [13]. Among these, snus - a Scandinavian oral tobacco product - consists of ground tobacco mixed with salt, water, and flavorings and is placed under the upper lip, avoiding combustion-related harms [7,14]. Other STPs, such as gutka and various forms of chewing tobacco, remain widely used in some regions but pose distinct health risks due to their composition, which often includes areca nut and other additives [15].

Finally, NRTs, including patches, gums, lozenges, and inhalers, provide a medically approved and regulated method for nicotine intake without tobacco use. Recognized by the World Health Organization as essential medicines, NRTs are a cornerstone of smoking cessation strategies, offering controlled nicotine delivery to support individuals attempting to quit smoking [16,17].

The oral cavity is the first area exposed to tobacco and NCNPs, making it especially susceptible to their effects. Tobacco cigarette use is linked to a range of oral health issues, such as dry mouth, red and white oral mucosal lesions with having the potential for malignant transformation, oral cancers, gingival and periodontal diseases, as well as dental staining and mucosal pigmentation (smoker's melanosis) [18–21]. Similarly, the use of inhalable products like e-cigs and HTPs also leads to direct contact between the released aerosols and the oral epithelial cells for a significant duration [22,23]. Some evidence suggests that NRTs like nicotine gum may increase the risk of oral side effects, such as aphthous ulcers [24,25]. However, these findings often come from analyses that included products such as patches and nasal sprays, which do not have direct contact with the oral mucosa. Randomized controlled trials (RCTs) on individual products – such as nicotine sublingual tablet [26], Swedish snus [27,28], and e-cigs [29,30] - generally report good oral tolerability, although user surveys report oral irritation as one of the most frequent side effects of e-cigarettes [31]. Nevertheless, a systematic comparison of the specific oral effects of different NCNPs is lacking. Given their growing use, conducting a comparative analysis to assess their relative safety remains important.

We conducted the first systematic review and network meta-analysis to assess the oral health effects of NCNPs, both as monotherapies and in combination therapies, compared with each other, placebo, standard of care, no treatment, and combustible cigarette smoking. The primary objective was to assess the impact of product type, formulation, and mode of use (whether administered alone or in combination) on oral health. As a secondary objective, the influence of different nicotine doses within product categories was examined. This analysis provides valuable insights into the safety of NCNPs and informs clinical practice, public health policy, and decision-making for patients, physicians, and regulators concerning treatment options.

2. Materials and methods

This systematic review and network meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) guidelines [32]. The protocol has been registered in PROSPERO under the identifier CRD42024565118 and previously published [33].

2.1. Research question

What oral signs and symptoms are linked to NCNP use as monotherapies or combination therapies in current smokers, when compared with each other, placebo, standard of care, no treatment, and conventional cigarette smoking?

2.2. Selection criteria

2.2.1. Population

2.2.1.1. Inclusion criteria. We included all adult smokers (≥18 years) of any gender, nationality, and ethnicity.

2.2.1.2. Exclusion criteria. Studies that recruited adults with mental health conditions [34,35], neurological disorders, alcohol or other substance abuse, non-smoking individuals, and pregnant women [36] were excluded. If an eligible study had missing information regarding inclusion criteria, study authors were contacted to obtain clarification.

2.2.2. Interventions

The interventions included non-combustible nicotine products, such as ENDS (i.e., e-cigs and HTPs); NRT in the form of chewing gum, mouth spray, inhalator, lozenges/sublingual tablets, and mouth strips; smokeless tobacco products such as Swedish-style snus and gutka; and oral nicotine pouches. These interventions were considered either individually or in combination (e.g., e-cigarette + NRT).

Depending on the manufacturer and country-specific regulations, the nicotine concentration in ENDS and HTPs is categorized as low, medium, or high, and is typically expressed in mg/mL or as a percentage (% v/v). In most countries, concentrations range from 0 (0 %, nicotine-free) to ≥15 mg/mL (1.5 %) per cartridge [37–39]. Nicotine inhalers generally provide a standard dose (10 mg) or a high dose (15 mg) per cartridge, whereas lozenges and chewing gums range from low doses (≤2 mg) to high doses (4 mg) [39]. Further details are provided in the published protocol [33].

To ensure that potential effect modifiers, such as study and patient-level covariates, were balanced across pairwise comparisons - some interventions were excluded. These included NRT delivered as skin patches and nasal sprays, as well as the concurrent use of multiple NRT formulations not listed in this study (e.g., skin patch plus chewing gum) [24]. Pharmacological treatments were also excluded as detailed in the published protocol [33]. Moreover, trial arms permitting multiple undefined interventions were excluded.

2.2.3. Control

Eligible comparators were other active interventions as well as placebo, standard of care, no treatment, and combustible cigarette smoking. "Placebo" referred to placebo NRT, nicotine-free pouches, or ENDS with non-nicotine liquid [39]. "Standard of care" was defined as counseling with the possibility of using, as needed, any of the included interventions. "No treatment" referred to participants who did not receive any medication or placebo. "Combustible cigarette smoking" referred to individuals who continued smoking their usual brand of cigarettes.

2.2.4. Outcomes

The primary outcomes focused on any oral health effects, defined as the number of participants reporting any oral signs or symptoms that, in the opinion of the trial investigators, could be attributed to the intervention. These included oral irritation/inflammation, dryness of the mouth/lips, sore mouth/lips/tongue, buccal erosions or ulcers, local reactions in the floor of the mouth such as dryness, burning, parakeratosis, or hyperkeratosis (including leukoplakia), periodontal

diseases such as gingivitis and periodontitis, jaw pain from chewing, broken teeth, tooth or restoration staining, mucosal pigmentation, dental caries, and altered taste. Any other oral side effects reported were also included under this denomination. Additionally, primary outcomes included the number of patients with side effects categorized by type (i.e., aphthous ulcers, dry mouth, and mouth irritation).

Secondary outcomes included dental issues, periodontal problems such as gingivitis and gingival bleeding, jaw disorders, and other specific oral side effects reported. Serious oral side effects (defined as events that resulted in death, were life-threatening, required hospitalization, or caused significant disability [40]) and drop-outs due to oral adverse events were also recorded.

2.2.5. Study design

Randomized controlled trials were eligible. For cross-over studies, only data from the first period (i.e., before the cross-over) were used in order 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 were excluded.

2.2.6. Time frame

Acute (24/48 h) or subacute (< 1 month) studies were excluded, as these often reflect short-term effects observed under experimental conditions rather than real-world use, potentially leading to overestimation of transient adverse events. No other restrictions on follow-up duration were applied.

2.3. Search strategy

2.3.1. Electronic searches

We searched the following electronic databases from their inception to August 2024: PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). An updated search was performed in February 2025, before the analyses were finalized. No language restrictions were applied. A comprehensive search strategy was implemented 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 was applied. The complete search strategies for each database are provided in the **Appendix 1**.

2.3.2. Secondary sources

References of the included articles and review papers were further screened for other potentially relevant studies. Included studies were also “citation chased” (i.e., snowball search) through Google Scholar. The most impactful peer-reviewed scientific journals in dentistry and tobacco harm reduction were also hand-searched. Additionally, three medical experts were consulted to identify relevant studies on the topic that might not have been found through the previous methods. A comprehensive gray literature search was conducted on the websites of the most relevant oral health-related medical organizations.

The complete list of journals and gray literature sources searched is available in the published protocol [33]. Secondary searches were conducted between September and October 2024.

2.4. Selection of studies

Using EndNote version 21 (Clarivate), two independent reviewers (GRMLR and RP) screened titles and abstracts independently, following training and calibration exercises. Duplicates were identified and deleted using the specific features of Endnote software. Any discrepancies were resolved through consensus between the two reviewers. In cases where consensus could not be reached, a discussion was held with a senior author to resolve disagreements (IC). Articles with any uncertainty regarding inclusion proceeded to the next stage. Subsequently, the two same reviewers independently reviewed the full texts of trials identified as potentially eligible. Discrepancies were resolved through consensus between the two authors, with a senior author (IC) acting as an arbitrator if necessary. In cases where multiple reports referred to the same study, we planned to use the most complete dataset, prioritizing the report with the longest follow-up or the most comprehensive outcome data. Missing data were requested from authors via email where possible.

2.5. Data extraction

A pre-pilot data extraction form was developed, and the following data were extracted from each eligible study by one reviewer (GRMLR) and independently checked by a second reviewer (JK). For the outcome findings, the same two reviewers independently extracted the data from reports of each study.

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

2.6. Risk of bias assessment

Two review authors (GRMLR and SM) independently evaluated the risk of bias using the revised version of the Cochrane risk of bias tool, RoB 2 [41]. 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 research group from the University of Bristol and adopted by Cochrane (https://www.riskofbias.info/welcome/rob-2–0-tool), the risk of bias associated with each domain and the overall judgment was assessed. As specified in the RoB 2 tool, authors are expected to indicate whether the assessment targets the effect of assignment or adherence to the intervention. Given the safety focus of this review, we evaluated the effect of adhering to the intervention (“per protocol effect”) for primary outcomes [41]. To ensure consistency in the risk of bias assessment, the review authors conducted a calibration exercise using the RoB 2 tool. Based on this initial pilot phase, and to address interpretation challenges specific to the interventions and outcomes considered, the team developed a detailed implementation document, following the approach adopted in a previous review [42], available on the Open Science Framework platform (https://osf.io/4×7ye/files/osfstorage). This document provides practical guidance and examples for answering each signaling question. After finalizing the document, all included studies were reassessed accordingly. Judgments indicated a risk of bias as “High,” “Some concerns”, and “Low”. A study was classified as having a high risk of bias if any domain was rated as high risk. If at least one domain was rated as

having some concerns (and none as high risk), the study was classified as having some concerns overall. Studies were considered at low risk of bias only if all domains were rated as low risk.

2.7. Data analysis

2.7.1. Measure of treatment effect

Effect sizes were estimated as odds ratios (OR) with 95 % confidence intervals (CIs) for dichotomous outcomes.

2.7.2. Statistical analysis

First, pairwise meta-analyses for all comparisons for which direct evidence were available were conducted with a random effects approach. The extent and impact of heterogeneity among the included studies were assessed through forest plot inspection and calculation of I^2 statistics. Heterogeneity statistics were reported unless only one study contributed data, in which case heterogeneity assessment was not applicable.

Second, network meta-analyses within a frequentist framework were performed with a random effects model. We assumed a common heterogeneity parameter (τ) across all comparisons [43]. The network of evidence was visually represented using nodes and lines connecting treatments that were compared in at least one study (also called direct evidence). For the primary analysis, we considered a network where interventions in different formulations were treated as separate nodes, regardless of nicotine doses. In studies with three or more arms, where some arms shared the same treatment but with different doses (e.g., A dose 1, A dose 2, control), we summarized the number of events and the sample sizes of the same treatment provided at different doses. A secondary analysis of the primary outcomes was planned for a network formed of interventions at different nicotine dose categories.

In order to assess the transitivity assumption, the distribution of potential effect modifiers (e.g., age, sex, oral health status, dose regimen) across treatment comparisons were visually explored using box plots and histograms.

Incoherence between direct and indirect sources of evidence was assessed at both global and local levels. Globally, the design-by-treatment interaction test was used to estimate inconsistencies in effect estimates between intervention comparisons. Locally, where applicable, the loop-specific approach was applied to evaluate statistical agreement between direct and indirect evidence for specific comparisons [44].

Ranking probabilities for each intervention were estimated, and the treatment hierarchy was summarized using the surface under the cumulative ranking curve (SUCRA) [45]. The SUCRA values range from 0 % to 100 %, with higher values indicating a greater probability that the intervention is among the most well tolerated. They provide a practical summary of the relative ranking of treatments within the network.

The confidence in evidence derived from the network meta-analysis was assessed using the CINeMA web application (CINeMA: Confidence in Network Meta-Analysis, University of Bern 2017, available at https://cinema.ispm.unibe.ch/) by three reviewers (GRMLR, CDG and SM). This tool evaluates the confidence of the evidence based on six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [46]. The average method was used to assess within-study bias and indirectness. Relative OR estimates below 0.8 or above 1.25 were considered clinically important. Each domain was evaluated and classified as no concerns, some concerns, or major concerns. Reporting bias was assessed using the ROB-MEN tool, and the level of concern was categorized as low, moderate, or high [47,48]. Subsequently, the overall confidence in the evidence for each treatment comparison was graded as high, moderate, low, or very low.

All analyses were conducted on the number of participants who completed the study (completers), corresponding to a per-protocol approach. The analyses were performed using STATA/BE v.17 statistical software (StataCorp LT, College Station, TX, USA).

2.7.3. Management of missing data

We reached out to study authors whenever essential data, including outcome information, were missing. An initial request was sent via email, followed by a reminder after two weeks if no response was received. If no response was obtained from study authors, the corresponding data were either excluded from the analysis or, when narratively reported, presented in summary tables. No imputation methods were applied to handle missing data; only data available from the published reports or obtained through author contact were included in the analysis.

For cross-over trials, if reports did not provide pre-crossover data, we contacted the authors to request this information. Studies were excluded if the necessary data could not be obtained.

2.7.4. Additional analyses

To assess the potential impact of effect modifiers on the outcomes, we planned to conduct subgroup analyses based on sex (male vs. female), age (18–45 years vs. ≥46 years), oral health status (healthy vs. pre-existing oral conditions), and treatment regimen (forced dose vs. optimized).

The robustness of the results was evaluated through sensitivity analyses by excluding studies that: 1) had a follow-up period of less than six months, 2) received industry-funding, and 3) were classified as having a high overall risk of bias.

3. Results

3.1. Search findings

The search process identified a total of 802 records through database searches. After removing duplicates, 643 records remained for title and abstract screening. Of these, 77 records were selected for full-text assessment with 52 studies excluded. Additionally, 19 extra studies were identified by screening the reference lists of the included articles; among these, eight were excluded after full-text review. A total of 60 studies were excluded after full-text screening because they did not meet the inclusion criteria. The primary reasons for exclusion were the lack of oral health data ($n = 27$), inadequate follow-up ($n = 17$), and type of intervention ($n = 8$). Additional reasons included study design ($n = 5$), inadequate comparator ($n = 2$), and population criteria ($n = 1$).

The full selection process is outlined in Fig. 1, and details on the exclusions are provided in **Appendix 2**.

Ultimately, 36 studies were included in the systematic review [26–30,49–79]. A total of 21 studies provided quantitative data for the network meta-analysis [26–30,54–59,61,63,66,69,71,72,74–76,78].

3.2. Overview

Most of the 36 studies were double-blinded (23 RCTs; 64 %), 12 (33 %) were open-label [29,49,50,53,58,59,63,67,68,70,71,75], and one study (3 %) implemented blinding of outcome assessors only [79]. The publication dates of the included studies ranged from 1982 to 2024.

These studies assessed eight different interventions across 12,454 participants. All studies employed a parallel-group design. The average sample size was 346, ranging from 43 [72] to 1246 [29] participants.

Among the 36 studies, 21 (58.3 %) were conducted at a single center, while 14 (39 %) were multicenter trials [27–29,53,54,58–60,64,65,69,70,72,78]. In one study (3 %), the number of study centers was not clearly reported [77].

The studies were conducted globally, with 17 (47 %) in North America, 15 (42 %) in Europe, two (5 %) in Asia and one each in Africa (3 %) and South America (3 %). All studies were conducted in high-income countries, except for three carried out in South Africa [49], Thailand [72], and Venezuela [60], respectively. Sixteen studies (44 %)

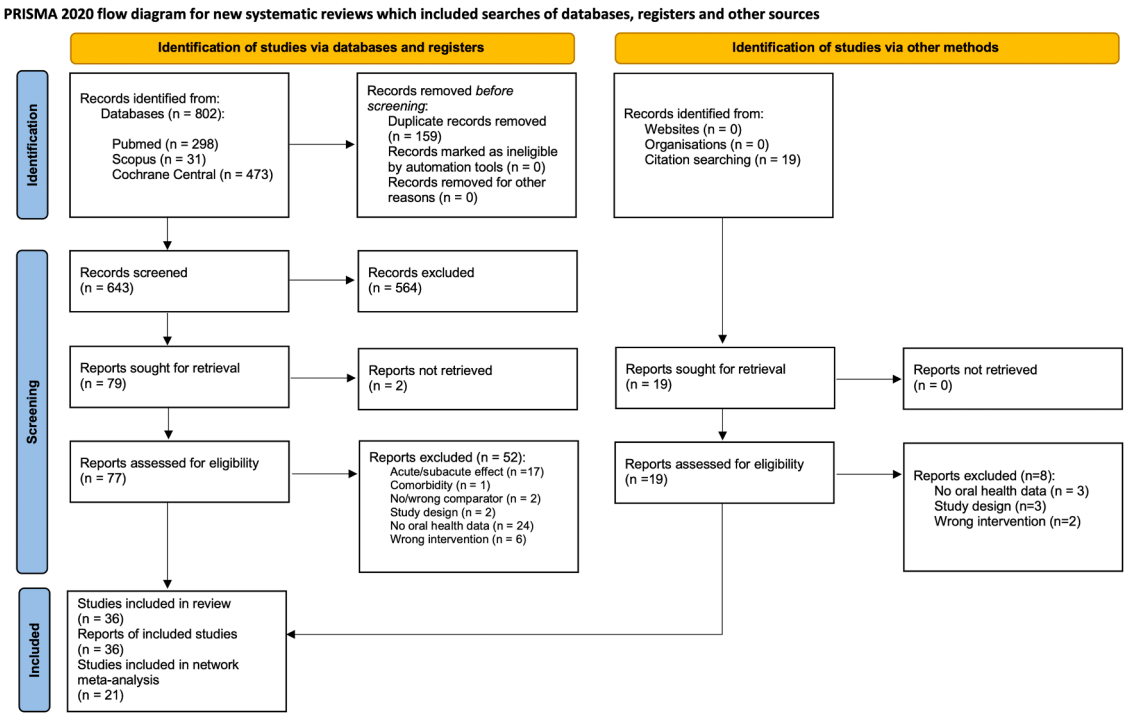


Fig. 1. Flow diagram of the search process.

were conducted in the United States; four (11 %) in Denmark and three each in Sweden and United Kingdom (8%). Switzerland, Serbia, Italy, Ireland, Canada, and the Republic of Korea each contributed one study (3 % each). One study [78] was conducted in both Denmark and Germany.

Most of the 36 trials (30 RCTs, 83 %) used a two-arm design, while six (17 %) were multi-arm studies [49,54–56,59,76]. Among the multi-arm trials, two (5 %) examined the same product at different dose levels [56,76], one (3 %) compared at least two different interventions [49] and the others (8 %) evaluated one intervention versus multiple controls.

The intervention periods lasted between six weeks [50,61,62,66,75] and 12 months [73], with follow-up durations ranging from three [49, 72,79] to 24 [55,58,60,76] months. Sixteen studies (44 %) reported only short-term outcomes (<6 months), nine (25 %) assessed medium-term outcomes (6 to <12 months), and 11 (30 %) studies included long-term follow-up (≥12 months) (Table 1).

Eighteen trials (50 %) recruited current smokers from the general population, often through newspaper or social media advertisements [26,28–30,49,50,54–57,59,68,69,71,73,74,77,78]. Twelve studies (33 %) involved outpatients seeking treatment at clinical sites [58,60–66,70, 75,76,79] while 2 (5 %) were recruited from university campuses [51, 52]. Two studies (5 %) recruited participants from both the general population and medical databases [27,53]. Finally, the source of the population was not specified in two studies (5 %) [67,72].

3.3. Participants

The participants had a mean age of 43 years ± 11 standard deviations. The sample was largely equally distributed between males (n = 5668; 48 %) and females (n = 6220; 52 %). Age and gender information was not provided for 993 participants across three studies [52,55,65] and 566 participants across three studies [52,65,76], respectively (Table 1).

Eight studies excluded patients with oral disorders, including jaw disorders or chewing difficulties [58,60,64,71], oral lesions at baseline [26,69,78], or other dental issues [51]. One study [63] included smokers diagnosed with periodontitis, characterized by interproximal probing pocket depths (PPDs) of ≥ 5 mm at ≥ 8 sites.

3.4. Interventions

The 36 studies included a diverse range of interventions and comparisons. Overall we included eight treatments: e-cigs, HTPs, snus, NRT in the gum, mouth spray, tablet, lozenge, and inhaler formats. We had the following comparisons: active treatment versus placebo, active treatment versus another active treatment, and active treatment versus another comparator (standard of care/no treatment). Two studies compared an active intervention with cigarette use [53,59]. For the primary analysis, the data for studies that involved multiple parallel arms comparing different dosages of the same medication against a placebo were merged into a single "arm" [56,76]. Two studies compared different dosages of NRT gum without a placebo and were included only in the secondary analysis based upon nicotine dosage comparison [66, 75].

3.4.1. Active treatment vs. placebo: 23 studies

NRT gum (n = 12) [51,52,55,56,60,61,64,65,67,72,73,76]
NRT inhaler (n = 3) [62,74,77]
NRT mouth spray (n = 2) [69,78]
NRT tablet (n = 2) [26,57]
Snus (n = 2) [27,28]
E-cig (n = 2) [30,54]

3.4.2. Active treatment vs. another active treatment: five studies

NRT gum vs NRT inhaler vs NRT mouth spray (n = 1) [49]
NRT gum vs e-cig (n = 1) [68]
NRT lozenge vs snus (n = 1) [70]
NRT gum vs NRT lozenge (n = 1) [71]
NRT gum vs NRT tablet (n = 1) [79]

Table 1
Characteristics of the included studies.

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
Auer 2024 [29]	Multicenter, individually-randomized, open-label, parallel-group trial	Switzerland	*N* = 1246	Free e-cigs (Innokin Endura T20-S) and e-liquids (19.6 mg, 11 mg, 6 mg, and 0 mg per milliliter-free choice), standard-of-care smoking-cessation counseling, and optional (not free) NRT (*N* = 622).	Standard counseling and a voucher for any purpose including NRT (*N* = 624).	6 months	Control=39 [30–52] (median [IQR]); Intervention=37 [28–51].	Control=295 (47.3); Intervention=290 (46.6).	Median age began smoking (IQR), yr: Control=16 (15–19); Intervention=16 (15–18). Median No. cig. per day (IQR): Control=15 (10–20); Intervention=15 (10–20).	The Swiss National Science Foundation, the Swiss Tobacco Prevention Fund, Swiss Cancer Research, and LungeZürich.
Bolliger 2007 [49]	Single-center, individually-randomized, open-label, parallel-group trial	South Africa	*N* = 100	NicoNovum mouth spray (1 mg/actuation) (*N* = 50); Nicorette gum (2 mg) (*N* = 25); Nicorette inhaler (10 mg/blister) (*N* = 25).	NA	3 months 12 months	Spray=42.5 ± 10.9 (mean±SD); Gum=43.0 ± 11.3; Inhaler= 44.3 ± 12.2.	Spray=24 (48 %); Gum=7 (28 %); Inhaler= 9 (36 %).	Mean±SD No.cig.per day: Spray=23.0 ± 8.8; Gum=23.7 ± 6.8; Inhaler= 23.9 ± 8.2. Mean±SD No. pack per year: Spray=21.0 ± 15.6; Gum=25.6 ± 12.5; Inhaler=24.3 ± 18.2.	NicoNovum AB
Caponnetto 2013 [30]	Single-center, double-blind, individually-randomized parallel-group trial	Italy	*N* = 300	"Original" 7.2 mg nicotine (2.27 ±0.13 % nicotine) (*N* = 100), "Original" (6 wks) + "Categoria" 5.4 mg nicotine (1.71 ±0.09 % nicotine) (6 wks) (*N* = 100).	"Original" without nicotine ("sweet tobacco" aroma) (*N* = 100).	12 weeks 12 months	Control= 42.2 ± 12.5 (mean ±SD); Intervention= 44.9 ± 12.5.	Control=37 (37 %); Intervention=73 (36.5 %).	Age at initiation (mean±SD): Control=16.9 ± 3.5; Intervention=16.85 ±4.1. Median (IQR) cig. per day: Control= 22.0 (15.0–27.0); Intervention=20 (14.5–25.5). Median(IQR) No. pack per year: Control= 25.5 (12.0–35.0); Intervention=24.65 (15.6–37.9).	Lega Italiana AntiFumo
Carpenter 2017 [50]	Single-center, open-label, individually-randomized parallel-group trial	US	*N* = 1236	Camel Snus (2.5–2.6 mg nicotine per pouch) (*N* = 626).	No treatment (*N* = 610).	6 weeks	Control= 48.7 ± 12.6 (mean ±SD); Intervention= 48.7 ± 12.5.	Control=396 (65 %); Intervention=438 (70 %).	Age at initiation (mean±SD): Control=17.0 ± 4.4; Intervention=16.9 ± 3.7. Mean±SD No. cig. per day: Control= 19.9 ± 8.4; Intervention=20.1 ± 8.7.	The National Cancer Institute of the National Institutes of Health (US); the National Center for Advancing Translational Science of the National Institutes of Health (US).
Christen 1984 [51]	Single-center, double-blind, individually-randomized parallel-group trial	US	*N* = 208	Nicotine-containing chewing gum 2 mg (Nicorette) (*N* = 105).	Placebo gum (0 mg of nicotine per piece) (*N* = 103).	15 weeks	Control=35.5 (no further info); Intervention= 33.2.	Control=61 (59 %); Intervention=62 (59 %).	No.cig.per day: Control=30.5 (no further info); Intervention=30.1. No. years smoked: Control=17.6 (no further info); Intervention=15.2.	Merrell Dow Pharmaceutic, Inc, Cincinnati.
Christen 1985 [52]	Single-center, double-	US	*N* = 193	Nicotine-containing chewing gum 2	Placebo gum (0 mg of nicotine per	15 weeks	Adult participants (no further information).	NR	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
	blind, individually-randomized, parallel-group trial			mg (Nicorette) (*N* = 97).	piece) (*N* = 96).					
Edmiston 2022 [53]	Multicenter, individually-randomized, open-label, parallel-group trial	US	*N* = 150	MarkTen Bold Classic (test product 1) (*N* = 48) and MarkTen Bold Menthol (test product 2) (*N* = 50) e-cigs, both at 4.0 % nicotine by weight.	Own brand of commercially available conventional cigarettes (*N* = 52).	12 weeks 24 weeks	Control= 45.6 ± 9.86 (mean ±SD); Intervention= 43.8 ± 9.58.	Control=27 (52 %); Intervention=49 (50 %).	Mean±SD No.cig.per day: Control=17.7 ± 5.65; Intervention=17.5 ± 4.57. Mean±SD years smoked: Control=26.5 ± 11.19; Intervention=23.8 ± 9.24.	Altria Client Services LLC
Eisenberg 2020 [54]	Multicenter, double-blind and open label, individually-randomized parallel-group trial	Canada	*N* = 376	E-cig (NJOY Inc, Scottsdale, Arizona) (15 mg nicotine/mL) plus individual counseling (*N* = 128).	Non-nicotine e-cigarettes plus individual counseling (*N* = 127); Individual counseling alone (*N* = 121).	12 weeks	Individual counseling= 53±12 (mean±SD); Non-nicotine e-cig=52±13; E-cig=53±13.	Individual counseling=57 (47 %); Non-nicotine e-cig=56 (44 %); E-cig=65 (51 %).	Mean±SD No.cig.per day: Individual counseling=21±11; Non-nicotine e-cig=21±11; E-cig=21±9. Mean±SD years smoked: Individual counseling=35±13; Non-nicotine e-cig=35±14; E-cig=35±14.	Canadian Institutes of Health Research
Fagerström 2012 [27]	Multicenter, double-blind, individually-randomized, parallel-group trial	US	*N* = 250	Nicotine snus (Swedish Match AB) in two different sachet sizes for free choice (0.5 or 1.0 g) (*N* = 125).	Placebo snus (identical sanchet with no tobacco or nicotine) (*N* = 125).	16 weeks (with tapering of product use during the last 3 wks) 28 weeks	Control=46 (mean); Intervention=44.	Control=71 (57 %); Intervention=81 (65 %).	Mean No.cig.per day: Control=21; Intervention=20.	Swedish Match AB, Stockholm, Sweden
Fortmann 1988 [55]	Single-center, double-blind, individually-randomized, parallel-group trial	US	*N* = 600	Nicotine-containing chewing gum (polacrilex) 2 mg "Ad Lib" (*N* = 152) and "Fixed" Dosage (*N* = 147).	Placebo gum (0 mg of nicotine per piece) (*N* = 148) (ad lib); no treatment (*N* = 153).	3-week treatment period followed by a 6-week tapering period 24 months	Aged 18–65 years (per inclusion criteria).	No treatment=85 (56 %) Placebo=71 (48 %) Intervention=158 (53 %)	Mean±SD No.cig.per day: No treatment=25.5 ± 13.2;Placebo=26.0 ± 11.5; Intervention=23.70±11.90. Mean±SD years smoked: No treatment=25.3 ± 11.4; Placebo=25.5 ± 10.04; Intervention=25.25±10.71.	The National Cancer Institute and the Merrell Dow Research Institute, Cincinnati.
Garvey 2000 [56]	Single-center, double-blind, individually-randomized, parallel-group trial	US	*N* = 608	Nicotine-containing chewing gum 2 mg (*N* = 202) and 4 mg (*N* = 203).	Placebo gum (0 mg of nicotine per piece) (*N* = 203).	2 months 12 months	Control= 40.1 ± 11.6 (mean ±SD); Intervention= 41.2.8 ± 12.	Control=105 (52 %); Intervention=207 (51 %).	Mean±SD No.cig.per day: Control=23.3 ± 11.1; Intervention= 23.6 ± 11.2. Mean±SD age began smoking (years): Control=16.9 ± 4.2; Intervention= 16.75±4.15.	The National Institute on Drug Abuse and the Department of Veterans Affairs (Boston, MA, US).
Glover 2002 [57]	Single-center, double-blind, individually-	US	*N* = 241	Nicotine-containing sublingual tablet 2 mg (*N* = 120).	Placebo tablet (0 mg of nicotine per tablet) (*N* = 121). Each	6 months (3-month treatment period followed by	Control= 41.8 ± 11.6 (mean ±SD); Intervention= 43.9.8 ± 10.	Control=67 (55.37 %); Intervention=63 (52.5 %).	Mean±SD No.cig.per day: Control=29.4 ± 10.05; Intervention= 28.5 ± 11.5. Mean±SD years smoked: Control=24.2 ± 11.3;	Pharmacia & Upjohn

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
	randomized, parallel-group trial				placebo tablet contained 3 μg of capsaicin.	a 3-month tapering period) 6 months			Intervention= 25.8 ± 10.4.	
Harackiewicz 1988 [58]	Multicenter, open-label, individually-randomized, parallel-group trial	US	*N* = 197	Nicotine-containing chewing gum (Nicorette) with self-help manual (*N* = 99).	Self-help manual only (*n* = 52); and a short booklet only, with tips for stopping smoking (*n* = 46).	Supplies of gum were freely dispensed for six months. 3 months	Tot.=Aged 18–76 years, mean=36.	Tot.=124 (63 %)	Mean [range] No.cig.per day: 26.5 [10–75] Mean age began smoking (years):16; Mean±SD years smoked: 17.	Merrell Dow Pharmaceuticals, Inc., Cincinnati, OH, US.
Haziza 2020 [59]	Multicenter, open-label, individually-randomized, parallel-group trial	US	*N* = 160	Menthol Tobacco Heating System 2.2. (mTHS) with 1.21 mg/stick nicotine (*N* = 80).	Preferred commercially available brand of menthol cigarette (mCC) (*N* = 41); smoking abstinence (SA) (no treatment) (*N* = 39).	5-day in a confined setting and 86-day ambulatory period. Additional 28-day safety period.	SA=38.8 ± 11.42, [22–58] (mean ±SD, [range]); mCC= 33.7 ± 10.17, [23–60]; mTHS= 39.2 ± 11.72, [22–66].	SA=15 (38.5 %); mCC=17 (41.5 %); mTHS=32 (40.0 %).	Daily mCC consumption, n (%): 10–19 SA=18 (46.2 %); mCC=21 (51.2 %); mHTP= 43 (53.8 %). >19 SA=21 (53.8 %); mCC=20 (48.8 %); mHTP=36 (45.0 %).	Philip Morris International.
Herrera 1995 [60]	Multicenter, double-blind, individually-randomized parallel-group trial	Venezuela	*N* = 322	Nicotine-containing chewing gum (Nicorette) 2 mg (*N* = 157) and 4 mg (*N* = 87), with Behavioral Supportive Treatment.	Placebo gum (0 mg of nicotine per piece) with Behavioral Suportive Treatment (*N* = 78).	3 months 24 months	Tot.=38.6 ± 9.22 (mean±SD)	Tot.=139 (43.16 %)	Mean±SD No.cig.per day: Tot.=24.93±8.54.	NR
Hjalmarson 1984 [61]	Single-center, double-blind, individually-randomized, parallel-group trial	Sweden	*N* = 206	Nicotine-containing chewing gum (Nicorette) 2-mg with group therapy (*N* = 106).	Placebo gum (0 mg of nicotine per tablet) (*N* = 100). It was flavored with pepper (capsaicin).	6 weeks 6 months	Control= 41.3 ± 13.62 (mean±SD); Intervention= 42.8 ± 11.23.	Control=59 (59 %); Intervention=57 (53.77 %).	Mean±SD No.cig.per day: Placebo=24.2 ± 10.28; Intervention=23.9 ± 9.85.	NR
Hjalmarson 1997 [62]	Single-center, double-blind, individually-randomized parallel-group trial	Sweden	*N* = 247	Nicotine inhaler (about 10 mg nicotine and 1 mg menthol) (*N* = 123).	Placebo inhaler (*N* = 124). It contained only menthol.	6 weeks 12 months	Control=47.0 ± 9.5 (mean±SD); Intervention= 48.0 ± 10.6.	Control= 82 (66.12 %); Intervention= 76 (61.78 %).	Mean±SD No. of cigarettes smoked per day: Control=21.0 ± 7.8; Intervention= 21.7 ± 8.1. No. of years smoked: Control=28.9 ± 8.7; Intervention= 30.0 ± 10.3.	Pharmacia & Upjohn, Helsingborg, Sweden.

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
Holliday 2019 [63]	Single-center, open-label, individually-randomized parallel-group pilot trial	UK	$N = 80$	E-cig (Vype eTank clearomizer, Nicoventure Trading Limited, Blackburn, UK) starter kit. Nicotine strength concentrations: 0mg/ml, 6mg/ml, 12mg/ml, 18mg/ml ($N = 40$).	Standard counseling ($N = 40$).	6 months	Control=44.6 ± 9.5 (mean±SD); Intervention= 44.0 ± 11.8.	Control= 20 (50 %); Intervention=22 (55 %).	Mean±SD No. of cigarettes smoked per day: Control=17.5 ± 6.9; Intervention= 17.4 ± 6.4. Age started smoking: Control=16.0 ± 2.8; Intervention= 15.3 ± 3.2.	National Institute for Health Research.
Hughes 1989 [64]	Multicenter, double-blind, individually-randomized parallel-group trial	US	$N = 315$	Nicotine-containing chewing gum 2 mg (Nicorette) ($N = 210$).	Placebo gum (0 mg of nicotine per piece) ($N = 105$).	3 months 12 months	Control=36.3 ± 10.3 (mean±SD); Intervention= 37.4 ± 9.7.	Control= 62 (59 %); Intervention= 115 (55 %).	Mean±SD No. of cigarettes smoked per day: Control=29.2 ± 12.0; Intervention= 29.8 ± 10.7. Duration of smoking, years: Control=18.7 ± 10.2; Intervention= 19.7 ± 9.1.	Th National Institute on Drug Abuse, Washington, DC.
Jamrozik 1984 [65]	Multicenter, double-blind, individually-randomized parallel-group trial	UK	$N = 200$	Nicotine-containing chewing gum 2 mg ($N = 101$).	Placebo gum (0 mg of nicotine per piece) ($N = 99$).	12 weeks 6 months	NR	NR	NR	The Oxford District Research Committee and the Nuffield DominionsTrust.
Jarvis 1982 [66]	Single-center, double-blind, Individually-randomized parallel-group trial	UK	$N = 116$	Nicotine-containing chewing gum, 1 mg ($N = 58$) and 2mg ($N = 58$).	NA	6 weeks	1-mg gum=38.4 (mean); 2-mg gum=41.0.	1-mg gum= 35 (60.34 %); 2-mg gum= 29 (50 %).	Mean No. of cigarettes smoked per day: 1-mg gum=26.5; 2-mg gum=30.9.	Medical Research Council and Department of Health and Social Security.
Jensen 1990 [67]	Single-center, open-label, individually-randomized parallel-group trial	Denmark	$N = 496$	Nicotine-containing chewing gum 2 mg (Nicorette, Lundbeck, Denmark) ($N = 211$).	Silver acetate chewing gum (Fertin Laboratories, Vejle, Denamrk) ($N = 203$); ordinary unflavoured, sugar free chewing gum (V6,Fertin Laboratories) ($N = 82$).	12 week 6 months	Silver acetate= 41.8 ± 11.8 (mean ±SD); Ordinary= 41.4 ± 12.4; Nicotine gum=42.7 ± 12.4.	Silver acetate= 117 (57.63 %); Ordinary= 41 (50 %); Nicotine gum= 116 (54.97 %).	Mean±SD No. of cigarettes smoked per day: Silver acetate=21.7 ± 9.9; Ordinary=21.0 ± 9.7; Nicotine gum=21.8 ± 8.2. Smoking duration (years): Silver acetate=22.8 ± 8.8; Ordinary=21.6 ± 8.3; Nicotine gum=23.1 ± 8.8.	NR

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
Joksić 2011 [28]	Multicenter, double-blind, individually-randomized parallel-group trial	Serbia	N = 319	Sweden snus (Swedish Match AB) with a nicotine content of c. 1 % (N = 158).	Placebo snus (no tobacco or nicotine) (N = 161).	48 weeks	Control= 44.0 ± 10.3 (mean ±SD); Intervention= 43.3 ± 9.9.	Control= 97 (60.2 %); Intervention=99 (62.7 %).	Mean±SD No. of cigarettes smoked per day (last year): Control=25.7 ± 9.0; Intervention= 27.6 ± 10.5. Age started smoking: Control=18.8 ± 4.0; Intervention= 19.2 ± 5.3.	Swedish Match AB, Stockholm, Sweden.
Lee 2019 [68]	Single-center, open-label, individually-randomized parallel-group pilot trial	Republic of Korea	N = 150	E-cig (eGO-C Ovale, nicotine 0.01 mg/mL; Janty-Korea Co., Janty-Asia Co., Seoul, Republic of Korea) (N = 75); Nicotine gum (Nicoman, nicotine 2 mg/ gum; Daewoong Pharmaceuticals, Seongnam, Republic of Korea) (N = 75).	NA	12 weeks 24 weeks	E-cig=44.0 ± 7.8 (mean±SD); NRT gum=40.7 ± 8.4.	E-cig= 0 (0 %); Nicotine gum=0 (0 %).	Mean±SD No. pack. of cigarettes smoked per day: E-cig=1.05±0.37; Nicotine gum=0.96±0.36. Smoking duration (years): Ecig=23.26 ±7.60; Nicotine gum=20.69±9.67.	None.
Nelson 2019 [70]	Multicenter, open-label, individually-randomized parallel-group trial	US	N = 649	4-mg nicotine polacrilex lozenges (Nicorette, GlaxoSmithKline Consumer Healthcare, Moon Township, PA) (N = 213), Camel Snus (600 mg per pouch, R. J. Reynolds Tobacco, Winston- Salem, NC) with (N = 218) or without (N = 218) SLT Health-Related Information.	NA	12 weeks 12 months	Lozenge= 41.4 ± 12.1 (mean ±SD); Snus= 42.45±11.8.	Lozenge= 110 (51.6 %); Snus= 221 (50.7 %).	Mean±SD No. of cigarettes smoked per day: Lozenge=19.2 ± 7.3; Snus=19.05±7.15. Duration of smoking, years: Lozenge=22.1 ± 11.9;Snus=23.15±12.	R.J. Reynolds Tobacco Company.
Nides 2020 [69]	Multicenter, double-blind, individually-randomized parallel-group trial	US	N = 1198	1-mg nicotine mouth spray (McNeil AB, Sweden) (N = 597).	Placebo mouth spray (N = 601). It contained capsaicin.	12 weeks 6 weeks	Control= 51.2 ± 11.7 (mean ±SD); Intervention= 51.5 ± 11.7.	Control= 319 (53.1 %); Intervention= 332 (55.6 %).	Mean±SD No. of cigarettes smoked per day: Control=17.9 ± 7.8; Intervention= 18.1 ± 8.5. Age started smoking, years: Control=17.7 ± 6.1; Intervention= 17.8 ± 6.6.	GlaxoSmithKline/McNeil AB.

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
Pack 2008 [71]	Single-center, open-label, individually-randomized parallel-group trial	US	N = 408	Nicotine gum plus Quit Line or Self-Help (N = 203); nicotine lozenge plus Quit Line or Self-Help (N = 205).	NA	8 weeks	Nicotine gum=41.80±11.44 (mean±SD); Nicotine lozenge=43.30 ±12.89.	Nicotine gum=114 (56.15 %); Nicotine lozenge=115 (56.09 %).	Mean±SD No. of cigarettes smoked per day in last month: Nicotine gum= 22.60±9.7; Nicotine lozenge= 23.55±10.05. Smoking duration (years): Nicotine gum= 25.30±11.39; Nicotine lozenge= 26.25±12.39.	National Cancer Institute; the National Institute on Drug Abuse.
Rungruanghiranya 2008 [72]	Multicenter, double-blind, individually-randomized parallel-group trial	Thailand	N = 43	Nicotine polyestex gum, 2 mg, with Behavioral Support (N = 20).	Placebo gum (0 mg of nicotine per piece) with Behavioral Support (N = 23).	12 weeks	Control= 43.00±11.86 (mean±SD); Intervention=45.05 ±11.83.	Control= 1 (4.3 %); Intervention= 0 (0 %).	Mean±SD No. of cigarettes smoked per day: Control= 20.78±+5.80 (median=20); Intervention= 19.70±5.25 (median=20). Duration of smoking, years: Control= 23.09±9.30 (median=23); Intervention= 26.20±10.60 (median=25).	NR
Schneider 1983 [73]	Single-center, double-blinded, individually-randomized, parallel-group trial	US	N = 60	Nicotine-containing chewing gum 2 mg (A.B. Leo, Sweden) (N = 30).	Placebo gum (0 mg of nicotine per piece) (N = 30).	12 months	Control=37 (mean); Intervention=40.	Control= 19 (63.33 %); Intervention= 17 (56.66 %).	Mean No. of cigarettes smoked per day: Control=31; Intervention=35. Duration of smoking, years: Control=20; Intervention=23.	National Institute on Drug Abuse; Medical Research Service of the Veterans Administration.
Schneider 1996 [74]	Single-center, double-blind, individually-randomized parallel-group trial	US	N = 223	Nicotine inhaler (10-mg nicotine and 1-mg menthol) (N = 112).	Placebo inhaler (N = 111). It contained only menthol.	6 months	Control= 44.4 ± 10.8 (mean ±SD); Intervention= 43.7 ± 11.3.	Control= 42 (37.8 %); Intervention= 40 (35.7 %).	Mean±SD No. of cigarettes smoked per day: Control=26.2±+9.8; Intervention= 29.2 ± 11.3. Duration of smoking, years: Control=26.1 ± 10.8; Intervention= 25.3 ± 11.2.	Pharmacia & Upjohn, Sweden.
Tønnesen 1988a [75]	Single-center, open-label, individually-randomized parallel-group trial	Denmark	N = 172	Nicotine-containing chewing gum (Nicorette, AB Leo, Sweden) 2 mg (N = 62) and 4 mg (N = 54) with group meetings. The mean number of 2-mg of nicotine gum in the first month was 306 (n = 34) versus	No treatment (N = 56).	6 weeks 22 months	Tot.=44.8 mean [range 18–79 years].	Tot.=95 (55.23 %).	Mean [range] No.cig.per day: 21.6 [10–52]; Age began smoked (years): 19.1 [9–49].	H. Lundbeck A/S, Denmark and the Danish National Tuberculosis Society.

(*continued on next page*)

Table 1 (*continued*)

Author year	Study design	Country	Sample size	Intervention	Control	Study period Follow-up	Age (years)	Sex (female, n, %)	Smoking history	Funder
				252 pieces of 4 mg ($n = 34$).						
Tønnesen 1988b [76]	Single-center, double-blind, individually-randomized parallel-group trial	Denmark	$N =$ 173	Nicotine-containing chewing gum (AB, Leo, Sweden) 2 mg ($N = 93$) and 4 mg ($N = 27$), with six group counseling session.	Placebo gum ($N = 53$). It contained only capsaicin.	2 months 6 weeks	Control= 45.5 ± 11.7 (mean ±SD); Intervention= 45.22±10.42.	NR	Mean±SD No. of cigarettes smoked per day: Control=19.3±+5.5; Intervention= 23.73 ± 8.09.	Danish National Tubercolosis Foundation.
Tønnesen 1993 [77]	Double-blind, individually-randomized parallel-group trial	Denmark	$N =$ 286	Nicotine inhaler (10 mg nicotine and an additive) ($N = 145$).	Placebo inhaler ($N =$ 141). It contained only the additive.	6 months 6 weeks	Control= 39±14 (mean±SD); Intervention= 39±12.	Control= 89 (63 %); Intervention= 84 (58 %).	Mean±SD No. of cigarettes smoked per day: Control=20±+7; Intervention=20±6. Duration of smoking, years: Control=20±11; Intervention=21±10.	Kabi Pharmacia Therapeutics, Helsingborg, Sweden.
Tønnesen 2012 [78]	Multicenter, double-blind, individually-randomized parallel-group trial	Denmark, Germany	$N =$ 479	Nicotine mouth spray (1 mg/ spray after priming) (McNeil AB, Helsingborg, Sweden) ($N =$ 318).	Placebo mouth spray ($N = 161$). It contained only capsaicin.	12 weeks	Control= 45.5 ± 11.7 (mean ±SD); Intervention= 47.0 ± 10.9.	Control= 73 (45.3 %); Intervention= 137 (43.1 %).	Mean±SD No. of cigarettes smoked per day: Control=22.7 ± 8.7; Intervention= 22.7 ± 8.8. Age started smoking, years: Control=16.5 ± 3.6; Intervention= 16.6 ± 3.6 ($N = 317$).	McNeil AB.
Wallström 2000 [26]	Single-center, double-blind, individually-randomized parallel-group trial	Sweden	$N =$ 247	Nicotine-containing sublingual tablet 2 mg (Nicorette Microtab, Pharmacia & Upjohn) ($N =$ 123).	Placebo tablet (0 mg of nicotine per tablet) ($N =$ 124). Each placebo tablet contained 3 μg of capsaicin.	3 months 12 months	Control= 44.7 ± 11.4 (mean ±SD); Intervention= 44.5 6 ± 11.6.	Control= 68 (54.83 %); Intervention= 78 (63.41 %).	Mean±SD No. of cigarettes smoked per day: Control=20.6±+6.8; Intervention= 18.2 ± 5.4. Duration of smoking, years: Control=26.9 ± 9.8; Intervention= 26.1 ± 10.3.	NR
Whelton 2012 [79]	Single-center, operator-blinded, individually-randomized, parallel-group trial	Ireland	$N =$ 200	Nicotine-containing polacrilex gum (Nicorette Freshmint) 2 mg or 4 mg ($N =$ 102) and sublingual tablet 2 mg (Nicorette Microtab) ($N =$ 98).	NA	12 weeks	Nicotine gum=35.2 (mean); Nicotine tablet=36.3.	Nicotine gum= 52 (51.0 %); Nicotine tablet= 44 (44.9 %).	Mean (min, max) No. of cigarettes smoked per day: Nicotine gum= 18.7 (5, 40); Nicotine tablet= 19.8 (5, 60).	McNeil AB (manufacturer of the test and control products).

Legend. E-cig: e-cigarette; NA: Not Applicable; NR: Not Reported; NRT: nicotine-replacement therapy; SLT: smokeless tobacco; UK: United Kingdom; US: United States.
Follow-up refers to the maximum duration over which oral adverse events were recorded.

3.4.3. Active treatment vs. another comparator: seven studies

3.4.3.1. Standard of care. E-cig ($n = 3$) [29,54,63]
NRT gum ($n = 1$) [58]

3.4.3.2. No treatment. NRT gum ($n = 1$) [55]
Snus ($n = 1$) [50]
HTP ($n = 1$) [59]

For each study, we outlined specific details regarding the dosage regimen, including the maximum dose, composition, and usage pattern, in the **Appendix 3**.

3.5. Outcomes

Twenty-one studies provided quantitative data on oral adverse events, while the others reported oral adverse events in a narrative format or in a way that made data extraction unfeasible. See **Appendix 3** for details on the reported outcomes.

Among the studies that provided quantitative data on outcomes, 18 reported data for the primary outcomes [27–30,54–59,61,63,69,71,72,74,76,78], 12 provided data for the secondary outcomes [26,27,29,55–59,69,72,74,78]. Jarvis et al. (1982) [66] and Tønnesen et al. (1988) [75] contributed data exclusively to the primary outcomes network based on nicotine dosage, specifically for aphthous ulcers [66,75] and mouth irritation [75]. For the primary outcomes, six out of 36 studies (17 %) provided data on the number of participants with any oral adverse event [27,28,30,61,69,71] within six weeks [69] to one year [30]. Nine studies (25 %) provided data on the number of participants with aphthous ulcers [29,54–56,58,61,63,74,76] within six weeks [58,76] to two years [55]. Six studies (17 %) reported data on participants with dry mouth [29,54,57,59,74,78], occurring within six weeks [57] to six months [29,74], and 13 studies (36 %) reported on mouth irritation [28–30,54,55,57,58,63,71,72,74,76,78], with events occurring within six weeks [57,58,76] to two years [55], respectively.

The following secondary outcomes were included:

Number of participants with dental issues (three studies) [29,56,59]
Number of participants with periodontal issues (two studies) [27,29]
Number of participants with jaw disorders (four studies) [55,56,58,72]
Number of participants with oral mucosal abnormalities (four studies) [26,57,69,78]
Number of participants with dry lips (two studies) [59,74]
Number of participants with lip irritation (one study) [74]
Number of participants with tongue irritation (two studies) [56,74]
Number of participants with oral numbness (one study) [74]
Number of participants with oral burning (two studies) [74,78]
Number of participants with any oral serious adverse events (one study) [29]
Number of participants who discontinued due to oral adverse events (two studies) [27,74]

Regarding the last two secondary outcomes - number of participants with any oral serious adverse events and number of participants who discontinued due to oral adverse events - it is worth noting that most of the studies that explicitly reported on these outcomes did not observe any such events in any of the treatment groups. Specifically, no serious oral adverse events were reported in 16 studies [27,28,30,50,53,54,57,59,61,63,68,69,72,74,77,79], while 9 studies [26,28,51,56,66,68,72,77,79] reported no discontinuations due to oral adverse events.

3.6. Correspondence with study authors

Four of the manuscripts with missing data were quite old, dating back to before 2000, making it difficult to contact the authors [60,64,67,73]. For the remaining six manuscripts [49,50,53,68,70,79], emails were sent to the authors requesting the missing data. However, only three authors were successfully reached, and the full data were no longer available [50,53,79].

3.7. Funding sources

Thirty studies clearly disclosed their funding sources: 16 received support from pharmaceutical/tobacco companies [27,28,49,51,53,57–59,62,69,70,74,75,77–79], while 13 were funded by non-profit organizations or institutional sources [29,30,50,54–56,63–66,71,73,76]. One study reported no funding [68], and six studies did not provide any information regarding their funding sources [26,52,60,61,67,72].

3.8. Risk of bias of the included studies

Study risk of bias assessments, including domain judgments and summary plots for each domain, are presented in Fig. 2. Word files, one for each study and outcome, with responses to the signaling questions, are available on the Open Science Framework platform (https://osf.io/4×7ye/files/osfstorage).

3.8.1. Number of participants with any oral adverse event

Three studies were identified as having concerns regarding the overall risk of bias, primarily due to missing outcome data [27,30,61]. Two studies were assessed as having a high risk of bias due to bias arising from the randomization process (i.e., lack of a random allocation sequence, which was not concealed until participants were enrolled and assigned to interventions) [69] or in the measurement of the outcome (i.e., knowledge of the assigned intervention could influence assessment) [71].

3.8.2. Number of participants with aphthous ulcers

The majority of the studies were assessed as having some concerns due to bias in the randomization process, deviations from the intended intervention, missing outcome data, and selection of the reported result [29,56,61,63,74]. For the Eisenberg study, only the comparison between e-cig versus standard of care was assessed as having some concerns [54]. Three studies were at high risk of bias due to bias in outcome measurement (i.e., only self-reported) [55,76] or missing outcome data (i.e., significant loss to follow-up) [58].

3.8.3. Number of participants with dry mouth

Two studies were judged to be at high risk of bias due to bias in outcome measurement (i.e., knowledge of the assigned intervention could influence assessment) [29,59]. For the Eisenberg study, only the comparison between e-cig versus standard of care was assessed as having a high risk of bias [54]. Two studies were assessed as having some concerns regarding bias arising from the randomization process, missing outcome data, and selection of the reported result [57,74].

3.8.4. Number of participants with mouth irritation

The studies assessed as having a high risk of bias were rated as such due to concerns related to outcome measurement (i.e., knowledge of the assigned intervention could influence assessment, or outcomes were self-reported) [29,55,58,63,71,76]. For the Eisenberg study, only the comparison between e-cig and standard of care was assessed as having a high risk of bias [54]. In addition, Harackiewicz's study was also considered at high risk due to missing outcome data, as a result of significant losses to follow-up [58]. Four studies were assessed as having some concerns due to bias arising from the randomization process, missing outcome data, and selection of the reported results [30,57,72,74].

3.9. Network geometry and meta-analysis estimates

The network plots for primary and secondary outcomes are presented in Fig. 3 and **Appendix 4**. Each line connects treatments that

have been directly compared in studies, with line thickness representing the number of studies contributing to each direct comparison. The size of each circle corresponds to the total number of participants who received that treatment.

Results of the pairwise meta-analyses and related heterogeneity for each outcome are reported in the **Appendix 5**.

Results of the network meta-analyses are reported in Fig. 4 for each primary outcome and in **Appendix 6** for secondary outcomes, using placebo as reference treatment. Network estimates for the primary outcomes for each pairwise comparison are presented in Table 2.The SUCRA (Surface Under the Cumulative Ranking) probabilities for each outcome are reported in **Appendix 7**.

3.9.1. Primary outcomes

3.9.1.1. Number of participants with any oral adverse event. Six RCTs, including a total of 2681 participants, reported any oral adverse event by comparing NRT gum, NRT mouth spray, snus, and e-cig with placebo [27,28,30,61,69] and NRT gum with NRT lozenge [71] at the longest follow-up (Fig. 3).

Using placebo as a common comparator, e-cig (OR=1.46, 95 % CI 0.53–4.02), NRT mouth spray (OR=1.53, 95 % CI 0.71–3.30), snus (OR=1.63, 95 % CI 0.36–7.31), NRT lozenge (OR=1.63, 95 % CI 0.41–6.44) and NRT gum (OR=1.64, 95 % CI 0.61–4.39) showed no statistically significant difference in the number of people who experience any oral adverse event (Fig. 4a). We did not observe differences between treatments (Table 2).

3.9.1.2. Number of participants with aphthous ulcers. Nine RCTs, involving a total of 3709 participants, evaluated the occurrence of aphthous ulcers by comparing NRT gum, NRT inhaler, and e-cig with placebo [54–56,61,74,76], as well as NRT gum and e-cig with standard of care [29,54,58,63] at the longest follow-up (Fig. 3).

There was no statistically significant difference in the number of participants reporting aphthous ulcers between placebo and e-cig (OR = 1.00, 95 % CI 0.51–1.98), NRT gum (OR = 1.29, 95 % CI 0.88–1.89) and NRT inhaler (OR = 1.37, 95 % CI 0.78–2.41) (Fig. 4b). Table 2 provides network estimates for aphthous ulcers, comparing each treatment against the others within the network. The odds of developing aphthous ulcers were significantly higher in the NRT gum group compared with standard of care (OR = 2.36, 95 % CI 1.05–5.30) (Table 2).

3.9.1.3. Number of participants with dry mouth. Five RCTs, involving a total of 2565 participants, reported the number of individuals experiencing dry mouth by comparing NRT inhaler, NRT mouth spray, NRT tablet, and e-cig with placebo [54,57,74,78], as well as e-cig with standard of care [29,54] at the longest follow-up (Fig. 3). The study by Haziza et al. (2020) was excluded from the network meta-analysis as it formed a disconnected sub-network and could not be linked to the main analysis [59].

When using the placebo group as the common comparator, NRT inhaler (OR = 0.84, 95 % CI 0.27–2.59), e-cig (OR = 0.88, 95 % CI 0.52–1.51), NRT mouth spray (OR = 0.92, 95 % CI 0.54–1.57) and NRT tablet (OR = 1.53, 95 % CI 0.25–9.30) showed no significant difference in the number of participants experiencing dry mouth (Fig. 4c). We did not observe differences between treatments (Table 2).

3.9.1.4. Number of participants with mouth irritation. Thirteen RCTs, including a total of 4685 participants, reported the number of people experiencing mouth irritation by comparing NRT gum, NRT inhaler, NRT mouth spray, NRT tablet, snus and e-cig with placebo [28,30,54,55,57,58,72,74,76,78], NRT gum and e-cig with standard of care [29,54,63], and NRT gum with NRT lozenge [71] at the longest follow-up (Fig. 3).

There was no statistically significant difference in the number of people experiencing mouth irritation between placebo and e-cig (OR = 1.42, 95 % CI 0.66–3.07), NRT lozenge (OR = 1.49, 95 % CI 0.37–5.93), NRT gum (OR = 1.49, 95 % CI 0.77–2.88), NRT mouth spray (OR = 1.53, 95 % CI 0.57–4.13), NRT tablet (OR = 1.54, 95 % CI 0.33–7.28), NRT inhaler (OR = 1.56, 95 % CI 0.47–5.24), and snus (OR = 4.76, 95 % CI 0.44–51.09) (Fig. 4d).

The odds were significantly higher for snus (OR = 13.56; 95 % CI: 1.07–171.52), e-cig (OR = 4.06; 95 % CI: 1.67–9.85), NRT mouth spray (OR = 4.36; 95 % CI: 1.14–16.63), and NRT gum (OR = 4.25; 95 % CI: 1.51–11.94) compared to standard of care, with wide confidence intervals observed across these estimates (Table 2).

3.9.2. Secondary outcomes

It was possible to perform a network meta-analysis for the following secondary outcomes: the number of participants with jaw disorders, the number of participants with oral abnormalities, the number of participants with tongue irritation, the number of participants reporting oral burning, and the number of participants who discontinued due to oral adverse events.

No overall significant differences were observed between the active treatments and placebo, or among the active treatments. The only significant findings were a reduced odds ratio for NRT gum compared with placebo for jaw disorders (OR = 0.42, 95 % CI: 0.26–0.67) and an increased odds ratio for NRT inhaler compared with placebo for oral burning (OR = 11.98, 95 % CI: 4.77–30.07) (**Appendix 6**).

3.10. Network geometry and meta-analysis estimates – nicotine dose-based network

The network plots showing treatments categorized both by nicotine content (i.e., high, standard, low, extra low, mix) and by type of product are shown in **Appendix 8**. No significant differences emerged between any of the nicotine-containing treatments and placebo, nor among the treatments themselves (**Appendix 8**). Statistically significant differences were observed only for high-nicotine NRT gum (OR = 3.57; 95 % CI: 1.10–11.59) and standard-nicotine e-cig (OR = 2.47; 95 % CI: 1.26–4.85) compared with standard of care, for the outcomes of aphthous ulcers and mouth irritation, respectively.

3.11. Evaluation of heterogeneity and incoherence in the network meta-analysis

The distribution of key potential effect modifiers (e.g., age, sex, oral health status, and dose regimen) was visually inspected across treatment comparisons to assess the transitivity assumption (**Appendix 9**).

The common heterogeneity (τ^2) estimates are reported in **Appendix 10**. We found high heterogeneity variance for the number of participants with any oral adverse event and for the number of participants with mouth irritation. For the remaining primary outcomes, no substantial heterogeneity was detected . Results from the local and global incoherence assessments are reported in **Appendix 11**, whenever possible. No evidence of global and local statistical incoherence was found for aphthous ulcers and dry mouth. Global incoherence was found for the outcome mouth irritation ($\chi^2 = 8.99$; Prob > $\chi^2 = 0.0295$). For the same outcome, one loop (NRT gum–standard of care–placebo) showed statistically significant incoherence (inconsistency factor = 2.22, 95 % CI: 0.74 to 3.69).

Results for heterogeneity and incoherence for the secondary analysis by dose are reported in **Appendix 10** and **11**.

3.12. Subgroup and sensitivity analyses

3.12.1. Subgroup analysis

Subgroup analyses based on gender, age, oral status, and regimen dose were initially planned as per the protocol [33]; however, due to insufficient data, it was not possible to perform these analyses.

Fig. 2. Risk of bias assessment (RoB 2) for the studies included in the network meta-analysis for each primary outcome.
SC: Standard of care; Cig: cigarette; HTP: heated tobacco product; NT: no treatment;

3.12.2. Sensitivity analysis

Sensitivity analyses showed results largely consistent with those from the primary network meta-analysis (see **Appendices 12–14**). In the sensitivity analysis that excluded studies at high risk of bias, the odds ratio for the number of participants receiving NRT gum who experienced aphthous ulcers compared with standard of care was no longer statistically significant (OR = 2.72; 95 % CI: 0.50–14.76) (**Appendix 14**).

In the analysis that excluded industry-funded studies, the comparison between e-cig and placebo became statistically significant (OR = 1.74; 95 % CI: 1.06–2.86), while the difference between nicotine gum and standard of care was no longer significant (OR = 1.76; 95 % CI: 0.81–3.80) for the outcome mouth irritation (**Appendix 12**). For the same outcome, when we restricted the analysis to studies with a follow-up longer than six months, the comparison between e-cig and standard of care lost statistical significance (OR = 5.71; 95 % CI: 0.99–32.86), whereas a significant difference was observed for NRT inhaler vs. standard of care (OR = 13.45; 95 % CI: 1.64–109.97), although the confidence interval was wide (**Appendix 13**). When we excluded studies at high risk of bias, the comparison between e-cig and placebo reached statistical significance (OR = 1.70; 95 % CI: 1.03–2.80), while the overall direction and magnitude of effect remained similar to the main analysis (**Appendix 14**).

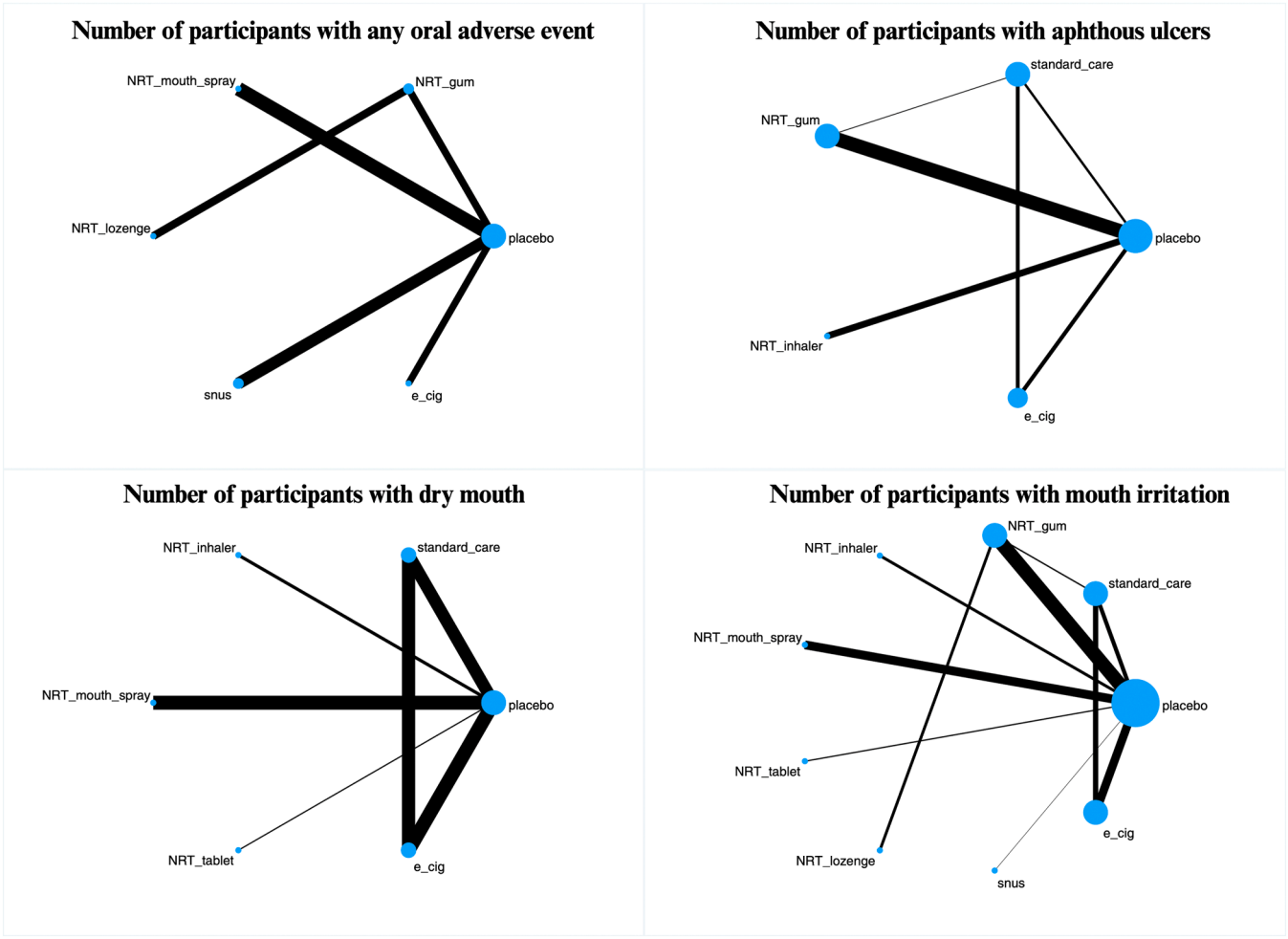


Fig. 3. Network plots of treatment comparisons for each primary outcome.
Node size is proportional to the number of participants, and line thickness represents the number of studies per comparison.

3.13. Certainty of the evidence (CINeMA)

The overall certainty of the evidence for primary outcomes was rated as low to very low, due to concerns related to study risk of bias, imprecision, and heterogeneity (**Appendices 15** and **16**).

4. Discussion

To our knowledge, this is the first systematic review to investigate oral adverse effects associated with the use of NCNPs by applying a network meta-analysis approach. A total of 36 randomized controlled trials comparing NCNPs, including locally delivered NRT, ENDS, and snus - with placebo, standard of care, or no treatment were included. Of these, 21 studies were included for the network meta-analysis, while the remaining trials reported adverse events either narratively or with insufficient detail for inclusion in the quantitative synthesis. Nevertheless, these studies documented patterns of oral adverse effects that were generally consistent with those observed in the studies included in the network meta-analyses.

We selected as primary outcomes the number of patients reporting any oral adverse event, aphthous ulcers, dry mouth, and oral mucosal irritation. This choice is justified by the clinical relevance of these events in the context of the treatments analyzed. Specifically, any oral adverse event serves as a broad and inclusive category, allowing for the capture of any potential oral manifestations related to treatment, thus ensuring a comprehensive assessment of oral toxicity. Additionally, we focused on specific clinical manifestations - aphthous ulcers, dry mouth, and oral mucosal irritation, due to their higher prevalence and tendency to become chronic, which can significantly impact long-term quality of life [80–82].

The results did not show significant differences between NCNPs and placebo in the number of patients reporting any oral AE, as well as for the specific events analyzed. Similarly, no relevant differences emerged among the various NCNPs tested or across products with different nicotine dosages.

According to the available data reported in the included studies, both overall and specific oral AEs were generally described as events of mild intensity and commonly observed in clinical practice. These events occurred at comparable rates between treatment and placebo groups. Furthermore, where assessed, they did not significantly contribute to treatment discontinuation due to adverse effects. Although the quality of the evidence ranged from low to very low, principally due to the small number of studies available for each comparison and the insufficient reporting of adverse events, the findings suggest that NCNPs are generally well tolerated at the oral level and do not appear to negatively affect treatment adherence.

Significantly higher odds of aphthous ulcers (NRT gum) and mouth irritation (e-cig, NRT gum, snus, and NRT spray) were observed only when NCNPs were compared with standard of care. In contrast, when the same treatments were compared with placebo, no significant increases in oral adverse events were found. This distinction suggests that the observed irritation is likely linked to the physical mode of administration (e.g., chewing or inhalation) rather than the pharmacological effect of nicotine itself. This interpretation is supported by the secondary

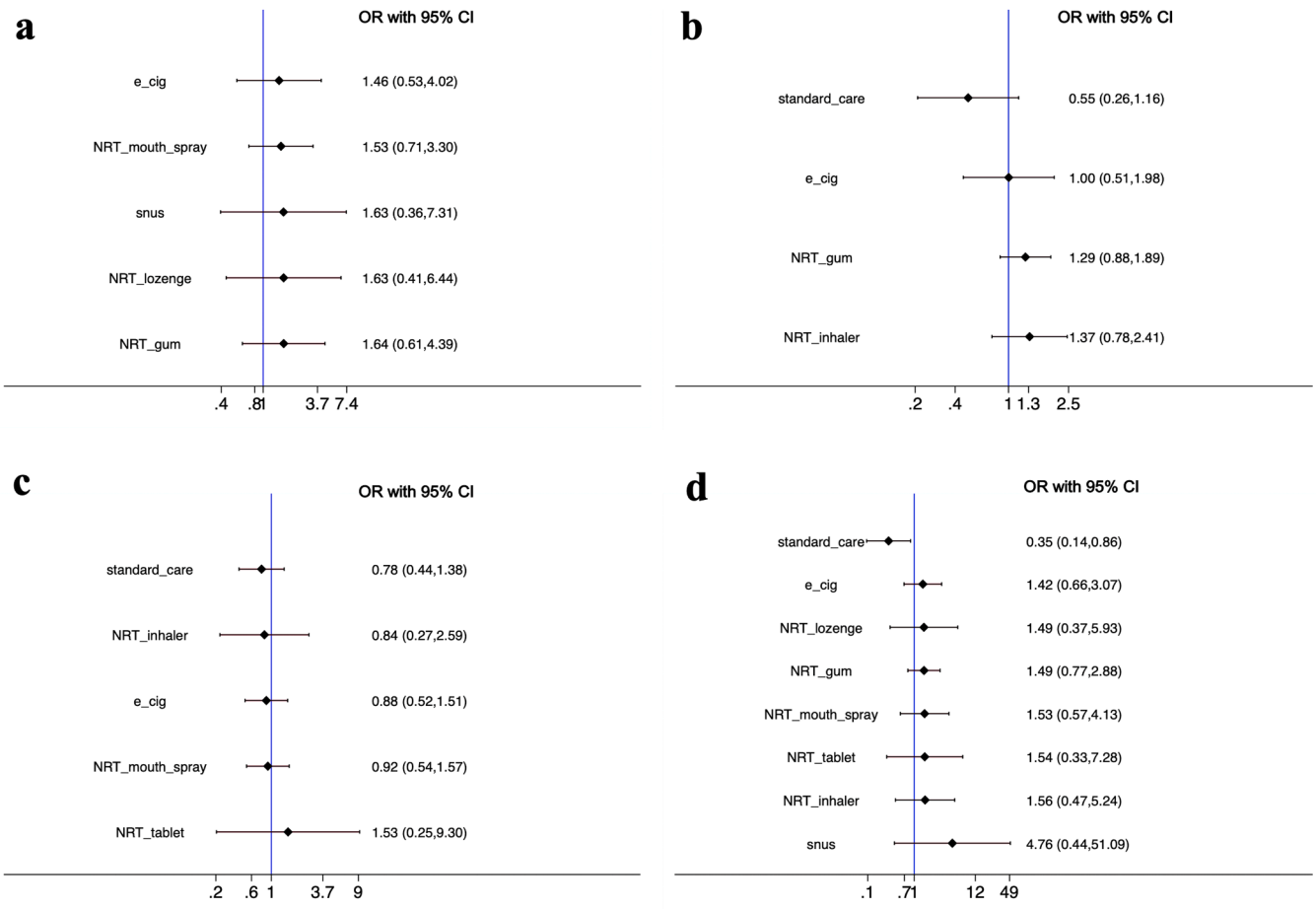


Fig. 4. Network estimates for each primary outcome using placebo as the reference treatment. (a) Number of participants with any oral adverse event; (b) Number of participants with aphthous ulcers; (c) Number of participants with dry mouth; (d) Number of participants with mouth irritation.

network analysis based on nicotine dose, which showed no significant differences across products with varying nicotine concentrations. In line with previous findings, mechanical stimulation of the oral mucosa (e.g., from gum chewing or aerosol inhalation) has been reported as a potential source of local irritation, independent of the active compound administered [83,84]. This aligns with evidence showing that oral mucosa is highly vascularized, variably keratinized, and particularly sensitive to repeated physical or chemical exposure, with irritation often resolving quickly once the triggering agent is removed [85]. Consistently, mouth irritation was generally described as mild and transient and did not result in treatment discontinuation in the majority of studies. However, in the case of e-cigs, non-nicotine liquids (which were used as placebo in two trials) may have irritating effects due to propylene glycol being used as a solvent. Propylene glycol is a humectant, and its inhalation is known to cause irritation in both animal [86,87] and human studies [88,89]. One study suggested that the propylene glycol concentration inhaled by using non-nicotine e-cigs may exceed the threshold for irritation [90]. Thus, it is possible that, at least for e-cigs, the non-nicotine products used as placebo may increase the number of cases with oral side effects in the control group, potentially masking or reducing the apparent difference compared to nicotine-containing e-cigs.

Regarding secondary outcomes, no consistent or clinically relevant differences were observed between the active interventions and placebo across most comparisons. A variety of oral adverse conditions were reported, including dental and periodontal issues, oral mucosa abnormalities, and localized irritations (e.g., lips, tongue, and oral burning). However, statistically significant differences emerged only for jaw disorders, with lower odds in the NRT gum group compared with placebo, and for oral burning, with higher odds in the NRT inhaler group compared with placebo, although the confidence interval was notably wide. Although jaw disorders represent a common side effect in both groups due to the route of administration, the reduced odds observed in the active NRT gum group compared with placebo may be explained by differences in treatment adherence and chewing behavior [55]. Participants in the active group, being more engaged with the intervention, may have followed a more regular and balanced chewing pattern over time, which could help prevent the muscular overload typically associated with excessive or asymmetrical mastication [91]. This structured use-pattern may mitigate the risk of jaw-related adverse events commonly reported with gum-based formulations. These are tentative explanations and require confirmation in larger samples and in individuals with different jaw conditions.

A previous network meta-analysis found that the use of NRTs is associated with significant oral side effects [25]. The differences with our results may be explained by the type of interventions included in the previous analysis. In the review by Sivaramakrishnan & Sridharan [25], all forms of NRTs, including NRT patches and nasal sprays, were considered. Furthermore, the inclusion of studies focusing on smoking reduction [92], rather than only smoking cessation, may have introduced a confounding factor, as the simultaneous use of smoking could have influenced the outcomes investigated.

Another meta-analysis reported an increased risk of various oral adverse effects associated with NRT use, including mouth or throat irritation, oral soreness, and gastrointestinal symptoms [24]. The difference compared to our findings may be explained by the inclusion of

Table 2
Network league tables for each primary outcome.

Number of participants with any oral adverse event									
snus	0.62 (0.14,2.77)	0.90 (0.15,5.51)	0.94 (0.17,5.10)	1.00 (0.13,7.69)	1.01 (0.17,6.08)				
1.63 (0.36,7.31)	**placebo**	1.46 (0.53,4.02)	1.53 (0.71,3.30)	1.63 (0.41,6.44)	1.64 (0.61,4.39)				
1.11 (0.18,6.79)	0.68 (0.25,1.87)	**e_cig**	1.05 (0.29,3.72)	1.11 (0.20,6.12)	1.12 (0.27,4.58)				
1.06 (0.20,5.75)	0.65 (0.30,1.41)	0.96 (0.27,3.40)	**NRT_mouth_spray**	1.07 (0.22,5.14)	1.07 (0.31,3.73)				
1.00 (0.13,7.63)	0.61 (0.16,2.42)	0.90 (0.16,4.93)	0.94 (0.19,4.53)	**NRT_lozenge**	1.00 (0.39,2.60)				
0.99 (0.16,6.01)	0.61 (0.23,1.64)	0.90 (0.22,3.68)	0.94 (0.27,3.27)	1.00 (0.38,2.59)	**NRT_gum**				
Number of participants with aphthous ulcers									
standard_care	1.83 (0.86,3.91)	1.84 (0.90,3.76)	2.51 (0.98,6.47)	**2.36 (1.05,5.30)**					
0.55 (0.26,1.16)	**placebo**	1.00 (0.51,1.98)	1.37 (0.78,2.41)	1.29 (0.88,1.89)					
0.54 (0.27,1.11)	1.00 (0.50,1.97)	**e_cig**	1.37 (0.56,3.31)	1.29 (0.60,2.75)					
0.40 (0.15,1.02)	0.73 (0.41,1.28)	0.73 (0.30,1.77)	**NRT_inhaler**	0.94 (0.48,1.86)					
0.42 (0.19,0.95)	0.78 (0.53,1.13)	0.78 (0.36,1.67)	1.06 (0.54,2.10)	**NRT_gum**					
Number of participants with dry mouth									
standard_care	1.28 (0.72,2.26)	1.13 (0.65,1.96)	1.95 (0.29,12.96)	1.17 (0.54,2.56)	1.07 (0.30,3.78)				
0.78 (0.44,1.38)	**placebo**	0.88 (0.52,1.51)	1.53 (0.25,9.30)	0.92 (0.54,1.57)	0.84 (0.27,2.59)				
0.89 (0.51,1.54)	1.13 (0.66,1.94)	**e_cig**	1.73 (0.26,11.40)	1.04 (0.49,2.22)	0.95 (0.27,3.31)				
0.51 (0.08,3.41)	0.66 (0.11,3.99)	0.58 (0.09,3.81)	**NRT_tablet**	0.60 (0.09,3.96)	0.55 (0.07,4.63)				
0.85 (0.39,1.87)	1.09 (0.64,1.87)	0.96 (0.45,2.06)	1.66 (0.25,10.97)	**NRT_mouth_spray**	0.92 (0.26,3.19)				
0.93 (0.26,3.28)	1.19 (0.39,3.66)	1.05 (0.30,3.64)	1.81 (0.22,15.24)	1.09 (0.31,3.79)	**NRT_inhaler**				
Number of participants with mouth irritation									
standard_care	**13.56 (1.07,171.52)**	**2.85 (1.16,7.00)**	**4.06 (1.67,9.85)**	4.38 (0.73,26.38)	**4.36 (1.14,16.63)**	4.24 (0.86,20.89)	4.45 (0.99,20.07)	**4.25 (1.51,11.94)**	
0.07 (0.01,0.93)	**snus**	0.21 (0.02,2.25)	0.30 (0.02,3.62)	0.32 (0.02,5.51)	0.32 (0.02,4.21)	0.31 (0.02,4.87)	0.33 (0.02,4.71)	0.31 (0.03,3.68)	
0.35 (0.14,0.86)	4.76 (0.44,51.09)	**placebo**	1.42 (0.66,3.07)	1.54 (0.33,7.28)	1.53 (0.57,4.13)	1.49 (0.37,5.93)	1.56 (0.47,5.24)	1.49 (0.77,2.88)	
0.25 (0.10,0.60)	3.34 (0.28,40.50)	0.70 (0.33,1.51)	**e_cig**	1.08 (0.19,6.11)	1.08 (0.31,3.77)	1.05 (0.22,4.95)	1.10 (0.26,4.60)	1.05 (0.40,2.76)	
0.23 (0.04,1.37)	3.09 (0.18,52.74)	0.65 (0.14,3.07)	0.93 (0.16,5.23)	**NRT_tablet**	1.00 (0.16,6.28)	0.97 (0.12,7.73)	1.01 (0.14,7.26)	0.97 (0.18,5.23)	
0.23 (0.06,0.87)	3.11 (0.24,40.69)	0.65 (0.24,1.76)	0.93 (0.27,3.26)	1.01 (0.16,6.34)	**NRT_mouth_ spray**	0.97 (0.18,5.32)	1.02 (0.21,4.87)	0.97 (0.30,3.20)	
0.24 (0.05,1.16)	3.20 (0.21,49.83)	0.67 (0.17,2.67)	0.96 (0.20,4.53)	1.03 (0.13,8.27)	1.03 (0.19,5.64)	**NRT_lozenge**	1.05 (0.17,6.58)	1.00 (0.30,3.38)	
0.22 (0.05,1.01)	3.05 (0.21,43.74)	0.64 (0.19,2.15)	0.91 (0.22,3.82)	0.99 (0.14,7.06)	0.98 (0.21,4.69)	0.95 (0.15,5.98)	**NRT_inhaler**	0.96 (0.24,3.78)	
0.24 (0.08,0.66)	3.19 (0.27,37.45)	0.67 (0.35,1.29)	0.95 (0.36,2.52)	1.03 (0.19,5.57)	1.03 (0.31,3.37)	1.00 (0.30,3.36)	1.05 (0.26,4.15)	**NRT_gum**	

In the lower triangle, the odds ratios should be read from left to right and they are the estimates of the treatment on the top-left versus the treatment on the right, whereas in the upper triangle the odds ratio should be read from right to left. Bold values indicate statistical differences.

more recent trials in our network meta-analysis, as well as potential variability in study populations and intervention characteristics between the two analyses.

Although no suitable studies on nicotine pouches were identified at the time of our literature search, a very recent RCT investigating this product has since been published [12]. Due to the timing of our analysis and the complexity of re-running the network, this study was not included. However, its exclusion is unlikely to have significantly influenced our findings. The comparator in the new RCT was traditional cigarettes, which did not contribute to our network, and overall, only a few oral adverse events were reported, with just one case of oral ulceration. Therefore, the potential impact of this new evidence on our conclusions is expected to be limited. Particularly for nicotine pouches, despite the availability of published trials, the reporting of effects on the oral cavity is often limited or based on acute exposure studies [6,93,94]. This highlights the need for prospective randomized studies explicitly designed to monitor their long-term safety on oral health.

Assessing the quality of evidence represents a key aspect in the interpretation of findings. For all four primary outcomes considered, the risk of bias was generally moderate or high, potentially affecting the strength and generalizability of the evidence [95]. Specifically, for the outcome measure of “any oral adverse event”, most studies were rated as having some concerns, primarily due to bias related to missing outcome data. In the case of "aphthous ulcers", the majority of studies also presented some concerns, mainly due to problems in the randomization process, deviations from intended interventions, and the absence of a pre-registered protocol, which limits the transparency and replicability of the study designs [96]. The outcomes “dry mouth” and “mouth irritation” were associated with a high risk of bias, primarily due to their subjective nature and the fact that they were assessed through self-report alone, without researcher control or standardized evaluation procedures. This approach increases the likelihood of measurement bias, as participants’ perceptions of symptoms like dryness or irritation may vary widely [97–99]. Future trials should aim to incorporate clinician-rated evaluations or validated instruments (e.g., visual analog scales, standardized xerostomia indices) to improve the reliability and comparability of outcome reporting.

Overall, no relevant statistical inconsistency was observed across the networks for the primary outcomes. Direct and indirect evidence were generally consistent within the network loops. However, for mouth irritation, a specific loop involving NRT gum, standard of care, and placebo showed signs of inconsistency. This may be explained by differences in follow-up durations: while most studies assessed outcomes at approximately 12 weeks [54,55,72], one study in the NRT gum vs placebo comparison reported adverse events at 6 weeks [76]. Such variation may have contributed to the inconsistency observed in the loop. In these cases, relying on direct comparisons is recommended for more robust interpretation.

A number of comparisons were informed by a limited number of trials and, in some cases, by studies with small sample sizes. This contributed to wide confidence intervals and increased imprecision in the estimated effects. Considering the cumulative impact of these limitations, including risk of bias and imprecision, the overall quality of the evidence was judged to be from low to very low, underscoring the need for more rigorously designed and transparently reported studies in future research.

Some differences emerged across the sensitivity analyses, particularly for the outcome “mouth irritation”. In a few comparisons (e.g., involving e-cig, NRT inhaler, and NRT gum), statistical significance varied depending on the inclusion or exclusion of studies at high risk of bias, short follow-up duration, or industry funding. These changes likely reflect the limited number of available studies and the wide confidence intervals observed in some estimates, rather than meaningful changes in effect direction. As such, these findings should be interpreted with caution and considered hypothesis-generating rather than conclusive. Overall, the general consistency across most comparisons supports the robustness of the primary analysis.

This systematic review and network meta-analysis has several methodological strengths. The study was conducted following a pre-registered and published protocol [33] and adhered to current best

practices, including comprehensive literature searches, rigorous risk of bias assessment, and evaluation of evidence certainty using CINeMA. Importantly, the network geometry was robust and well connected, with multiple direct comparisons across interventions, thereby strengthening the validity of indirect estimates and supporting the overall credibility of the findings. These elements enhance the reliability and clinical applicability of the results, despite the inherent limitations of the available evidence.

However, some limitations should be acknowledged. Firstly, comparisons involving some treatments, such as NRT tablets or snus were based on a very limited number of small-sample studies, which affected the robustness of the analysis and the quality of evidence. The lack of sufficient data for HTPs and nicotine pouches in the network meta-analysis is a major evidence gap given their increasing popularity. More and larger RCTs are needed to strengthen conclusions in these areas. Secondly, the quality of reporting on oral adverse events was generally low across several studies. Given that these products are administered orally, poor reporting may underestimate adverse effects and affect treatment acceptability, and the improvement of the reporting standards is therefore essential. A more detailed assessment of reporting quality of the trials included in this analysis will be addressed in a forthcoming publication. Our analysis focused on per-protocol data, which reflects the effect in participants who adhered to treatment; this may differ from intention-to-treat effects and could potentially underestimate harms if dropouts due to adverse events were imbalanced [100], though our discontinuation data did not strongly suggest this. To preserve transitivity assumption in the network meta-analysis, we excluded specific populations (e.g., pregnant women, individuals with mental or neurological disorders) and some pharmacological interventions [33]. Interestingly, not all NCNPs are universally licensed for use during pregnancy, and their safety profiles remain not fully established. Their potential impact on oral health remains an open area for future investigation. Finally, the results of this study are based on currently published literature and may change as new research becomes available. We intend to monitor the evidence and, if feasible, update the findings within the next three years.

Given the direct exposure of the oral cavity to non-combustible nicotine products, their impact on oral health deserves careful attention. This aspect is particularly relevant in dental settings, where professionals are in a strategic position to identify tobacco users and support cessation efforts [101], especially in patients at increased risk due to comorbidities [102]. However, many dentists report barriers such as lack of time, confidence, and training, which limit their engagement [103]. While no standardized guidelines for smoking cessation interventions in dental settings are currently available, the Fédération Dentaire Internationale (FDI) recommends brief structured models such as the 5A or 3A approach [104]. Training and the use of clear protocols could help dental professionals take into account product-specific aspects, such as potential oral adverse effects, in cessation strategies. This approach may lead to greater treatment acceptability and better patient outcomes. In addition, it is important to highlight that this review focused on assessing the local, medium-term effects of NCNPs on the oral cavity. Future research should include longer follow-up periods to evaluate potential long-term consequences, including structural or pathological changes in the oral mucosa over time. In parallel, active surveillance by dental professionals remains essential to detect and monitor possible long-term adverse effects in routine clinical practice.

Despite the limitations discussed, the findings of the present review may offer preliminary indications for guiding product selection when comparable safety profiles are observed. In such cases, patient preferences and individual needs could be considered. For instance, in individuals with pre-existing jaw disorders, it may be advisable to avoid NRT gum, as the repetitive chewing required for its use could potentially exacerbate symptoms. In these cases, alternative delivery methods, such as sprays or inhalers might be more suitable. Dental professionals are well positioned to support patients in selecting the most appropriate non-combustible nicotine product as part of a personalized cessation plan, also by monitoring potential oral adverse events during follow-up. Building on this role, future clinical guidelines could encourage the systematic integration of standardized, clinician-assessed oral health outcomes, complementing or, where appropriate, prioritizing over less standardized self-reporting into NCNP-based cessation programs, to further optimize patient outcomes and support product safety assessment.

5. Conclusions

This systematic review and network meta-analysis provides an updated synthesis of the available evidence on oral adverse effects associated with the use of non-combustible nicotine products. While NCNPs generally did not increase oral adverse events compared with placebo, some products were associated with higher rates of aphthous ulcers and mild, local irritation when compared with standard care, likely due to the physical mode of administration. Overall, the adverse events reported were mild, transient, and did not compromise treatment adherence. However, the quality of evidence was generally low, highlighting the need for better-designed trials with more rigorous and transparent reporting. In this context, dentists and oral health professionals can play a key role in supporting smoking cessation by guiding product selection and monitoring oral health during NCNP use. Oral health should be systematically monitored in cessation contexts, with dental professionals equipped with the necessary tools and training to address product-specific risks.

Funding

This work is supported by the Department of Clinical and Experimental Medicine (MEDCLIN), University of Catania (UPB: 6C725202048/2024) and by the Tobacco Harm Reduction Scholarship Programme (THRSP), delivered by Knowledge•Action•Change (K•A•C) as part of the 2024/25 funding cycle. MEDCLIN specifically contributed to covering publication fees. The THRSP awarded a research scholarship to Dr. Giusy Rita Maria La Rosa to support work in the field of tobacco harm reduction. The THRSP is implemented by K•A•C with support from a grant provided by Global Action to End Smoking (also known as the Foundation for a Smoke-Free World), an independent, U.S.-based nonprofit 501(c)(3) grant-making organization. The content, selection, and presentation of information in this work, as well as the views expressed, are the sole responsibility of the authors and should not be interpreted as representing the views or positions of the funders.

CRediT authorship contribution statement

Giusy Rita Maria La Rosa: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Cinzia Del Giovane:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Data curation. **Silvia Minozzi:** Writing – review & editing, Validation, Supervision, Software, Methodology, Data curation. **Jan Kowalski:** Writing – review & editing, Visualization, Validation, Data curation. **Iain Chapple:** Writing – review & editing, Visualization, Validation, Data curation. **Amaliya Amaliya:** Writing – review & editing, Visualization, Validation, Data curation. **Konstantinos Farsalinos:** Writing – review & editing, Visualization, Validation, Data curation. **Riccardo Polosa:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

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, SM, JK, IC, AA** and **KF** 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, Neuro-Search 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 E63C22000900006) and 341/2022 (CUP E63C22002080006), 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).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jdent.2025.105910.

References

[1] GBD 2019 Collaborators, Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019, Lancet 397 (10292) (2021) 2337–2360.

[2] T. Jerzyński, J. Harding, G.V. Stimson, Global survey of consumer organizations advocating for safer nicotine products, Public Health Chall. 2 (1) (2023).

[3] P. Caponnetto, D. Campagna, M. Maglia, F. Benfatto, R. Emma, M. Caruso, G. Caci, B. Busa, A. Pennisi, M. Ceracchi, M. Migliore, M. Signorelli, Comparing the effectiveness, tolerability, and acceptability of heated tobacco products and refillable electronic cigarettes for cigarette substitution (CEASEFIRE): randomized controlled trial, JMIR Public Health Surveill. 9 (2023) e42628.

[4] J.Y. Levett, K.B. Filion, P. Reynier, C. Prell, M.J. Eisenberg, Efficacy and Safety of E-cigarette use for smoking cessation: a systematic review and meta-analysis of randomized controlled trials, Am. J. Med. 136 (8) (2023) 804–813, e4.

[5] G.R.M. La Rosa, A. Di Stefano, D. Gangi, R. Emma, V. Fala, A. Amaliya, H. G. Yilmaz, R. Lo Giudice, S.A. Pacino, E. Pedulla, R. Gorska, J. Kowalski, R. Polosa, Dental plaque quantitation by light induced fluorescence technology in exclusive electronic nicotine delivery systems (ENDS) users, J. Dent. 147 (2024) 105223.

[6] D. Azzopardi, J. Ebajemito, M. McEwan, O.M. Camacho, J. Thissen, G. Hardie, R. Voisine, G. Mullard, Z. Cohen, J. Murphy, A randomised study to assess the nicotine pharmacokinetics of an oral nicotine pouch and two nicotine replacement therapy products, Sci. Rep. 12 (1) (2022) 6949.

[7] S. Miluna, R. Melderis, L. Briuka, I. Skadins, R. Broks, J. Kroica, D. Rostoka, The correlation of swedish snus, nicotine pouches and other tobacco products with oral mucosal health and salivary biomarkers, Dent. J. 10 (8) (2022) (Basel).

[8] A. Theodoulou, S.C. Chepkin, W. Ye, T.R. Fanshawe, C. Bullen, J. Hartmann-Boyce, J. Livingstone-Banks, A. Hajizadeh, N. Lindson, Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation, Cochrane Database Syst. Rev. 6 (6) (2023) CD013308.

[9] P. Hajek, A. Phillips-Waller, D. Przulj, F. Pesola, K.Myers Smith, N. Bisal, J. Li, S. Parrott, P. Sasieni, L. Dawkins, L. Ross, M. Goniewicz, Q. Wu, H.J. McRobbie, A randomized trial of E-cigarettes versus nicotine-replacement therapy, N. Engl. J. Med. 380 (7) (2019) 629–637.

[10] D. Kusonic, K. Bijelic, N. Kladar, B. Bozin, L. Torovic, B. Srdenovic Conic, Comparative health risk assessment of heated tobacco products versus conventional cigarettes, Subst. Use Misuse 58 (3) (2023) 346–353.

[11] J. Liu, J. Rensch, J. Wang, X. Jin, A. Vansickel, J. Edmiston, M. Sarkar, Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users, Psychopharmacology 239 (9) (2022) 2863–2873 (Berl).

[12] J. Liu, J.S. Edmiston, J. Wang, K.R. Milleman, J.L. Milleman, A.L. Yoder, M. Gogova, M.A. Sarkar, Oral health effects among adults switching from cigarettes to on!(R) nicotine pouches compared to those who continue smoking, Oral Health Prev. Dent. 23 (2025) 189–201.

[13] C. Hajat, E. Stein, L. Ramstrom, S. Shantikumar, R. Polosa, The health impact of smokeless tobacco products: a systematic review, Harm. Reduct. J. 18 (1) (2021) 123.

[14] E. Lunell, K. Fagerstrom, J. Hughes, R. Pendrill, Pharmacokinetic comparison of a novel non-tobacco-based nicotine pouch (ZYN) with conventional, tobacco-based Swedish Snus and American Moist Snuff, Nicotine Tob. Res. 22 (10) (2020) 1757–1763.

[15] F. Javed, F. Vohra, A.A. Al-Kheraif, H. Malmstrom, G.E. Romanos, Comparison of periodontal inflammatory conditions among habitual gutka chewers and betel quid chewers, Oral Dis. 21 (4) (2015) 437–442.

[16] N. Lindson, S.C. Chepkin, W. Ye, T.R. Fanshawe, C. Bullen, J. Hartmann-Boyce, Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation, Cochrane Database Syst. Rev. 4 (4) (2019) CD013308.

[17] K.Myers Smith, A. Phillips-Waller, F. Pesola, H. McRobbie, D. Przulj, M. Orzol, P. Hajek, E-cigarettes versus nicotine replacement treatment as harm reduction interventions for smokers who find quitting difficult: randomized controlled trial, Addiction 117 (1) (2022) 224–233.

[18] C.H. Chung, Y.H. Yang, T.Y. Wang, T.Y. Shieh, S. Warnakulasuriya, Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan, J. Oral Pathol. Med. 34 (8) (2005) 460–466.

[19] S. Gajendra, S. McIntosh, S. Ghosh, Effects of tobacco product use on oral health and the role of oral healthcare providers in cessation: a narrative review, Tob. Induc. Dis. 21 (2023) 12.

[20] F.R.M. Leite, G.G. Nascimento, F. Scheutz, R. Lopez, Effect of smoking on periodontitis: a systematic review and meta-regression, Am. J. Prev. Med. 54 (6) (2018) 831–841.

[21] M.A. Khan, T. Vichayanrat, Y. Ngoenwiwatkul, The association between smoking and smokeless tobacco use with dental caries among Pakistani patients, BMC Oral Health 24 (1) (2024) 723.

[22] C.L.C. Almeida-da-Silva, H. Matshik Dakafay, K. O'Brien, D. Montierth, N. Xiao, D.M. Ojcius, Effects of electronic cigarette aerosol exposure on oral and systemic health, Biomed. J. 44 (3) (2021) 252–259.

[23] P. Szumilas, A. Wilk, K. Szumilas, B. Karakiewicz, The effects of E-cigarette aerosol on oral cavity cells and tissues: a narrative review, Toxics 10 (2) (2022).

[24] G. Sivaramakrishnan, M. Alsobaiei, K. Sridharan, Oral side effects of locally delivered nicotine replacement therapy: a meta-analysis of randomized controlled trials, Int. J. Dent. Hyg. 21 (1) (2023) 3–17.

[25] G. Sivaramakrishnan, K. Sridharan, Nicotine replacement therapy and oral health: a network meta-analysis of adverse effects in randomized trials, Evid. Based. Dent. 26 (1) (2025) 68–69.

[26] M. Wallstrom, F. Nilsson, J.M. Hirsch, A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation, Addiction 95 (8) (2000) 1161–1171.

[27] K. Fagerstrom, L.E. Rutqvist, J.R. Hughes, Snus as a smoking cessation aid: a randomized placebo-controlled trial, Nicotine Tob. Res. 14 (3) (2012) 306–312.

[28] G. Joksic, V. Spasojevic-Tisma, R. Antic, R. Nilsson, L.E. Rutqvist, Randomized, placebo-controlled, double-blind trial of Swedish snus for smoking reduction and cessation, Harm. Reduct. J. 8 (2011) 25.

[29] R. Auer, A. Schoeni, J.P. Humair, I. Jacot-Sadowski, I. Berlin, M.J. Stuber, M. L. Haller, R.C. Tango, A. Frei, A. Strassmann, P. Bruggmann, F. Baty, M. Brutsche, K. Tal, S. Baggio, J. Jakob, N. Sambiagio, N.B. Hopf, M. Feller, N. Rodondi, A. Berthet, Electronic nicotine-delivery systems for smoking cessation, N. Engl. J. Med. 390 (7) (2024) 601–610.

[30] P. Caponnetto, D. Campagna, F. Cibella, J.B. Morjaria, M. Caruso, C. Russo, R. Polosa, EffiCiency and safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study, PLoS One 8 (6) (2013) e66317.

[31] K.E. Farsalinos, G. Romagna, D. Tsiapras, S. Kyrzopoulos, V. Voudris, Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers, Int. J. Environ. Res. Public Health 11 (4) (2014) 4356–4373.

[32] B. Hutton, G. Salanti, D.M. Caldwell, A. Chaimani, C.H. Schmid, C. Cameron, J. P. Ioannidis, S. Straus, K. Thorlund, J.P. Jansen, C. Mulrow, F. Catala-Lopez, P. C. Gotzsche, K. Dickersin, I. Boutron, D.G. Altman, D. Moher, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Ann. Intern. Med. 162 (11) (2015) 777–784.

[33] G.R.M. La Rosa, C. Del Giovane, E. Pedulla, J. Kowalski, I. Chapple, S. Minozzi, A. Amaliya, R. Polosa, Oral health effects of non-combustible nicotine products: protocol for a systematic review and network meta-analysis, Syst. Rev. 14 (1) (2025) 90.

[34] D.T. Tsoi, M. Porwal, A.C. Webster, Interventions for smoking cessation and reduction in individuals with schizophrenia, Cochrane Database Syst. Rev. 2013 (2) (2013) CD007253.

[35] R.M. van der Meer, M.C. Willemsen, F. Smit, P. Cuijpers, Smoking cessation interventions for smokers with current or past depression, Cochrane Database Syst. Rev. (8) (2013) CD006102.

[36] J. Lumley, C. Chamberlain, T. Dowswell, S. Oliver, L. Oakley, L. Watson, Interventions for promoting smoking cessation during pregnancy, Cochrane Database Syst. Rev. (3) (2009) CD001055.

[37] P. Marques, L. Piqueras, M.J. Sanz, An updated overview of e-cigarette impact on human health, Respir. Res. 22 (1) (2021) 151.
[38] J.M. Cameron, D.N. Howell, J.R. White, D.M. Andrenyak, M.E. Layton, J.M. Roll, Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions, Tob. Control 23 (1) (2014) 77–78.
[39] K.H. Thomas, M.N. Dalili, J.A. Lopez-Lopez, E. Keeney, D.M. Phillippo, M. R. Munafo, M. Stevenson, D.M. Caldwell, N.J. Welton, Comparative clinical effectiveness and safety of tobacco cessation pharmacotherapies and electronic cigarettes: a systematic review and network meta-analysis of randomized controlled trials, Addiction 117 (4) (2022) 861–876.
[40] M. Nakamura, A. Oshima, Y. Fujimoto, N. Maruyama, T. Ishibashi, K.R. Reeves, Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers, Clin. Ther. 29 (6) (2007) 1040–1056.
[41] J.A.C. Sterne, J. Savovic, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C. J. Cates, H.Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernan, S. Hopewell, A. Hrobjartsson, D.R. Junqueira, P. Juni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I. R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l4898.
[42] G. Filippini, S. Minozzi, F. Borrelli, M. Cinquini, K. Dwan, Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis, Cochrane Database Syst. Rev. 5 (5) (2022) CD013444.
[43] G. Salanti, Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool, Res. Synth. Methods 3 (2) (2012) 80–97.
[44] A.A. Veroniki, H.S. Vasiliadis, J.P. Higgins, G. Salanti, Evaluation of inconsistency in networks of interventions, Int. J. Epidemiol. 42 (1) (2013) 332–345.
[45] G. Salanti, A.E. Ades, J.P. Ioannidis, Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial, J. Clin. Epidemiol. 64 (2) (2011) 163–171.
[46] A. Nikolakopoulou, J.P.T. Higgins, T. Papakonstantinou, A. Chaimani, C. Del Giovane, M. Egger, G. Salanti, CINeMA: an approach for assessing confidence in the results of a network meta-analysis, PLoS Med. 17 (4) (2020) e1003082.
[47] V. Chiocchia, A. Nikolakopoulou, J.P.T. Higgins, M.J. Page, T. Papakonstantinou, A. Cipriani, T.A. Furukawa, G.C.M. Siontis, M. Egger, G. Salanti, ROB-MEN: a tool to assess risk of bias due to missing evidence in network meta-analysis, BMC Med. 19 (1) (2021) 304.
[48] V. Chiocchia, A. Holloway, G. Salanti, Semi-automated assessment of the risk of bias due to missing evidence in network meta-analysis: a guidance paper for the ROB-MEN web-application, BMC Med. Res. Methodol. 23 (1) (2023) 223.
[49] C.T. Bolliger, X. van Biljon, A. Axelsson, A nicotine mouth spray for smoking cessation: a pilot study of preference, safety and efficacy, Respiration 74 (2) (2007) 196–201.
[50] M.J. Carpenter, A.E. Wahlquist, J.L. Burris, K.M. Gray, E. Garrett-Mayer, K. M. Cummings, A.J. Alberg, Snus undermines quit attempts but not abstinence: a randomised clinical trial among US smokers, Tob. Control 26 (2) (2017) 202–209.
[51] A.G. Christen, J.L. McDonald Jr., B.L. Olson, C.A. Drook, G.K. Stookey, Efficacy of nicotine chewing gum in facilitating smoking cessation, J. Am. Dent. Assoc. 108 (4) (1984) 594–597.
[52] A.G. Christen, B.B. Beiswanger, M.E. Mallatt, C.E. Tomich, C.A. Drook, J. L. McDonald Jr., B.L. Olson, G.K. Stookey, Effects of nicotine-containing chewing gum on oral soft and hard tissues: a clinical study, Oral Surg. Oral Med. Oral Pathol. 59 (1) (1985) 37–42.
[53] J.S. Edmiston, K.M. Webb, J. Wang, D. Oliveri, Q. Liang, M. Sarkar, Biomarkers of exposure and biomarkers of potential harm in adult smokers who switch to e-vapor products relative to cigarette smoking in a 24-week, randomized, clinical trial, Nicotine Tob. Res. 24 (7) (2022) 1047–1054.
[54] M.J. Eisenberg, A. Hebert-Losier, S.B. Windle, T. Greenspoon, T. Brandys, T. Fulop, T. Nguyen, S. Elkouri, M. Montigny, I. Wilderman, O.F. Bertrand, J. A. Bostwick, J. Abrahamson, Y. Lacasse, S. Pakhale, J. Cabaussel, K.B. Filion, E. Investigators, Effect of e-cigarettes plus counseling vs counseling alone on smoking cessation: a randomized clinical trial, JAMA 324 (18) (2020) 1844–1854.
[55] S.P. Fortmann, J.D. Killen, M.J. Telch, B. Newman, Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford stop smoking project, JAMA 260 (11) (1988) 1575–1580.
[56] A.J. Garvey, T. Kinnunen, B.L. Nordstrom, C.H. Utman, K. Doherty, B. Rosner, P. S. Vokonas, Effects of nicotine gum dose by level of nicotine dependence, Nicotine Tob. Res. 2 (1) (2000) 53–63.
[57] E.D. Glover, P.N. Glover, M. Franzon, C.R. Sullivan, C.C. Cerullo, R.M. Howell, G. G. Keyes, F. Nilsson, G.R. Hobbs, A comparison of a nicotine sublingual tablet and placebo for smoking cessation, Nicotine Tob. Res. 4 (4) (2002) 441–450.
[58] J.M. Harackiewicz, L.W. Blair, C. Sansone, J.A. Epstein, R.N. Stuchell, Nicotine gum and self-help manuals in smoking cessation: an evaluation in a medical context, Addict. Behav. 13 (4) (1988) 319–330.
[59] C. Haziza, G. de La Bourdonnaye, A. Donelli, V. Poux, D. Skiada, R. Weitkunat, G. Baker, P. Picavet, F. Ludicke, Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 2.2 for 3 months (Part 1), Nicotine Tob. Res. 22 (4) (2020) 539–548.
[60] N. Herrera, R. Franco, L. Herrera, A. Partidas, R. Rolando, K.O. Fagerstrom, Nicotine gum, 2 and 4 mg, for nicotine dependence. A double-blind placebo-controlled trial within a behavior modification support program, Chest 108 (2) (1995) 447–451.
[61] A.I. Hjalmarson, Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study, JAMA 252 (20) (1984) 2835–2838.
[62] A. Hjalmarson, F. Nilsson, L. Sjostrom, O. Wiklund, The nicotine inhaler in smoking cessation, Arch. Intern. Med. 157 (15) (1997) 1721–1728.
[63] R. Holliday, P.M. Preshaw, V. Ryan, F.F. Sniehotta, S. McDonald, L. Bauld, E. McColl, A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis, Pilot Feasibility Stud. 5 (2019) 74.
[64] J.R. Hughes, S.W. Gust, R.M. Keenan, J.W. Fenwick, M.L. Healey, Nicotine vs placebo gum in general medical practice, JAMA 261 (9) (1989) 1300–1305.
[65] K. Jamrozik, G. Fowler, M. Vessey, N. Wald, Placebo controlled trial of nicotine chewing gum in general practice, Br. Med. J. Clin. Res. Ed. 289 (6448) (1984) 794–797.
[66] M.J. Jarvis, M. Raw, M.A. Russell, C. Feyerabend, Randomised controlled trial of nicotine chewing-gum, Br. Med. J. Clin. Res. Ed. 285 (6341) (1982) 537–540.
[67] E.J. Jensen, E. Schmidt, B. Pedersen, R. Dahl, Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation, Thorax 45 (11) (1990) 831–834.
[68] S.H. Lee, S.H. Ahn, Y.S. Cheong, Effect of electronic cigarettes on smoking reduction and cessation in Korean male smokers: a randomized controlled study, J. Am. Board. Fam. Med. 32 (4) (2019) 567–574.
[69] M. Nides, T. Danielsson, F. Saunders, R. Perfekt, R. Kapikian, J. Solla, S. J. Leischow, A. Myers, Efficacy and safety of a nicotine mouth spray for smoking cessation: a randomized, multicenter, controlled study in a naturalistic setting, Nicotine Tob. Res. 22 (3) (2020) 339–345.
[70] P.R. Nelson, P. Chen, D.R. Battista, J.L. Pillitteri, S. Shiffman, Randomized trial to compare smoking cessation rates of Snus, with and without smokeless tobacco health-related information, and a nicotine lozenge, Nicotine Tob. Res. 21 (1) (2019) 88–94.
[71] Q.R. Pack, D.E. Jorenby, M.C. Fiore, T. Jackson, P. Weston, M.E. Piper, T. B. Baker, A comparison of the nicotine lozenge and nicotine gum: an effectiveness randomized controlled trial, WMJ 107 (5) (2008) 237–243.
[72] S. Rungruanghiranya, C. Ekpanyaskul, Y. Hattapornsawan, Y. Tundulawessa, Effect of nicotine polyestex gum on smoking cessation and quality of life, J. Med. Assoc. Thai. 91 (11) (2008) 1656–1662.
[73] N.G. Schneider, M.E. Jarvik, A.B. Forsythe, L.L. Read, M.L. Elliott, A. Schweiger, Nicotine gum in smoking cessation: a placebo-controlled, double-blind trial, Addict. Behav. 8 (3) (1983) 253–261.
[74] N.G. Schneider, R. Olmstead, F. Nilsson, F.V. Mody, M. Franzon, K. Doan, Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial, Addiction 91 (9) (1996) 1293–1306.
[75] P. Tonnesen, V. Fryd, M. Hansen, J. Helsted, A.B. Gunnersen, H. Forchammer, M. Stockner, Two and four mg nicotine chewing gum and group counselling in smoking cessation: an open, randomized, controlled trial with a 22 month follow-up, Addict. Behav. 13 (1) (1988) 17–27.
[76] P. Tonnesen, V. Fryd, M. Hansen, J. Helsted, A.B. Gunnersen, H. Forchammer, M. Stockner, Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking, N. Engl. J. Med. 318 (1) (1988) 15–18.
[77] P. Tonnesen, J. Norregaard, K. Mikkelsen, S. Jorgensen, F. Nilsson, A double-blind trial of a nicotine inhaler for smoking cessation, JAMA 269 (10) (1993) 1268–1271.
[78] P. Tonnesen, H. Lauri, R. Perfekt, K. Mann, A. Batra, Efficacy of a nicotine mouth spray in smoking cessation: a randomised, double-blind trial, Eur. Respir. J. 40 (3) (2012) 548–554.
[79] H. Whelton, R. Kingston, D. O'Mullane, F. Nilsson, Randomized controlled trial to evaluate tooth stain reduction with nicotine replacement gum during a smoking cessation program, BMC Oral Health 12 (2012) 13.
[80] B. Rajan, J. Ahmed, N. Shenoy, C. Denny, R. Ongole, A. Binnal, Assessment of quality of life in patients with chronic oral mucosal diseases: a questionnaire-based study, Perm. J. 18 (1) (2014) e123–e127.
[81] M.D. Villanueva-Vilchis, P. Lopez-Rios, I.M. Garcia, L.A. Gaitan-Cepeda, Impact of oral mucosa lesions on the quality of life related to oral health. An etiopathogenic study, Med. Oral Patol. Oral Cir. Bucal. 21 (2) (2016) e178–e184.
[82] S. Hahnel, S. Schwarz, F. Zeman, L. Schafer, M. Behr, Prevalence of xerostomia and hyposalivation and their association with quality of life in elderly patients in dependence on dental status and prosthetic rehabilitation: a pilot study, J. Dent. 42 (6) (2014) 664–670.
[83] C.K. Tong, Y. Moayedi, E.A. Lumpkin, Merkel cells and keratinocytes in oral mucosa are activated by mechanical stimulation, Physiol. Rep. 12 (2) (2024) e15826.
[84] J. Chen, R. Ahmad, W. Li, M. Swain, Q. Li, Biomechanics of oral mucosa, J. R. Soc. Interface 12 (109) (2015) 20150325.
[85] C.C. Davis, C.A. Squier, G.E. Lilly, Irritant contact stomatitis: a review of the condition, J. Periodontol. 69 (6) (1998) 620–631.
[86] M.S. Werley, P. McDonald, P. Lilly, D. Kirkpatrick, J. Wallery, P. Byron, J. Venitz, Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs, Toxicology 287 (1–3) (2011) 76–90.
[87] T. Langston, J. Randazzo, U. Kogel, J. Hoeng, F. Martin, B. Titz, E. Guedj, T. Schneider, B. Prabhakar, J. Zhang, M. Oldham, K.M. Lee, Thirteen-week nose-only inhalation exposures of propylene glycol aerosols in Sprague Dawley rats with a lung systems toxicology analysis, Toxicol. Res. Appl. 5 (2021).

[88] S. Varughese, K. Teschke, M. Brauer, Y. Chow, C. van Netten, S.M. Kennedy, Effects of theatrical smokes and fogs on respiratory health in the entertainment industry, Am. J. Ind. Med. 47 (5) (2005) 411–418.
[89] G. Wieslander, D. Norback, T. Lindgren, Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects, Occup. Environ. Med. 58 (10) (2001) 649–655.
[90] A.S. Kienhuis, L.G. Soeteman-Hernandez, P.M. Bos, H.W. Cremers, W.N. Klerx, R. Talhout, Potential harmful health effects of inhaling nicotine-free shisha-pen vapor: a chemical risk assessment of the main components propylene glycol and glycerol, Tob. Induc. Dis. 13 (1) (2015) 15.
[91] R. Tabrizi, T. Karagah, E. Aliabadi, S.A. Hoseini, Does gum chewing increase the prevalence of temporomandibular disorders in individuals with gum chewing habits? J. Craniofac. Surg. 25 (5) (2014) 1818–1821.
[92] A. Batra, K. Klingler, B. Landfeldt, H.M. Friederich, A. Westin, T. Danielsson, Smoking reduction treatment with 4-mg nicotine gum: a double-blind, randomized, placebo-controlled study, Clin. Pharmacol. Ther. 78 (6) (2005) 689–696.
[93] F. Chapman, S. McDermott, K. Rudd, V. Taverner, M. Stevenson, N. Chaudhary, K. Reichmann, J. Thompson, T. Nahde, G. O'Connell, A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic, pharmacodynamic and safety and tolerability profiles of tobacco-free oral nicotine pouches relative to cigarettes, Psychopharmacology 239 (9) (2022) 2931–2943 (Berl).
[94] J. Rensch, J. Edmiston, J. Wang, X. Jin, M. Sarkar, A. Randomized, Controlled study to assess changes in biomarkers of exposures among adults who smoke that switch to oral nicotine pouch products relative to continuing smoking or stopping all tobacco use, J. Clin. Pharmacol. 63 (10) (2023) 1108–1118.
[95] G.H. Guyatt, A.D. Oxman, G. Vist, R. Kunz, J. Brozek, P. Alonso-Coello, V. Montori, E.A. Akl, B. Djulbegovic, Y. Falck-Ytter, S.L. Norris, J.W. Williams Jr., D. Atkins, J. Meerpohl, H.J. Schunemann, GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias), J. Clin. Epidemiol. 64 (4) (2011) 407–415.
[96] A.W. Chan, A. Hrobjartsson, Promoting public access to clinical trial protocols: challenges and recommendations, Trials 19 (1) (2018) 116.
[97] O.M. Bezzina, P. Gallagher, S. Mitchell, S.J. Bowman, B. Griffiths, V. Hindmarsh, B. Hargreaves, E.J. Price, C.T. Pease, P. Emery, P. Lanyon, M. Bombardieri, N. Sutcliffe, C. Pitzalis, J. Hunter, M. Gupta, J. McLaren, A.M. Cooper, M. Regan, I.P. Giles, D.A. Isenberg, V. Saravanan, D. Coady, B. Dasgupta, N.J. McHugh, S. A. Young-Min, R.J. Moots, N. Gendi, M. Akil, K. MacKay, W.F. Ng, L.J. Robinson, U.K.P.S.S.S. Registry, subjective and objective measures of dryness symptoms in primary Sjogren's syndrome: capturing the discrepancy, Arthritis Care Res. 69 (11) (2017) 1714–1723 (Hoboken).
[98] S. Ishimoto, K. Tsunoda, Y. Fujimaki, K. Okada, Y. Saito, M. Kinoshita, N. Takeuchi, Objective and non-invasive evaluation of dry mouth, Auris Nasus Larynx 35 (1) (2008) 89–93.
[99] A. Kojima, D. Ekuni, S. Mizutani, M. Furuta, K. Irie, T. Azuma, T. Tomofuji, Y. Iwasaki, M. Morita, Relationships between self-rated oral health, subjective symptoms, oral health behavior and clinical conditions in Japanese university students: a cross-sectional survey at Okayama University, BMC Oral Health 13 (2013) 62.
[100] S.K. Gupta, Intention-to-treat concept: a review, Perspect. Clin. Res. 2 (3) (2011) 109–112.
[101] J. Kowalski, G.R.M. La Rosa, A. Di Stefano, D. Gangi, V. Sahni, H.G. Yilmaz, V. Fala, R. Gorska, F.S. Ludovichetti, A. Amaliya, D. Alghalayini, M. Raganin, I. Chapple, B.I. Kim, R. Polosa, Navigating the dual burden of dental and periodontal care in individuals who also smoke: an expert review, J. Dent. 157 (2025) 105744.
[102] G.R.M. La Rosa, E. Pedulla, I. Chapple, J. Kowalski, M. Walicka, S. Piro, R. Polosa, A systematic review of oral health outcomes following smoking cessation in type 2 diabetes: clinical and research implications, J. Dent. 156 (2025) 105665.
[103] D. Goel, P.K. Chaudhary, A. Khan, B. Patthi, A. Singla, R. Malhi, R.S. Gambhir, Acquaintance and approach in the direction of tobacco cessation among dental practitioners-a systematic review, Int. J. Prev. Med. 11 (2020) 167.
[104] H.S. Sandhu, A practical guide to tobacco cessation in dental offices, J. Can. Dent. Assoc. 67 (3) (2001) 153–157.