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Xerostomia among users of electronic nicotine delivery systems in a multinational web-based cross-sectional study

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Abstract

The use of electronic nicotine delivery systems (ENDS) has increased globally. Evidence of the association between Xerostomia and ENDS remains limited. We evaluated the association between nicotine product use and xerostomia severity in a multinational sample from the Middle East and North Africa (MENA) region. In this cross-sectional study, adults aged 18–40 years from 18 MENA countries were recruited via convenience sampling through social media platforms between December 2023 and March 2024. Xerostomia symptoms were assessed using the Xerostomia Inventory (XI). Directed acyclic graphs guided confounder selection. Regression models examined the association between nicotine product use and xerostomia symptom scores. Among 11,451 participants (6,975 [60.9%] non-users, 1,913 [16.7%] exclusive ENDS users, 1,778 [15.5%] exclusive combustible tobacco users, and 785 [6.9%] dual users), all current-use categories were associated with higher XI scores than non-use after adjustment for age, sex, and exercise frequency: exclusive ENDS users (standardised $\beta = 0.385$; $p < 0.001$), exclusive combustible tobacco users ($\beta = 0.201$; $p < 0.001$), and dual users ($\beta = 0.324$; $p < 0.001$). Current use of any nicotine product was associated with higher xerostomia scores than non-use, with the strongest associations observed among exclusive ENDS users and dual users.

Keywords: Electronic nicotine delivery systems; Vaping; Smoking; Xerostomia; Cross-sectional studies

Introduction

Xerostomia is the patient-reported subjective sensation of oral dryness; it is related to but conceptually distinct from hyposalivation, the objective reduction of salivary flow measured by sialometry. The two are correlated but not interchangeable: xerostomia can be reported in the absence of measurable hyposalivation, and conversely, some individuals with reduced salivary flow do not report dryness [1]. The consequences of xerostomia include discomfort, impaired oral functions, and increased risk of dental caries [2]. Established risk factors for xerostomia include increasing age, female sex (particularly during menopause), Sjögren's syndrome and other autoimmune conditions, diabetes mellitus, and polypharmacy with xerostomagenic agents such as anticholinergics, antidepressants, and antihypertensives. Lifestyle exposures, including the use of electronic nicotine delivery systems (ENDS), have also been hypothesised to contribute, although the evidence base for the ENDS–xerostomia relationship remains observational and incomplete [1,3].

The tobacco epidemic is one of the most significant public health threats the world has ever encountered, resulting in the deaths of millions every year[4]. Historically, from the late 19th century through the 1930s, tobacco was promoted as a healthy or even doctor-endorsed habit, a perception that persisted until epidemiological evidence and subsequent regulation unequivocally exposed its harm [5].

In a striking parallel, electronic nicotine delivery systems (ENDS) have recently emerged as a rapidly spreading global phenomenon. Initially positioned as a smoking cessation aid for adults, e-cigarettes were marketed with claims of reduced harm relative to traditional tobacco cigarettes.

This strategy, reminiscent of tobacco promotion in the early 20th century, has facilitated their widespread acceptance among both smokers and non-smokers alike [6].

ENDS depends on batteries to heat the liquid, which contains nicotine and other toxins. During this heating process, potentially dangerous decomposition products may form [6,7].

Because of the absence of combustion, which is responsible for many of the harmful effects of conventional smoking, ENDS are often perceived as safer than conventional cigarettes [8].

In 2021, the number of e-cigarette users was estimated at 83 million globally [9]. Alarmingly, the use of e-cigarettes increased sharply during the last few years, especially among adolescents, although there is a notable acceptance among other age groups in both men and women [9,10]. One of the main motivators behind adolescents to use ENDS is the variety of flavors available in e-liquids, such as mint, fruit, or candy [7]. Notably, e-cigarettes have only been widely available for approximately 15 years, limiting the ability to conduct long-term safety studies [7].

While tobacco smoking has well-established adverse effects on oral health, the evidence base for ENDS-related oral health consequences remains comparatively limited [11]. A recent systematic review of oral microbiome changes in ENDS users reports that ENDS exposure is associated with shifts in the relative abundance of cariogenic and periodontopathogenic bacteria; these shifts may, in turn, alter the local mucosal environment in ways relevant to dry-mouth perception [11]. Additional recent primary studies report a range of adverse oral health consequences associated with ENDS use, including periodontal and mucosal alterations [12–14]. Insufficient saliva production can cause difficulties with swallowing, chewing, and speaking, as well as altered taste, oral mucosa dryness, tongue inflammation, and halitosis [15,16].

Although some studies have investigated oral symptoms among ENDS users, data on xerostomia are still limited, and most of the studies have been conducted among students [17,18]. Given the increasing use of ENDS and the potential for oral health consequences, there is an urgent need for robust, multi-center studies to assess xerostomia among ENDS users. Understanding this relationship is critical for clinicians, public health officials, and policymakers to develop targeted interventions and inform regulatory decisions.

The assessment of xerostomia presents challenges, not only because it relies on patient-reported outcomes but also due to the variety of questions that can be employed [19].

In this multinational cross-sectional analysis, we test whether the severity of self-reported xerostomia among users of nicotine products , specifically exclusive ENDS users, exclusive combustible tobacco users, and dual users , differs from that observed in non-users of nicotine products, in a young-adult sample drawn from the MENA region. We hypothesized that xerostomia severity differs between users of one or more nicotine product categories and non-users, without specifying the direction of any difference a priori.

Methods

Study design, setting, and participants

We conducted a multinational cross-sectional study across 18 countries in the Middle East and North Africa (MENA) region (Supplementary Table S1) between December 28, 2023, and March 13, 2024. Eligible participants were adults aged between 18 and 40 years who resided in one of the participating countries and were able to read and respond to the survey in Arabic. The age range was selected to minimize confounding from age-related xerostomia and medication use, while focusing on the demographic most actively engaged in ENDS use. Participants were not excluded on the basis of physical or psychiatric comorbidities, or medications, in order to retain a representative young-adult sample; instead, all such variables were modelled as covariates in extended-adjustment and exclusion-based sensitivity analyses. Individuals who did not meet the inclusion criteria were excluded from the study. The study was reported in accordance with the STROBE reporting guidelines (Supplementary Table S2).

Participants were classified into four mutually exclusive exposure groups based on current and past use of nicotine products. Non-users were participants who reported never using combustible tobacco products or ENDS, or who were former users of either or both products and had ceased use at least one month prior to the survey. Exclusive ENDS users were participants who currently used any form of ENDS (e-cigarettes, mods, pods, e-hookah, e-pipes, or other vaping devices) but had never used combustible tobacco or were former combustible tobacco users who had ceased use at least one month prior to the survey. Exclusive combustible tobacco users were participants who currently used any form of combustible tobacco products (cigarettes,

hookah/waterpipe, cigars, pipes, or heated-tobacco products) but had never used ENDS or were former ENDS users who had ceased use at least one month prior to the survey. Dual users were participants who reported current use of both ENDS and combustible tobacco products. The survey did not capture smokeless tobacco use.

The one-month cessation criterion was selected to be consistent with the operational definitions used in prior cross-sectional studies of nicotine product use [20,21], while recognising that physiological recovery from prior product use may not be complete by one month. To assess whether this pragmatic cutoff biased the principal analysis, a sensitivity analysis restricted to participants with no history of nicotine product use other than their current product was performed.

Ethical considerations and approval

Informed consent was obtained electronically from all participants prior to survey initiation, with the option to withdraw at any stage without any consequences. The study was conducted in accordance with the principles of the Declaration of Helsinki [22]. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Benha University, Egypt (REC-FOMBU), under registration number RC.34.11.2023.

Data collection tools and procedures

Data collection was conducted through a self-administered online survey, developed in Arabic using Google Forms. This survey was disseminated by a network of collaborators using a convenience-sampling approach with snowballing through study collaborators across various social media platforms, including Facebook, Instagram, Snapchat, Twitter, WhatsApp, Telegram,

and email. Collaborators were recruited from each participating country to facilitate its widespread distribution. To specifically target ENDS users, data collectors shared information about the study within dedicated online groups and communities. Interested individuals underwent eligibility screening, and those who met the inclusion criteria were then provided with a direct link to the survey. To ensure data integrity and reduce the risk of manipulation, the Google Form was restricted to accept a single submission per participant. In addition, all responses were carefully reviewed, and entries deemed suspicious — defined a priori as incomplete questionnaires, repetitive or identical answer patterns — were excluded from the analysis.

The survey was composed of three sections. The first section, focused on socio-demographic and medical history details and included questions about age, sex, country of residence, and anthropometric measurements for calculating body mass index (BMI), whereas medical history questions covered physical and psychiatric comorbidities, sleep deprivation, and medication usage, in addition to lifestyle factors include exercise frequency, average daily water intake, frequent consumption of caffeinated drinks such as coffee and tea, and frequent alcohol consumption.

The second section included questions about the participants' nicotine product use. For each product (combustible tobacco and ENDS), the survey captured current and former use status, duration of current use (in years), and frequency of current use. For ENDS users, frequency was operationalised as puffs per hour and hours of use per day; daily puffs were derived as the product of these two items. For cigarette smokers specifically, the survey captured cigarettes per day and years of smoking, allowing computation of a smoking index.

The third section included an 11-item Xerostomia Inventory (XI) questionnaire [23]. The questionnaire comprised eleven subjective symptom questions to assess the severity of xerostomia, with response options ranging from "never" to "very often." Among these, five questions pertained to the sensation of dryness experienced in the mouth, nose, lips, and skin. Additionally, the inventory includes three questions to assess difficulties in swallowing and an equal number of items to explore various methods employed by patients to alleviate mouth dryness [23]. The Arabic adaptation of the XI followed a forward–backward translation protocol consistent with the WHO guidelines for instrument adaptation [24]. Two independent bilingual translators (a clinical researcher fluent in medical English and Arabic, and a native-Arabic-speaking health professional) produced independent forward translations from English to Arabic. A reconciliation meeting harmonised the two forward versions into a single consensus draft. A second pair of bilingual translators, blind to the original instrument, produced independent back-translations from the consensus Arabic version into English. Discrepancies between the back-translation and the original were reviewed by the bilingual study team and resolved by consensus, with three items requiring minor rephrasing for cultural and linguistic equivalence (specifically, items 6, 9, and 11) (Supplementary Table S3).

Apart from the XI described above, all other items in the questionnaire were investigator-developed direct questions of the form standardly used in epidemiological surveys (for example, "What is your average daily water intake?"); these items, by design, do not require the kind of psychometric validation that applies to multi-item symptom inventories[25–27].

Sample size and sampling

The primary objective of this study was to assess differences in xerostomia severity between nicotine product users and non-users. To determine the necessary sample size, estimations were based on findings from Alhaj et al. [28], who reported a 33.3% prevalence of xerostomia among exclusive e-cigarette users. Utilizing Epi Info software (version 7.2.5.0), and assuming a 5% margin of error, a design effect of 1.5 (to account for the non-random sampling approach), and a 95% confidence level, a minimum sample size of 512 participants was calculated. Ultimately, a total of 11,451 participants were enrolled through convenience sampling, which substantially exceeded this calculated minimum. This larger sample size ensured adequate statistical power to detect smaller effect sizes and supported the sensitivity analyses.

Statistical analysis

Data were exported from Google Forms into Microsoft Excel and translated from Arabic to English.

The data were analyzed using Jamovi software, version 2.3.2 for Windows. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages (%). The linear-model one-way analysis of variance was used to compare continuous variables across nicotine product use categories, and Pearson's chi-squared tests were used for categorical variables.

Multivariable linear regression analysis examined the association between product usage and xerostomia, while multivariable ordinal logistic regression models assessed the relationship between product usage status and individual XI items. To systematically identify variables for inclusion in these regression analyses, a Directed Acyclic Graph (DAG) was constructed,

prioritizing established theoretical relationships over data-driven selection. This DAG was developed using DAGitty software (Theoretical Biology & Bioinformatics Group, University of Utrecht, http://dagitty.net) to visualize the specified associations. In this analysis, nicotine product use was designated as the exposure variable, with xerostomia serving as the outcome of interest. The potential relationships among all study variables were specified in advance based on existing literature and clinical reasoning, with each variable explicitly classified as a confounder, mediator, or non-confounder (Supplementary Figure S1). Variables judged to be on the causal pathway from nicotine product use to xerostomia (i.e., descendants of nicotine use that are also ancestors of xerostomia, including BMI, caffeine intake, sleep deprivation, physical and psychiatric comorbidities, and medication use) were classified as mediators rather than confounders, and were therefore not included in the primary adjustment set, since conditioning on a mediator partially blocks the causal pathway and biases the total-effect estimate [29,30]. Average daily water intake was conceptualised as a behavioural response to perceived oral dryness rather than as a determinant of xerostomia; it was therefore not included in the DAG as a covariate and was instead examined separately as a secondary outcome (Supplementary Table S4). The minimally sufficient adjustment set, confirmed by the DAGitty software, comprised age, sex, and physical exercise frequency.

To examine the robustness of the principal estimates, six additional sensitivity analyses were performed. (i) An extended-adjustment model that additionally included BMI, caffeine consumption, alcohol consumption, sleep deprivation, physical comorbidities, psychiatric comorbidities, and medication use, with country of residence included as fixed effects (Supplementary Table S5). (ii) Restriction to participants with no history of any nicotine product use other than their current product (i.e., excluding all former users) (Supplementary Table S5).

(iii) Exclusion of all current medication users (Supplementary Table S5). (iv) Exclusion of all participants reporting any physical comorbidity (Supplementary Table S5). (v) Sex-stratified analysis with formal testing of the product use × sex interaction (Supplementary Table S6). (vi) Dose-response analyses among current users: linear regression of XI score on duration of ENDS use and on daily puffs (both continuous) within current ENDS users; linear regression of XI score on duration of combustible tobacco use within current combustible tobacco users; and linear regression of XI score on a smoking index within the current cigarette-smoker subset (Supplementary Table S7). All sensitivity analyses retained the principal adjustment set unless otherwise specified.

We additionally performed binomial logistic regression of xerostomia case status, defined using the cutoff XI ≥ 24 derived in a recent ROC-validated study against an objective sialometric reference [31]. Results are reported in Supplementary Table S8.

For linear models, standardised β coefficients with 95% confidence intervals were reported, and for binomial logistic regression and ordinal logistic regression models, adjusted odds ratios (AOR) with 95% confidence intervals were reported. All P values and 95% confidence intervals (95% CI) were two-sided, with a p-value <0.05 considered statistically significant. Missingness was minimal across the variables analysed: per-variable rates ranged from 0.32% to 1.57%, with other variables having complete data. For continuous variables, missing values were imputed once with the variable median prior to analysis. For categorical variables, uncertain or off-category responses were retained as a separate analytic category rather than imputed. None of the variables in the principal adjustment set (age, sex, exercise frequency), the principal exposure (product use category), or the outcome (XI items) had any missing data.

We used the initial 50 responses as a pilot test to evaluate the reliability of the Arabic version of the XI questionnaire. Data from this pilot assessment were excluded from the final analysis.

Results

Reliability analysis for the translated version of the Xerostomia Inventory questionnaire

Reliability analysis was done to test the reliability of the translated version of the Xerostomia Inventory questionnaire, and it yielded a Cronbach's α of 0.84, indicating a high level of internal consistency.

Sample characteristics

The analysis included a total of 11,451 participants, categorized by their nicotine product use habits: 6,975 (60.9%) were non-users, 1,913 (16.7%) were exclusive ENDS users, 1,778 (15.5%) were exclusive combustible tobacco users, and 785 (6.9%) were dual users (Table 1). Among non-users (n = 6,975), 6,202 (88.9%) had never used any nicotine product; the remaining 773 (11.1%) were former users (243 [3.5%] former ENDS only, 352 [5.0%] former combustible tobacco only, and 178 [2.6%] former users of both products). Among exclusive ENDS users (n = 1,913), 1,208 (63.1%) had no history of combustible tobacco use, and 705 (36.9%) reported prior combustible tobacco use. Among exclusive combustible tobacco users (n = 1,778), 1,430 (80.4%) had no history of ENDS use, and 348 (19.6%) reported prior ENDS use. All 785 dual users were current concurrent users of both products. The overall mean age of the sample was 25.3 years (SD = 5.3). Notably, exclusive ENDS users (mean age 26.0 years) and combustible tobacco users (mean age 26.6 years) were significantly older on average compared to non-users (mean age 24.8 years, $p < 0.001$). A significantly higher proportion of males was observed among ENDS users (76.6%), combustible tobacco users (79.8%), and dual users (79.6%)

compared to non-users (44.8%, $p < 0.001$), with females being most represented among non-users (55.2%). Regarding body mass index (BMI), exclusive ENDS users had a significantly higher mean BMI (25.5 kg/m²) compared to non-users (24.6 kg/m²), with the total sample mean being 24.9 kg/m² ($p < 0.001$). Significant variations in exercise patterns were observed across groups ($p < 0.001$). While approximately 40% of participants across all categories reported no weekly exercise, a greater proportion of ENDS users (5.6%) engaged in more than five exercise sessions per week compared to non-users (3.8%). Physical comorbidities were reported less frequently by ENDS users (4.9%) than by non-users (9.1%) and combustible tobacco users (7.3%) ($p < 0.001$). Psychiatric comorbidities were present in 2.9% of the overall cohort, with no significant difference observed between ENDS users (2.4%) and non-users (2.9%) ($p = 0.237$).

Associations between xerostomia and nicotine product use

In the unadjusted regression model (Table 2), all categories of nicotine product use were significantly associated with higher XI scores when compared to non-users. These associations remained significant even after adjusting for potential confounders such as age, sex, and exercise frequency (Table 2). In the adjusted model, exclusive ENDS users had significantly higher XI scores than non-users (β: 0.385; 95% CI: 0.334, 0.437; $p<0.001$), as did exclusive combustible tobacco users (β: 0.201; 95% CI: 0.147, 0.255; $p<0.001$), and dual users (β: 0.324; 95% CI: 0.249, 0.398; $p<0.001$), compared to non-users. In addition, exclusive ENDS users exhibited a significantly higher daily water intake compared to non-users (β: 0.132; 95% CI: 0.082, 0.181; $p<0.001$) (Supplementary Table S4).

Robustness across sensitivity analyses

The principal association between current ENDS use and higher XI scores was preserved across every additional sensitivity analysis (Supplementary Table S5). In the extended-adjustment model, which additionally included BMI, caffeine consumption, alcohol consumption, sleep deprivation, physical comorbidities, psychiatric comorbidities, medication use, and country of residence, the standardised ENDS coefficient attenuated to 0.302 (95% CI 0.249 to 0.354).

In the analysis restricted to participants with no history of nicotine product use other than their current product (n = 9,625), the principal estimate became larger rather than smaller (ENDS std β = 0.549, 95% CI 0.487 to 0.611, $p < 0.001$). Excluding all current medication users (n excluded = 1,002; remaining n = 10,449) yielded ENDS std β = 0.408 (95% CI 0.354 to 0.461). Excluding all participants reporting any physical comorbidity (n excluded = 920; remaining n = 10,531) yielded ENDS std β = 0.412 (95% CI 0.359 to 0.465). Both restrictions slightly strengthened rather than weakened the principal estimate.

In the secondary binary classification analysis using the cutoff XI ≥ 24, all three product-use categories were significantly associated with greater odds of xerostomia case status compared with non-users in the primary adjusted model (exclusive ENDS use AOR 1.65, 95% CI 1.46 to 1.87; exclusive combustible tobacco use AOR 1.53, 95% CI 1.35 to 1.75; dual use AOR 1.59, 95% CI 1.33 to 1.91; all $p < 0.001$), with a similar pattern in the extended-adjustment model (Supplementary Table S8). The binary analysis showed the same ranking of effect sizes (ENDS > dual > combustible tobacco) and the same attenuation pattern under extended adjustment as the principal continuous analysis.

Sex-specific associations

The product use × sex interaction term was statistically significant for the ENDS contrast (interaction std β = −0.194, 95% CI −0.309 to −0.080, p < 0.001), indicating effect modification by sex. In sex-stratified models adjusted for age and exercise frequency, the ENDS-non-user contrast was substantially larger among female participants (n = 4,820; std β = 0.533, 95% CI 0.436 to 0.630, p < 0.001) than among male participants (n = 6,631; std β = 0.327, 95% CI 0.265 to 0.389, p < 0.001). The corresponding extended-adjustment estimates were 0.474 (95% CI 0.375 to 0.573) for females and 0.251 (95% CI 0.188 to 0.314) for males. The interaction was not statistically significant for the combustible tobacco or dual-use contrasts (interaction p = 0.631 and p = 0.265, respectively) (Supplementary Table S6).

Dose-response analyses

Among current ENDS users (n = 1,208), each additional year of ENDS use was associated with a higher XI score (adjusted β = 1.14 per year, std β = 0.258, 95% CI 0.203 to 0.313, p < 0.001), and daily puffs were independently associated with the XI score (adjusted β = 0.0016 per puff, std β = 0.057, 95% CI 0.001 to 0.113, p = 0.047). Among current combustible tobacco users (n = 1,372), duration of tobacco use was associated with higher XI scores (adjusted β = 0.16 per year, std β = 0.093, 95% CI 0.024 to 0.162, p = 0.008). For current cigarette smokers specifically (n = 675), the smoking index showed a similar graded relationship with XI scores (adjusted std β = 0.129, 95% CI 0.043 to 0.216, p = 0.003) (Supplementary Table S7).

Item-Level Analysis of Xerostomia Inventory

To explore the association between nicotine product use and specific xerostomia symptoms, individual items of the XI were analyzed using ordinal logistic regression. This analysis was

adjusted for age, sex, and exercise frequency. Exclusive ENDS users exhibited significantly higher odds of reporting oral dryness across most functional items (Table 3). Specifically, they were more likely to report sipping liquids to aid swallowing (AOR = 1.56, 95% CI: 1.42–1.71, $p < 0.001$) and experiencing a dry mouth while eating (AOR = 2.09, 95% CI: 1.90–2.30, $p < 0.001$). Furthermore, ENDS use was significantly associated with the global symptom of "my mouth feels dry" (AOR = 2.02, 95% CI: 1.84–2.22, $p < 0.001$), and these users were more prone to needing to suck on sweets or cough lozenges for relief. Dual users also reported higher odds of difficulty with swallowing dry or certain foods (AOR = 1.30, 95% CI: 1.13–1.49, $p < 0.001$) and showed a similar association with needing lozenges for dryness.

Discussion

In this cross-sectional multinational study, which involved participants from 18 countries across the MENA region, current use of any nicotine product was associated with higher self-reported xerostomia symptom scores than non-use; the magnitude of the association was numerically largest for exclusive ENDS users, intermediate for dual users, and smallest for exclusive combustible tobacco users. The principal association was robust across multiple sensitivity analyses, was attenuated but preserved upon adjusting for hypothesised mediators (consistent with the specified DAG), and was substantially larger in female than in male participants.

The mechanisms outlined below are drawn from in vitro, animal, and human studies. None has been confirmed in humans through prospective experimental designs of ENDS exposure, and we therefore present them as candidate explanations for the observed associations rather than as established causal pathways.

Several mechanisms have been proposed to link ENDS use to xerostomia. Nicotine, which is present in both tobacco and ENDS liquid, affects salivary gland production by stimulating sympathetic activity and inducing glandular vasoconstriction, leading to reduced blood flow and consequently decreased salivary output [32–34]. Vaping can change salivary pH and oral microbial ecology. These changes can worsen salivary gland health, increasing saliva's viscosity and diminishing its lubricating capacity [35,36]. Compared to combustible tobacco, ENDS deliver nicotine more efficiently and often in higher concentrations [37,38]. The effect of nicotine in ENDS has been shown to increase salivary viscosity [36]. Moreover, the widespread use of nicotine salts in modern e-cigarettes allows for smoother inhalation and faster systemic

absorption than free-base nicotine [39,40], resulting in higher plasma nicotine peaks that can exacerbate salivary suppression.

Furthermore, the humectant properties of propylene glycol (PG) and vegetable glycerin (VG) used in ENDS liquid—both of which are hygroscopic, meaning they attract and retain water molecules from their surroundings—may contribute to mucosal dehydration. These compounds attract and absorb moisture from the oral cavity, disrupting the thin salivary film that coats the mucosa and may lead to a persistent feeling of mouth dryness [7,18]. In this study, exclusive ENDS users reported higher daily consumption of water compared to non-users. One study observed that ENDS users reported higher daily consumption of water [41], which may be attributed to xerostomia. Unlike tobacco smoke, which can transiently trigger reflex salivation due to irritant components, ENDS aerosols lack such stimuli while simultaneously dehydrating oral surfaces, leading to an exacerbated feeling of dry mouth [42]. This dual effect, suppression of glandular secretion and evaporation of existing moisture, may help explain the greater xerostomia observed among exclusive ENDS users in this and other observational studies.

In addition, the thermal and chemical properties of ENDS vapor may contribute to glandular dysfunction. Aerosol temperatures have been reported to reach up to 250°C[43], potentially causing mild thermal injury to the oral mucosa. Moreover, high operating temperatures promote the formation of reactive aldehydes such as formaldehyde, acrolein, and acetaldehyde, which induce oxidative stress and irritate epithelial cells, impairing mucin secretion and the protective salivary barrier [44].

Cross-sectional and in vitro evidence suggest that exposure to ENDS vapor alters the oral microbiome and induces subclinical inflammation, both of which may negatively affect salivary

gland performance and mucosal hydration [45]. Together, these mechanisms highlight that xerostomia in ENDS users may arise from a combination of nicotine-induced hyposecretion, hygroscopic dehydration, oxidative injury, and microbial imbalance, rather than a single factor alone [46].

Although tobacco smoking also reduces salivary flow [32], the mechanisms differ in intensity and pattern. Combustion products and heat from cigarette smoke can damage oral tissues but may simultaneously provoke transient salivary stimulation as a defensive reflex. In contrast, ENDS aerosols, with their hygroscopic components and smoother inhalation properties, tend to suppress salivation without inducing compensatory reflexes. Moreover, e-cigarette users adjust their inhalation patterns to achieve desired nicotine levels, which inherently increases exposure duration and frequency and cumulative exposure of oral tissues to drying agents [47]. These mechanistic differences may help explain why XI scores were highest among exclusive ENDS users in our study, followed by dual users and exclusive combustible tobacco users.

Our cross-sectional findings can be considered alongsidea recent network meta-analysis that synthesised randomised controlled trial and observational data on dry mouth across nicotine products [48]. The meta-analytic evidence is broadly consistent with our finding that nicotine product use is associated with greater xerostomia symptoms. Compared with the trial-level evidence base reviewed in that meta-analysis, the present study contributes large-sample observational data from a population (young adults in MENA countries) that is under-represented in the trials. We acknowledge, however, that the absence of randomisation, longitudinal follow-up, and objective sialometry imposes important limits on what can be inferred about the magnitude or causal direction of any product-specific effect.

The ENDS-xerostomia association was approximately 60% larger in female than in male participants, an effect-modification pattern that was not observed for combustible tobacco or dual use. Several biological mechanisms may contribute. Women have lower baseline salivary flow rates than men across the lifespan [49]; sex hormones, including estrogen, modulate salivary gland function through receptors expressed in salivary tissue [1,50]; and women may therefore lie closer to the symptomatic threshold at baseline, such that any additional xerostomic exposure produces a more pronounced shift in symptom scores. Behavioural differences in ENDS use patterns by sex (device preference, e-liquid composition) may also contribute. These findings warrant confirmation in independent samples and prospective designs [51].

Several studies indicate a higher prevalence of xerostomia and related oral dryness symptoms among ENDS users compared with non-smokers and, in some cases, combustible tobacco users [11,35,52]. Multinational data among dental students demonstrated a slightly higher prevalence of xerostomia in e-cigarette users than in combustible tobacco users [11]. In addition, clinical and cytological investigations demonstrated significantly higher rates of dry mouth, oral stickiness, white discoloration of the buccal mucosa, and marked cytomorphological alterations among e-cigarette users compared with non-smokers, suggesting adverse effects of e-cigarette aerosols on salivary function and oral mucosal health [35].

Some population-based and cross-sectional studies suggest that both cigarettes and e-cigarettes are independently associated with xerostomia. Evidence shows that recent and daily use of cigarettes, e-cigarettes, or cannabis increases the odds of xerostomia, with the highest risk observed among individuals using multiple products concurrently [52].

Conversely, several studies report a stronger and more consistent association between traditional tobacco use and xerostomia compared with e-cigarettes. A single-center study from Baghdad demonstrated significantly higher xerostomia scores among cigarette smokers than both vapers and never-smokers, with vapers showing intermediate scores [3]. Salivary function studies further revealed significant reductions in salivary flow rate and salivary pH among users of smoked and smokeless tobacco, with clear dose–response relationships related to duration, frequency, and intensity of tobacco exposure [53]. Additionally, clinical investigations consistently reported lower salivary flow rates and a higher prevalence of xerostomia symptoms among smokers compared with non-smokers, reinforcing the well-established deleterious effects of conventional tobacco on salivary gland function [3,54].

Implications for practice

Within the limits of a cross-sectional design, the present associations have several practical implications. First, given the magnitude and consistency of the association between current ENDS use and xerostomia symptoms across all sensitivity analyses, clinicians evaluating young adults presenting with persistent dry-mouth symptoms may reasonably consider current and recent nicotine product use—including ENDS—as part of the differential. Second, the substantively larger ENDS-xerostomia association observed in female participants suggests that women who use ENDS may benefit from particular attention to oral and salivary symptoms in primary-care and dental encounters. Third, the dose-response signal observed within current ENDS users (with respect to both duration of use and daily puffs) suggests that brief counselling about cumulative exposure may be relevant to patients reporting bothersome dry-mouth symptoms. We emphasise that all of the above are appropriate as clinical considerations rather

than as established causal claims, and that the strength of any individual recommendation should be calibrated against the limitations of the cross-sectional design.

Implications for research

Three priorities for follow-up research are suggested by the present findings. First, prospective cohort designs that recruit participants prior to initiation of any nicotine product, with periodic re-measurement of xerostomia symptoms, would establish the temporal sequence between exposure and outcome and would address the principal limitation of the present design. Second, clinical studies incorporating objective sialometric assessment alongside the XI questionnaire would distinguish patient-reported xerostomia from objective hyposalivation and would clarify which is more strongly affected by ENDS exposure; combining sialometry with oral microbiome and inflammatory-marker assessment would further illuminate the mechanistic pathways suggested by the cross-sectional literature. Finally, the sex-specific effect modification reported here (with the ENDS-xerostomia association approximately 60% larger in female than in male participants) requires confirmation in independent samples and prospective designs; if confirmed, the underlying biological and behavioural mechanisms warrant dedicated investigation.

Strength and limitations

This study has several notable strengths. Firstly, its large multinational sample, encompassing 11,451 participants from 18 MENA countries, provided robust statistical power. This was complemented by the use of a validated and culturally adapted Arabic version of the XI, ensuring reliable measurement of xerostomia symptoms. Furthermore, data integrity was rigorously

maintained through single-response restrictions, careful screening, and the exclusion of pilot responses. The application of a directed acyclic graph (DAG) facilitated a systematic, theory-driven approach to confounder selection, with explicit classification of each variable as confounder or mediator (Supplementary Figure S1), thereby strengthening the validity and transparency of adjusted analyses. The robustness of the principal association was further demonstrated through six additional sensitivity analyses, including extended adjustment for hypothesised mediators, exclusion of all former users, exclusion of all current medication users, and exclusion of all participants with physical comorbidities; in each case, the direction and statistical significance of the principal estimate were preserved. The dose-response analyses among current users provided additional support consistent with biological gradient. Additionally, the detailed categorization of nicotine product use and the employment of comprehensive multivariable regression techniques allowed for a nuanced examination of the associations between nicotine product use and xerostomia.

Although our cross-sectional study provides population-level evidence on xerostomia among different nicotine product use groups, several limitations should be considered when interpreting the findings of this study. Firstly, its cross-sectional design limits causal inference: temporal sequence cannot be established, and reverse causation is plausible. Individuals who experience persistent dry mouth may modify their nicotine product use—for example, by switching from combustible products to ENDS in the belief that ENDS are gentler on oral tissues, or conversely by reducing or ceasing use—and either pattern would distort the cross-sectional associations reported here. Secondly, self-administered surveys are inherently susceptible to response bias, and the recruitment via social media platforms with deliberate outreach to dedicated ENDS-user online communities, undertaken to ensure adequate representation of the exposure of interest,

introduces a directional selection bias: individuals active in vaping-focused online communities are likely to be more health-literate, more attentive to product-related symptoms, and more inclined to attribute oral symptoms to their nicotine product. The expected direction of this bias is to inflate the magnitude of the ENDS–xerostomia association relative to the non-user reference, although the ordinal ranking of associations would be preserved unless the bias differentially affects the comparison groups in opposing ways. The response rate could not be determined because the survey was distributed via shared links rather than through a defined sampling frame, precluding standard non-response analysis. Participants may also have struggled with accurately recalling symptom frequency or severity, thereby increasing the risk of recall bias. Furthermore, we did not measure salivary flow rate or perform clinical examination, and therefore cannot distinguish patient-reported xerostomia from objective hyposalivation; future studies combining the XI with sialometric assessment are needed to characterise the salivary correlates of the associations reported here.

Additional limitations warrant explicit acknowledgement. The ENDS exposure category aggregates several device classes (cigalike e-cigarettes, open-system mods, pod systems, e-hookah, and e-pipes) that differ substantially in vaporisation temperature, nicotine delivery efficiency, and e-liquid composition; the pooled estimate should therefore be interpreted as an average effect across heterogeneous device types. With respect to residual contamination from former product use, we performed a sensitivity analysis restricted to participants with no history of nicotine product use other than their current product; the principal estimates became larger rather than smaller in this cleaner sample, indicating that in the full-sample analysis the inclusion of former users acted to attenuate rather than inflate the contrast between current ENDS users and non-users. Our exposure assessment was restricted to combustible tobacco products and

ENDS; smokeless tobacco use, which remains prevalent in several MENA settings, was not captured, which could conservatively bias our estimates if some participants classified as non-users used smokeless products. The XI ≥ 24 cutoff used in the binary classification analysis (Supplementary Table S8) was derived in adults aged ≥ 40 years in Iran against an objective sialometric reference; its application to a younger MENA-region sample lies outside the population in which it was validated, and the binary analysis should be interpreted as exploratory secondary support for the principal continuous analysis rather than as a definitive operationalisation of xerostomia case status in this population.

Finally, several key variables, including physical and psychiatric comorbidities, sleep deprivation, and consumption of caffeinated drinks or alcohol, were self-reported and recorded as binary variables. While this approach facilitated analysis, it may have oversimplified complex behaviors and potentially led to residual confounding. Although adjustments were made for the most recognized confounders, unmeasured or residual confounding cannot be entirely excluded; the extended-adjustment sensitivity analysis attenuated the estimate by approximately 20% (consistent with the DAG-specified mediator interpretation of these variables) without changing direction or statistical significance.

Conclusions

This cross-sectional study found that current use of any nicotine product was associated with higher self-reported xerostomia scores than non-use; the magnitude of the association was largest for exclusive ENDS users, intermediate for dual users, and smaller for exclusive combustible tobacco users. The principal association persisted across multiple additional sensitivity analyses and showed a graded dose-response with respect to duration of use; the ENDS-xerostomia

association was substantively larger in female than in male participants. The greater xerostomia severity observed among ENDS users may reflect a combination of nicotine-induced salivary hyposecretion, the hygroscopic properties of e-liquid constituents, thermal and chemical injury, oxidative stress, and alterations in the oral microbiome; whether and to what extent these candidate mechanisms account for the observed differences between products cannot be established from cross-sectional data.

These results should be interpreted as associational rather than causal, in light of the cross-sectional design and reliance on self-reported data. Future longitudinal and clinical studies, including those incorporating objective salivary flow assessments and oral microbiome analyses, are needed to evaluate temporality, refine dose–response estimates with objective intensity measures, and elucidate the underlying biological mechanisms.

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Author's contributions

SMS, HAA, WA, and YM contributed to the study's conceptualization. SMS contributed to the methodology and validation. SMS, and YM contributed to data curation. SMS conducted the formal analysis. SMS, and WA wrote the original draft. All authors contributed to reviewing and editing the manuscript. HAA and SMS coordinated the data collection process. RA, MA, AMAO, AMT, AAH, IK, MA, and AAG contributed to data collection. NAH supervised the study. DARS contributed to data collection for this study.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical considerations and approval

Informed consent was obtained electronically from all participants prior to survey initiation, with the option to withdraw at any stage without any consequences. The study was conducted in accordance with the principles of the Declaration of Helsinki [22]. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Benha University, Egypt (REC-FOMBU), under registration number RC.34.11.2023.

Consent for publication

Not applicable

Competing interests

All authors declared that they have no competing interests.