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RESEARCH

Xerogenic medications and clinical markers of salivary hypofunction

Yeon-Hee Lee[1,2] · Seonggwang Jeon[3] · Do-Hoon Kim[3] · Sunyoung Kim[4] · Tae-Seok Kim[2] · Sang-woo Lee[5] · Yung-Kyun Noh[3,6]

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Abstract

Objectives To determine whether xerogenic medication-class exposure and chair-side salivary markers contribute to risk stratification of objective salivary hypofunction across a broad clinical age spectrum, using conventional regression and explainable machine-learning approaches.

Materials and methods This retrospective cross-sectional study included 850 patients (mean age, 60.8 ± 15.6 years; 657 [77.3%] female) who underwent salivary flow assessment and oral clinical evaluation at Kyung Hee University Dental Hospital. Patients were categorized into four age groups: <40, 40–64, 65–79, and ≥80 years. Unstimulated salivary flow rate (UFR), stimulated salivary flow rate (SFR), and flow-rate-defined hyposalivation were analyzed using age-group comparisons, multivariable regression models, incremental gradient boosting models, and SHapley Additive exPlanations (SHAP)-based model interpretation.

Results Mean UFR was significantly lower in older age groups, ranging from 0.57 ± 0.30 mL/min in patients aged < 40 years to 0.36 ± 0.24 mL/min in those aged ≥ 80 years ($p < 0.001$), whereas age-group differences in SFR were less pronounced. SFR-defined hyposalivation was most frequent in the ≥80-year group (17.3%; $p = 0.007$). In adjusted models, the ≥80-year group had lower UFR than the <40-year group (β = −0.194; 95% CI, −0.272 to −0.115; $p < 0.001$) and higher odds of SFR-defined hyposalivation (OR = 5.47; 95% CI, 1.44–20.78; $p = 0.013$). Female sex was associated with lower UFR (β = −0.055; $p = 0.009$) and SFR (β = −0.369; $p < 0.001$). High-confidence xerogenic medication-class count was independently associated with SFR-defined hyposalivation (OR = 1.63; 95% CI, 1.12–2.36; $p = 0.010$). In incremental machine-learning models, adding salivary pH and buffer capacity produced the largest improvement in discrimination. AUROC increased from 0.468 to 0.723 for UFR-defined hyposalivation (ΔAUROC = 0.255; DeLong $p < 0.001$) and from 0.608 to 0.725 for SFR-defined hyposalivation (ΔAUROC = 0.116; DeLong $p = 0.005$). SHAP analysis ranked salivary buffer capacity as the leading contributor for both outcomes, with salivary pH also among the top predictors.

Conclusions Objective salivary hypofunction was not fully explained by age, systemic disease burden, or medication burden alone. Instead, chair-side salivary functional markers, particularly salivary pH and buffer capacity, captured clinically relevant information about current salivary status. These findings support a practical, layered approach to identifying patients who may require objective salivary flow assessment.

Clinical relevance Chair-side salivary pH and buffer capacity may help clinicians identify patients who warrant objective salivary flow assessment, particularly when considered together with age, sex, and xerogenic medication-class exposure.

Keywords Xerostomia · Hyposalivation · Salivary flow rate · Xerogenic medications · Salivary pH · Machine learning

Introduction

Saliva plays an essential role in maintaining oral homeostasis through lubrication, buffering capacity, antimicrobial activity, taste, swallowing, and mucosal protection. Dry mouth is a common complaint, with prevalence estimates reaching approximately 22% in the general population, although reported rates vary by definition, assessment method, and study population [1]. Reduced salivary flow can affect oral comfort and is also linked to mucosal symptoms,

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dental caries risk, halitosis, and oral health-related quality of life [2, 3]. In older adults, dry mouth is particularly clinically relevant because it may interfere with mastication, swallowing, taste, denture retention, communication, social interaction, and sleep-related comfort, especially when accompanied by nocturnal oral dryness or mouth breathing [4, 5]. However, subjective xerostomia and objectively measured salivary hypofunction do not always coincide [6, 7]. This makes salivary flow rate an important functional endpoint, not simply a substitute for symptom assessment.

Dry mouth and salivary hypofunction are common concerns in older adults, especially those aged ≥ 80 years. In these age groups, systemic diseases and medication use often accumulate. Age, comorbidity, polypharmacy, and xerogenic medications have all been associated with xerostomia or reduced salivary flow, but their effects are difficult to separate in routine clinical data [8, 9]. Some medication classes have shown more consistent xerogenic potential, including antimuscarinic urological medications, antidepressants, and psycholeptic or sedative-hypnotic agents [10, 11]. Still, few studies have examined how medication exposure relates, within the same dataset, to oral discomfort, measured salivary flow reduction, and objective flow-rate-defined hyposalivation.

Salivary function is also shaped by the local oral environment. Chair-side markers such as salivary pH, buffer capacity, visual analog scale (VAS) scores, sticky saliva, tongue coating, and halitosis may reflect aspects of current salivary function that are not captured by systemic disease or medication history alone [12, 13]. Machine learning approaches have recently been applied to xerostomia and salivary-flow-related prediction, suggesting that combinations of demographic, systemic, medication-related, and oral clinical variables can help identify patients with salivary hypofunction [7, 14, 15]. However, traditional regression, incremental prediction modeling, and explainable machine-learning interpretation have rarely been applied together to the same salivary flow dataset.

The present study evaluated whether xerogenic medication-class exposure and chair-side salivary markers contribute to risk stratification of objective salivary hypofunction across age groups. We first characterized age-stratified differences in systemic disease burden, medication exposure, unstimulated salivary flow rate (UFR), stimulated salivary flow rate (SFR), and flow-rate-defined hyposalivation, with particular attention to adults aged≥80 years. We then assessed the adjusted associations of systemic disease burden, medication burden, high-confidence xerogenic medication classes, and oral/salivary clinical variables with salivary outcomes. Finally, we used incremental prediction models and SHapley Additive exPlanations (SHAP)-based interpretation to determine whether salivary pH and buffer capacity added information beyond demographic, systemic disease, and medication variables. We hypothesized that medication-class exposure and chair-side salivary markers would provide complementary information for identifying patients with objective salivary hypofunction.

Materials and methods

Study design and patients

This retrospective cross-sectional study included patients who underwent salivary flow assessment and oral clinical evaluation at Kyung Hee University Dental Hospital between January 2022 and December 2025. Salivary flow testing was routinely performed as part of the clinical evaluation of patients presenting to the oral medicine clinic with oral soft-tissue symptoms or conditions and was not limited to patients reporting dry mouth. This practice reflected the potential contribution of salivary dysfunction to the development or aggravation of a broad range of oral conditions. Patients were eligible if they had available age information and at least one recorded salivary flow outcome. Patients were excluded from the final analysis dataset if they lacked an oral clinical evaluation or analyzable salivary flow data. Other demographic, systemic disease, medication exposure, and oral/salivary clinical variables were analyzed when available. The study was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines. The study protocol was approved by the Institutional Review Board of Kyung Hee University Dental Hospital (KH-DT21025). The requirement for informed consent was waived because of the retrospective nature of the study.

Outcome definitions

The primary continuous outcomes were unstimulated salivary flow rate (UFR, mL/min) and stimulated salivary flow rate (SFR, mL/min). Flow-rate-defined hyposalivation was additionally analyzed as a binary outcome. UFR-defined hyposalivation was defined as UFR < 0.1 mL/min, and SFR-defined hyposalivation was defined as SFR < 0.7 mL/min [6, 16].

Variable definitions

Demographic variables

Age was analyzed as both a continuous and categorical variable. For categorical age-stratified analyses, patients were grouped as < 40 years (younger individuals), 40–64 years (middle-aged individuals), 65–79 years (elderly

individuals), and ≥ 80 years (adults aged ≥ 80 years) [17, 18]. These strata were selected to distinguish clinically interpretable age groups while maintaining adequate sample size in the oldest age group. The < 40-year stratum was labeled younger individuals because it included adolescents and younger adults. Sex was included as a binary covariate, with female sex coded as the indicator category.

Systemic disease variables

Systemic disease information was collected using a patient questionnaire. For each systemic disease category, patients were asked to indicate whether they had previously received a professional diagnosis from a physician or relevant medical specialist by selecting "yes" or "no." Based on these responses, systemic disease burden was assessed using any systemic disease category, systemic disease category count, and systemic disease category count groups of 0, 1, 2, and ≥3. Individual systemic disease categories included hypertension, diabetes mellitus, dyslipidemias, osteoporosis, cardiovascular diseases other than hypertension, thyroid diseases, mental and sleep disorders, urologic diseases, gastrointestinal diseases, and hypersensitivity. Hypertension was recorded as a separate questionnaire category because of its high prevalence and its corresponding medication category. The cardiovascular disease category therefore represented other cardiovascular conditions reported by the patient. Examples such as coronary artery disease and arrhythmia were provided only to assist patients in understanding the category; individual cardiovascular diagnoses were not separately recorded.

Medication exposure and burden variables

Medication information was collected using the patient questionnaire. Patients were asked to indicate whether they were currently taking medications in each medication class by selecting "yes" or "no." Medication exposure was therefore defined based on self-reported current medication use at the time of assessment. The medication classes evaluated in the medication-specific and sensitivity analyses included hypolipidemic agents, antihypertensive agents, bone density conservation agents, analgesics and anti-inflammatory agents, hypnotics and sedatives, hypoglycemic agents, antithrombotic agents, urological agents, antidepressive agents, thyroid hormones, gastrointestinal agents, hormone replacement therapy, anti-allergic agents, and anticonvulsants.

Medication burden was assessed using any current medication class, current medication class count, and current medication class count groups of 0, 1, 2, and ≥ 3. High-confidence xerogenic medication exposure was assessed using any high-confidence xerogenic medication class, high-confidence xerogenic medication class count, and high-confidence xerogenic medication class count groups of 0, 1, and ≥ 2. High-confidence xerogenic medication classes included antidepressive agents, hypnotics and sedatives, anti-allergic agents, urological agents, anticonvulsants, and antihypertensive agents. These classes were selected a priori based on prior evidence and biological plausibility for xerogenic effects, including anticholinergic, autonomic-modulating, sedative, or salivary gland–related mechanisms [10, 11, 19, 20].

Oral and salivary clinical variables

Subjective oral dryness severity was assessed using a 0–10 visual analog scale (VAS), with higher scores indicating greater perceived dryness. Unstimulated whole saliva was collected while the patient was seated at rest using the spitting method for 10 min. After UFR measurement, patients chewed an unflavored gum base for 2 min and then continued chewing while expectorating stimulated whole saliva into a graduated collection container for 5 min. The collected volumes were read directly in milliliters from graduated collection containers. UFR and SFR were calculated by dividing the collected volume by the respective collection duration and were expressed as mL/min. The collection procedures followed previously described methods [7, 21]. Salivary pH and buffer capacity were assessed using the GC Saliva-Check BUFFER kit (GC Corporation, Tokyo, Japan), as previously described [22]. Salivary pH was determined by immersing a test strip in unstimulated whole saliva and recording the corresponding value according to the color change. Stimulated whole saliva was applied to the buffer test strip using a pipette, and buffer capacity was scored from 0 to 12 according to the manufacturer's color-based criteria. Salivary pH values outside the physiologically plausible range of 5.0–9.0 were treated as missing before descriptive analysis and model fitting [23].

Sticky saliva was recorded when frothy or visibly viscous saliva was observed by the examining clinician. Dental calculus and tongue coating were clinically categorized as absent, moderate, or severe and coded as 0, 1, and 2, respectively. Calculus deposition was assessed based on visible calculus, whereas tongue coating was evaluated based on visible white or yellowish coating on the posterior two-thirds of the tongue. Halitosis was assessed as a patient-reported binary variable based on whether the patient perceived that they had bad breath (yes/no).

Machine-learning model structure and procedures

Machine-learning analyses were performed to evaluate whether systemic disease burden, medication burden, oral

clinical variables, and salivary functional variables provided risk-stratification information for salivary flow and flow-rate-defined hyposalivation. Two prediction tasks were performed: regression models for continuous UFR and SFR, and classification models for UFR-defined and SFR-defined hyposalivation. Four prespecified incremental models were constructed. Model 1, the demographic model, included age and sex. Model 2, the systemic-medication burden model, included Model 1 variables plus systemic disease category count, current medication class count, and high-confidence xerogenic medication class count. Model 3, the practical oral-systemic model, included Model 2 variables plus VAS, sticky saliva, dental calculus, tongue coating, and halitosis. Model 4, the full salivary oral-systemic model, included Model 3 variables plus salivary pH and salivary buffer capacity. Gradient boosting regression models were used for continuous salivary flow outcomes, and gradient boosting classification models were used for binary hyposalivation outcomes. For binary classification tasks, gradient boosting was implemented using extreme gradient boosting (XGBoost). Missing predictor values were imputed using median imputation within each training fold to avoid data leakage. Default model hyperparameters were used, and for binary classification tasks, the evaluation metric was set to log loss with the random seed fixed at 42 for reproducibility. Classification models were evaluated using repeated stratified 5-fold cross-validation with five repeats, preserving the proportion of hyposalivation events across folds and reducing dependence on a single train-test split [24]. In each repeat, the model was trained on four-fifths of the data and evaluated on the held-out fold, and the resulting out-of-fold predicted probabilities were averaged across repeats for model-performance estimation and pairwise model comparisons. To avoid data leakage, UFR was not included as a predictor for UFR-defined hyposalivation, and SFR was not included as a predictor for SFR-defined hyposalivation.

Model interpretation using SHAP analysis

To interpret the full salivary oral-systemic classification models, SHAP analysis was performed for Model 4. SHAP is a model-interpretation method based on cooperative game theory that quantifies how each predictor contributes to an individual prediction relative to the model's average prediction. It was used to identify the variables that contributed most strongly to predicted hyposalivation risk and to visualize the direction and magnitude of their contributions. For each binary outcome, the final Model 4 XGBoost classifier was fitted using patients with non-missing outcome labels, and SHAP values were calculated to estimate each predictor's contribution to the model output. Global feature importance was quantified using mean absolute SHAP values, with larger values indicating greater average contribution to model prediction regardless of direction [25]. Bootstrap 95% confidence intervals for mean absolute SHAP values were estimated using 2,000 participant-level bootstrap resamples. SHAP beeswarm plots were used to visualize both the magnitude and direction of predictor contributions. Positive SHAP values indicated increased predicted probability of hyposalivation, whereas negative SHAP values indicated decreased predicted probability.

Statistical analysis

Continuous variables were summarized as mean and standard deviation, and categorical variables as number and percentage. Age-group comparisons were performed using the Kruskal–Wallis test for continuous or ordinal variables and the chi-square test for categorical variables. Post-hoc pairwise comparisons were performed using Mann–Whitney U tests or Fisher's exact tests, with Benjamini–Hochberg false discovery rate (FDR) correction. Multivariable linear regression was used for continuous salivary flow outcomes, including UFR and SFR, and multivariable logistic regression was used for UFR-defined and SFR-defined hyposalivation. Primary adjusted models included age group, female sex, number of systemic disease categories, other current medication class count, and six-class high-confidence xerogenic medication class count. Other current medication class count was calculated as total current medication class count minus high-confidence xerogenic medication class count to avoid double counting. Effect estimates were reported with 95% confidence intervals (CIs), and logistic regression results were presented as odds ratios (ORs). Medication burden models evaluated current medication class count, high-confidence xerogenic medication class count, and any high-confidence xerogenic medication class. Medication-specific models were fitted separately for each high-confidence xerogenic medication class and adjusted for age group, female sex, number of systemic disease categories, and medication class count excluding the target class. Mutually adjusted sensitivity models included all 14 medication class variables simultaneously with age group, female sex, and number of systemic disease categories. Odds ratios were not estimated when no outcome events occurred among exposed patients or when model estimation was unstable.

For machine-learning analyses, regression performance was assessed using R^2, mean absolute error (MAE), and root mean squared error (RMSE), whereas classification performance was assessed using the area under the receiver operating characteristic curve (AUROC), area under the precision–recall curve (AUPRC), and Brier score. Pairwise AUROC comparisons between incremental models were

performed using DeLong's test based on cross-validated out-of-fold prediction scores. Statistical analyses were performed using Python version 3.12.13, with statsmodels version 0.14.6, SciPy version 1.16.3, scikit-learn version 1.6.1, and XGBoost version 3.2.0. Statistical significance was set at a two-sided p-value of <0.05.

Results

Patient characteristics and salivary outcomes across age groups

A total of 850 patients were included in the analysis (mean age, 60.8 ± 15.6 years; 77.3% female). Patients were grouped into four age strata: younger individuals (<40 years, $n=87$), middle-aged individuals (40–64 years, $n=361$), elderly individuals (65–79 years, $n=325$), and adults aged ≥80 years ($n=77$). Systemic, medication-related, oral clinical, and salivary characteristics according to age group are summarized in Table 1. Overall, systemic disease burden and current medication exposure were more prevalent in the older age groups, while age-group differences were more distinct for UFR than for SFR. UFR was significantly lower in the older age groups, whereas SFR did not differ significantly across age groups in the overall comparison. UFR-defined hyposalivation did not differ significantly across age groups, while SFR-defined hyposalivation was most frequent in the ≥80-year group. These age-group differences in continuous flow rates and flow-rate-defined hyposalivation are shown in Fig. 1 and Supplementary Figure S1. Several oral clinical variables also varied by age. Salivary pH was highest in patients aged <40 years and lower in older groups (overall $p<0.001$). VAS scores differed across age strata and were highest in the ≥80-year group. Tongue coating was also most prominent in the ≥80-year group. In contrast, salivary buffer capacity, sticky saliva, and halitosis did not show significant age-group differences after overall testing (Table 1).

Salivary flow rates and hyposalivation in older age groups

The two older age groups had higher systemic disease and medication burdens and lower resting salivary flow (Table 1). The prevalence of any systemic disease category and any current medication class was higher in the older age groups, reaching 77.5% and 62.2% in patients aged 65–79 years and 87.0% and 66.2% in those aged ≥80 years, respectively (both overall $p<0.001$; FDR-adjusted $p<0.001$; post-hoc: <40 < 40–64 < 65–79 = ≥80). High-confidence xerogenic medication exposure was also more frequent in the two older groups than in the younger groups (overall $p<0.001$; FDR-adjusted $p<0.001$; post-hoc: <40 = 40–64 < 65–79 = ≥80). Mean UFR was lower in the 65–79-year and ≥80-year groups than in younger patients (overall $p<0.001$; FDR-adjusted $p<0.001$; post-hoc: <40 > 40–64 > 65–79 = ≥80), whereas SFR-defined hyposalivation was most frequent in the ≥80-year group (17.3%; overall $p=0.007$; FDR-adjusted $p=0.011$; post-hoc: <40 = 40–64 = 65–79 < ≥80).

Associations of systemic disease and medication exposure with salivary outcomes

Adjusted associations of age group, sex, systemic disease burden, and medication burden with salivary outcomes are presented in Table 2. Compared with patients aged <40 years, adjusted UFR was lower in patients aged 40–64 years, 65–79 years, and ≥80 years. Female sex was also associated with lower UFR. By contrast, systemic disease category count, other current medication class count, and high-confidence xerogenic medication class count were not independently associated with continuous UFR after adjustment.

For SFR, female sex showed the strongest adjusted association with lower flow rate. Age-group estimates for SFR were directionally lower in older groups, but these associations were not statistically significant. Systemic disease category count and medication burden variables were also not significantly associated with continuous SFR in the fully adjusted model (Table 2).

For binary outcomes, age-group associations were more evident for SFR-defined hyposalivation than for UFR-defined hyposalivation. The ≥80-year group had higher adjusted odds of SFR-defined hyposalivation compared with the <40-year group. High-confidence xerogenic medication class count was also independently associated with SFR-defined hyposalivation, whereas it was not clearly associated with UFR-defined hyposalivation (Table 2). These findings indicate that age and xerogenic medication burden were more closely related to SFR-defined hyposalivation than to UFR-defined hyposalivation.

Medication burden and individual xerogenic medication-class associations

To further characterize medication-related signals, we examined medication burden variables and individual high-confidence xerogenic medication classes. Medication-related associations are summarized in Table 3 and visualized in Fig. 2. In medication burden models, current medication class count, any high-confidence xerogenic medication class, and high-confidence xerogenic medication class count were associated with higher odds of SFR-defined

Table 1 Age-related differences in systemic disease burden, medication exposure, and salivary/oral clinical profiles

Characteristic	Overall (n=850)	<40 years[1] (n=87)	40–64 years[2] (n=361)	65–79 years[3] (n=325)	≥80 years[4] (n=77)	p-value	FDR-adjusted p-value	Post-hoc
Demographics and salivary/oral clinical variables								
Age, years	60.8 (15.6)	28.4 (7.8)	54.4 (6.5)	71.1 (4.2)	83.3 (2.6)	—	—	—
Female sex[b]	657 (77.3)	63 (72.4)	284 (78.7)	247 (76.0)	63 (81.8)	0.427	0.465	NS
Unstimulated salivary flow rate, mL/min[a]	0.42 (0.26)	0.57 (0.30)	0.43 (0.25)	0.38 (0.24)	0.36 (0.24)	<0.001	<0.001	3=4<2<1
Stimulated salivary flow rate, mL/min[a]	1.45 (0.70)	1.53 (0.60)	1.47 (0.73)	1.44 (0.69)	1.33 (0.75)	0.154	0.203	NS
UFR-defined hyposalivation[b]	35 (4.1)	1 (1.1)	14 (3.9)	15 (4.7)	5 (6.6)	0.339	0.392	NS
SFR-defined hyposalivation[b]	70 (8.4)	3 (3.4)	33 (9.2)	21 (6.6)	13 (17.3)	0.007	0.011	1=2=3<4
Salivary pH[a]	6.59 (0.58)	6.86 (0.61)	6.58 (0.51)	6.55 (0.61)	6.43 (0.58)	<0.001	<0.001	3=4<2<1
Salivary buffer capacity[a]	9.31 (2.40)	9.67 (1.53)	9.28 (2.56)	9.26 (2.47)	9.21 (2.12)	0.785	0.785	NS
Visual analog scale[a]	3.06 (2.95)	2.47 (2.99)	2.75 (2.90)	3.29 (2.88)	4.20 (3.11)	<0.001	<0.001	1=2<3<4
Sticky saliva[b]	160 (18.9)	19 (22.1)	64 (17.7)	57 (17.6)	20 (26.7)	0.244	0.300	NS
Dental calculus[a]	0.66 (0.55)	0.58 (0.54)	0.61 (0.52)	0.72 (0.56)	0.75 (0.64)	0.036	0.049	NS
Tongue coating[a]	0.68 (0.61)	0.64 (0.63)	0.63 (0.59)	0.69 (0.62)	0.88 (0.63)	0.013	0.019	1=2=3<4
Halitosis[b]	113 (13.4)	18 (20.7)	48 (13.4)	37 (11.6)	10 (13.0)	0.181	0.231	NS
Systemic disease burden								
Any systemic disease category[b]	504 (59.3)	23 (26.4)	162 (44.9)	252 (77.5)	67 (87.0)	<0.001	<0.001	1<2<3=4
Number of systemic disease categories[a]	1.06 (1.14)	0.37 (0.67)	0.70 (0.94)	1.54 (1.23)	1.49 (1.01)	<0.001	<0.001	1<2<3=4
Systemic disease category count distribution[c]	—	—	—	—	—	<0.001	<0.001	1<2<3=4
0	346 (40.7)	64 (73.6)	199 (55.1)	73 (22.5)	10 (13.0)	—	—	—
1	246 (28.9)	14 (16.1)	94 (26.0)	102 (31.4)	36 (46.8)	—	—	—
2	158 (18.6)	9 (10.3)	53 (14.7)	80 (24.6)	16 (20.8)	—	—	—
≥3	100 (11.8)	0 (0.0)	15 (4.2)	70 (21.5)	15 (19.5)	—	—	—
Hypertension[b]	295 (34.7)	2 (2.3)	73 (20.2)	167 (51.4)	53 (68.8)	<0.001	<0.001	1<2<3<4
Diabetes mellitus[b]	107 (12.6)	1 (1.1)	32 (8.9)	64 (19.7)	10 (13.0)	<0.001	<0.001	1<2=4<3
Dyslipidemias[b]	187 (22.0)	3 (3.4)	67 (18.6)	102 (31.4)	15 (19.5)	<0.001	<0.001	1<2=4<3
Osteoporosis[b]	92 (10.8)	1 (1.1)	22 (6.1)	52 (16.0)	17 (22.1)	<0.001	<0.001	1=2<3=4
Cardiovascular diseases[b]	89 (10.5)	0 (0.0)	11 (3.0)	64 (19.7)	14 (18.2)	<0.001	<0.001	1=2<3=4
Thyroid diseases[b]	76 (8.9)	6 (6.9)	38 (10.5)	28 (8.6)	4 (5.2)	0.402	0.448	NS
Mental and sleep disorders[b]	80 (9.4)	9 (10.3)	19 (5.3)	46 (14.2)	6 (7.8)	0.001	0.002	1=2=4<3
Urologic diseases[b]	67 (7.9)	4 (4.6)	11 (3.0)	41 (12.6)	11 (14.3)	<0.001	<0.001	1=2<3=4
Gastrointestinal diseases[b]	61 (7.2)	0 (0.0)	23 (6.4)	30 (9.2)	8 (10.4)	0.016	0.024	1<2=3=4
Hypersensitivity[b]	38 (4.5)	3 (3.4)	22 (6.1)	11 (3.4)	2 (2.6)	0.265	0.316	NS
Medication burden and high-confidence xerogenic medication classes								
Any current medication class[b]	417 (49.1)	21 (24.1)	143 (39.6)	202 (62.2)	51 (66.2)	<0.001	<0.001	1<2<3=4
Number of current medication classes[a]	0.83 (1.08)	0.28 (0.54)	0.61 (0.94)	1.17 (1.22)	1.08 (1.04)	<0.001	<0.001	1<2<3=4
Current medication class count distribution[c]	—	—	—	—	—	<0.001	<0.001	1<2<3=4
0	433 (50.9)	66 (75.9)	218 (60.4)	123 (37.8)	26 (33.8)	—	—	—
1	235 (27.6)	19 (21.8)	94 (26.0)	95 (29.2)	27 (35.1)	—	—	—
2	112 (13.2)	1 (1.1)	32 (8.9)	60 (18.5)	19 (24.7)	—	—	—

Table 1 (continued)

Characteristic	Overall ($n=850$)	<40 years[1] ($n=87$)	40–64 years[2] ($n=361$)	65–79 years[3] ($n=325$)	≥80 years[4] ($n=77$)	*p*-value	FDR-adjusted *p*-value	Post-hoc
≥3	70 (8.2)	1 (1.1)	17 (4.7)	47 (14.5)	5 (6.5)	—	—	—
Any high-confidence xerogenic medication class[b]	204 (24.0)	11 (12.6)	59 (16.3)	108 (33.2)	26 (33.8)	<0.001	<0.001	1=2<3=4
High-confidence xerogenic medication class count[a]	0.30 (0.59)	0.14 (0.38)	0.21 (0.52)	0.42 (0.67)	0.40 (0.61)	<0.001	<0.001	1=2<3=4
High-confidence xerogenic class count distribution[c]	—	—	—	—	—	<0.001	<0.001	1=2<3=4
0	646 (76.0)	76 (87.4)	302 (83.7)	217 (66.8)	51 (66.2)	—	—	—
1	159 (18.7)	10 (11.5)	46 (12.7)	82 (25.2)	21 (27.3)	—	—	—
≥2	45 (5.3)	1 (1.1)	13 (3.6)	26 (8.0)	5 (6.5)	—	—	—
Antidepressive agents[b]	31 (3.6)	7 (8.0)	8 (2.2)	15 (4.6)	1 (1.3)	0.030	0.042	NS
Hypnotics and sedatives[b]	51 (6.0)	1 (1.1)	17 (4.7)	31 (9.5)	2 (2.6)	0.004	0.006	1=2=4<3
Anti-allergic agents[b]	14 (1.6)	3 (3.4)	6 (1.7)	4 (1.2)	1 (1.3)	0.542	0.573	NS
Urological agents[b]	32 (3.8)	0 (0.0)	3 (0.8)	23 (7.1)	6 (7.8)	<0.001	<0.001	1=2<3=4
Anticonvulsants[b]	12 (1.4)	1 (1.1)	7 (1.9)	3 (0.9)	1 (1.3)	0.722	0.742	NS
Antihypertensive agents[b]	116 (13.6)	0 (0.0)	34 (9.4)	62 (19.1)	20 (26.0)	<0.001	<0.001	1<2<3=4

Values are mean (standard deviation) or number (percentage). Patients were categorized as <40 years, 40–64 years, 65–79 years, and ≥80 years. Superscript numbers indicate age strata: [1] <40 years, [2] 40–64 years, [3] 65–79 years, and [4] ≥80 years. The <40-year stratum was referred to as younger individuals because it included adolescents and younger adults

[a] Kruskal–Wallis test for continuous or ordinal variables; [b] chi-square test for binary categorical variables; and [c] chi-square test for multi-category distribution variables. The FDR-adjusted p-value column shows Benjamini–Hochberg-adjusted p-values for the overall group tests across tested characteristics in this table. For post-hoc comparisons, pairwise Mann–Whitney U tests were used for continuous or ordinal variables, Fisher's exact tests were used for binary categorical variables, and pairwise chi-square tests were used for multi-category distribution rows. Pairwise p-values were adjusted using the Benjamini–Hochberg false discovery rate method. Post-hoc results are shown as compact ordered groupings using the age-stratum numbers; for example, 1<2=3 indicates that strata [2] and [3] were significantly higher than stratum [1] but did not significantly differ from each other. For multi-category distribution rows, post-hoc groupings indicate the direction of greater burden across the full distribution. NS indicates no significant post-hoc difference after adjustment

Salivary pH values outside the physiologically plausible range of 5.0–9.0 were treated as missing. Sticky saliva was defined as frothy or visibly viscous saliva observed by the examining clinician. Dental calculus and tongue coating were clinically categorized as absent, moderate, or severe (coded as 0, 1, and 2, respectively) and analyzed as ordinal scores. Halitosis was assessed as a patient-reported binary variable indicating perceived bad breath. UFR-defined hyposalivation was defined as UFR < 0.1 mL/min, and SFR-defined hyposalivation was defined as SFR < 0.7 mL/min. High-confidence xerogenic medication classes included antidepressive agents, hypnotics and sedatives, anti-allergic agents, urological agents, anticonvulsants, and antihypertensive agents. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate; FDR, false discovery rate

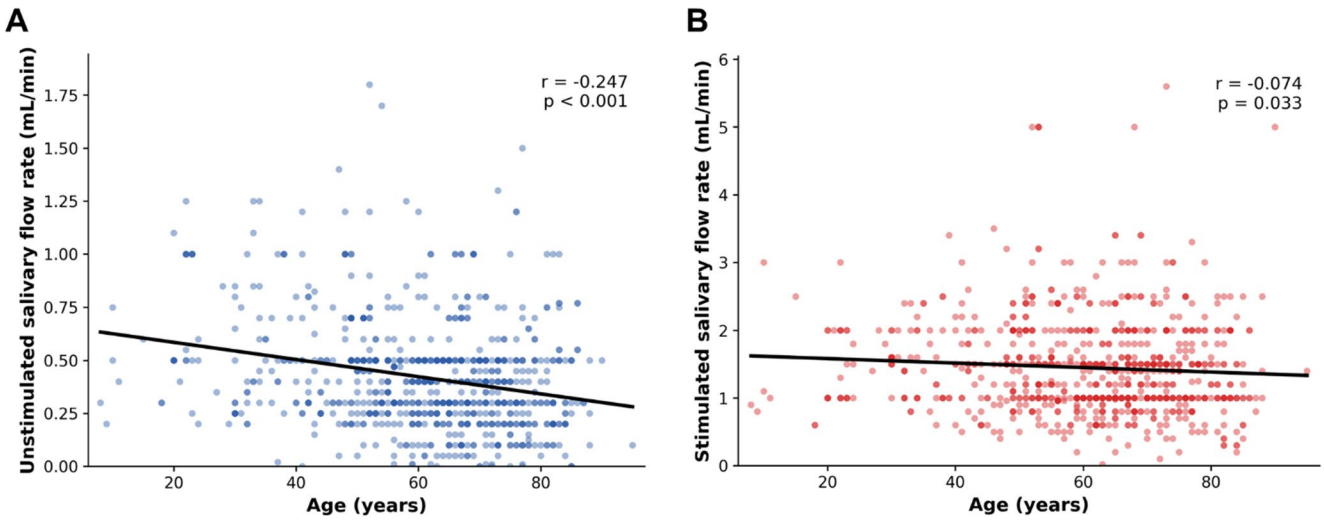

Fig. 1 Associations of age with unstimulated and stimulated salivary flow rates. Scatter plots show the associations between age and salivary flow rates. Each dot represents one participant. Linear trend lines are shown in black. Pearson correlation coefficients and p-values are displayed within each plot. (**A**) Unstimulated salivary flow rate (UFR) according to age. (**B**) Stimulated salivary flow rate (SFR) according to age. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate

hyposalivation. These associations were less consistent for continuous UFR, continuous SFR, and UFR-defined hyposalivation (Table 3).

In medication class-specific models, several individual high-confidence xerogenic medication classes showed nominal associations with salivary outcomes. Antidepressive agents and hypnotics/sedatives were associated with lower UFR before false-discovery-rate correction, and urological agents were associated with lower SFR. Antidepressive agents also showed a nominal association with SFR-defined hyposalivation. However, after correction across medication class tests, the class-specific findings were less stable than the medication-burden findings (Table 3; Fig. 2).

A sensitivity analysis including all 14 medication classes simultaneously showed attenuation of the individual medication-class associations. No individual medication class remained clearly associated with the binary hyposalivation outcomes after mutual adjustment and FDR correction, although several continuous-outcome estimates remained directionally consistent with the primary medication-class models (Supplementary Table S2). Descriptive plots according to high-confidence xerogenic medication class burden and combined systemic disease–medication burden are presented in Supplementary Figures S2 and S3.

Incremental value of chair-side salivary markers

Incremental model performance is summarized in Table 4. For continuous UFR prediction, model performance improved from the demographic model to the full salivary oral-systemic model. R^2 increased from 0.054 in Model 1 to 0.216 in Model 4, while MAE decreased from 0.189 to 0.168 and RMSE decreased from 0.249 to 0.227. For continuous SFR prediction, overall performance was weaker, but Model 4 again showed the best performance among the four models (Table 4).

For UFR-defined hyposalivation, AUROC increased from 0.468 in Model 1 to 0.723 in Model 4. For SFR-defined hyposalivation, AUROC increased from 0.608 in Model 1 to 0.725 in Model 4. AUPRC also increased most clearly after inclusion of salivary pH and buffer capacity in Model 4, particularly for SFR-defined hyposalivation (Table 4; Fig. 3).

Pairwise DeLong comparisons confirmed that the major gain in classification performance occurred after adding salivary pH and salivary buffer capacity. For UFR-defined hyposalivation, Model 4 outperformed both Model 3 and Model 1. For SFR-defined hyposalivation, Model 4 also improved discrimination compared with Model 3 and Model 1. In contrast, adding systemic-medication burden variables alone, or adding practical oral clinical variables before salivary pH and buffer capacity, did not produce a comparable improvement in AUROC (Fig. 3; Supplementary Table S1).

SHAP-based interpretation of salivary hypofunction models

SHAP-based feature importance for the full salivary oral-systemic classification models is summarized in Supplementary Table S3 and visualized in Fig. 4. For UFR-defined hyposalivation, the leading predictors were salivary buffer capacity, age, salivary pH, VAS, and tongue coating. For

Table 2 Adjusted associations of demographic, systemic disease, and medication burden variables with salivary outcomes

Predictor	UFR, mL/min[a] (*n* = 835)	*p*-value	FDR-adjusted *p*-value	SFR, mL/min[a] (*n* = 829)	*p*-value	FDR-adjusted *p*-value	UFR-defined hyposalivation[b] (*n* = 835/33)	*p*-value	FDR-adjusted *p*-value	SFR-defined hyposalivation[b] (*n* = 829/69)	*p*-value	FDR-adjusted *p*-value
40–64 vs. < 40 years	β = -0.137 (-0.195 to -0.078)	< 0.001	< 0.001	β = -0.034 (-0.197 to 0.130)	0.686	0.961	OR = 3.24 (0.42–25.17)	0.261	0.406	OR = 2.69 (0.80–9.05)	0.110	0.203
65–79 vs. < 40 years	β = -0.175 (-0.237 to -0.112)	< 0.001	< 0.001	β = -0.058 (-0.232 to 0.116)	0.515	0.901	OR = 3.09 (0.38–25.11)	0.290	0.406	OR = 1.76 (0.49–6.33)	0.385	0.449
≥ 80 vs. < 40 years	β = -0.194 (-0.272 to -0.115)	< 0.001	< 0.001	β = -0.155 (-0.375 to 0.065)	0.168	0.588	OR = 4.98 (0.55–45.23)	0.154	0.406	OR = 5.47 (1.44–20.78)	0.013	0.044
Female sex	β = -0.055 (-0.096 to -0.014)	0.009	0.015	β = -0.369 (-0.483 to -0.254)	< 0.001	< 0.001	OR = 1.74 (0.64–4.70)	0.276	0.406	OR = 1.17 (0.61–2.24)	0.637	0.637
Number of systemic disease categories	β = -0.002 (-0.020 to 0.015)	0.800	0.800	β = 0.000 (-0.050 to 0.050)	1.000	1.000	OR = 1.01 (0.71–1.44)	0.963	0.963	OR = 0.80 (0.61–1.06)	0.116	0.203
Other current medication class count	β = -0.012 (-0.037 to 0.013)	0.334	0.390	β = 0.002 (-0.069 to 0.073)	0.960	1.000	OR = 1.07 (0.66–1.72)	0.791	0.923	OR = 1.29 (0.91–1.83)	0.158	0.221
High-confidence xerogenic medication class count	β = -0.025 (-0.055 to 0.005)	0.107	0.149	β = -0.043 (-0.128 to 0.042)	0.323	0.754	OR = 1.41 (0.84–2.38)	0.195	0.406	OR = 1.63 (1.12–2.36)	0.010	0.044

Values are adjusted β coefficients or odds ratios (ORs) with 95% confidence intervals. Superscript letters after outcome names indicate the statistical model used: [a] multivariable linear regression for continuous salivary flow outcomes and [b] multivariable logistic regression for binary hyposalivation outcomes. Age strata were defined as <40 years, 40–64 years, 65–79 years, and ≥80 years, with <40 years used as the reference group. The <40-year stratum was referred to as younger individuals because it included adolescents and younger adults. Models included age group, female sex, number of systemic disease categories, other current medication class count, and 6-class high-confidence xerogenic medication class count. Other current medication class count was calculated as total current medication class count minus high-confidence xerogenic medication class count to avoid double counting. FDR-adjusted p-values were calculated using the Benjamini–Hochberg method across the listed predictor tests within each outcome. UFR-defined hyposalivation was defined as UFR < 0.1 mL/min, and SFR-defined hyposalivation was defined as SFR < 0.7 mL/min. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate; CI, confidence interval; FDR, false discovery rate

Table 3 Medication burden and medication class-specific associations with salivary outcomes

Exposure	Exposed, *n* (%)	UFR, mL/min[a] (*n* = 835)	*p*-value	FDR-adjusted *p*-value	SFR, mL/min[a] (*n* = 829)	*p*-value	FDR-adjusted *p*-value	UFR-defined hyposalivation[b] (*n* = 835/33)	*p*-value	FDR-adjusted *p*-value	SFR-defined hyposalivation[b] (*n* = 829/69)	*p*-value	FDR-adjusted *p*-value
Medication burden variables													
Current medication class count, per 1-class increase	—	β = -0.018 (-0.036 to 0.000)	0.054	0.160	β = -0.017 (-0.067 to 0.034)	0.512	0.767	OR = 1.21 (0.87–1.67)	0.252	0.317	OR = 1.44 (1.13–1.82)	0.003	0.008
Any high-confidence xerogenic medication class	204 (24.0)	β = -0.028 (-0.070 to 0.015)	0.203	0.203	β = -0.014 (-0.133 to 0.105)	0.815	0.815	OR = 1.51 (0.67–3.40)	0.317	0.317	OR = 1.90 (1.07–3.38)	0.030	0.030
High-confidence xerogenic medication class count, per 1-class increase	—	β = -0.025 (-0.055 to 0.005)	0.107	0.160	β = -0.043 (-0.128 to 0.042)	0.323	0.767	OR = 1.41 (0.84–2.38)	0.195	0.317	OR = 1.63 (1.12–2.36)	0.010	0.015
Individual high-confidence xerogenic medication classes													
Antidepressive agents	31 (3.6)	β = -0.096 (-0.186 to -0.006)	0.037	0.112	β = -0.154 (-0.405 to 0.098)	0.231	0.302	OR = 2.95 (0.80–10.93)	0.105	0.504	OR = 2.80 (1.01–7.72)	0.047	0.218
Hypnotics and sedatives	51 (6.0)	β = -0.095 (-0.167 to -0.023)	0.010	0.060	β = -0.151 (-0.356 to 0.054)	0.148	0.295	OR = 2.08 (0.68–6.38)	0.201	0.504	OR = 2.18 (0.93–5.12)	0.073	0.218
Anti-allergic agents	14 (1.6)	β = -0.029 (-0.160 to 0.102)	0.665	0.665	β = -0.214 (-0.579 to 0.152)	0.252	0.302	Not estimable	—	—	OR = 2.08 (0.43–9.94)	0.361	0.361
Urological agents	32 (3.8)	β = -0.036 (-0.131 to 0.060)	0.462	0.643	β = -0.293 (-0.559 to -0.028)	0.030	0.105	OR = 2.01 (0.39–10.38)	0.403	0.672	OR = 0.34 (0.04–2.68)	0.303	0.361
Anticonvulsants	12 (1.4)	β = 0.047 (-0.102 to 0.196)	0.536	0.643	β = -0.047 (-0.446 to 0.352)	0.817	0.817	OR = 1.99 (0.22–18.03)	0.540	0.675	OR = 2.36 (0.55–10.17)	0.249	0.361
Antihypertensive agents	116 (13.6)	β = 0.031 (-0.022 to 0.084)	0.254	0.507	β = 0.160 (0.011 to 0.309)	0.035	0.105	OR = 0.83 (0.29–2.36)	0.728	0.728	OR = 1.42 (0.70–2.90)	0.333	0.361

Values are adjusted β coefficients or odds ratios (ORs) with 95% confidence intervals. Exposed n (%) is shown for binary medication exposure variables and is not applicable to count variables. Superscript letters after outcome names indicate the statistical model used: [a] multivariable linear regression for continuous salivary flow outcomes and [b] multivariable logistic regression for binary hyposalivation outcomes

Medication burden models were adjusted for age group, female sex, and number of systemic disease categories. Models for any high-confidence xerogenic medication class and high-confidence xerogenic medication class count were additionally adjusted for other current medication class count. Medication class-specific models were fitted separately for each high-confidence xerogenic medication class and adjusted for age group, female sex, number of systemic disease categories, and medication class count excluding the target medication class. Age strata were defined as <40 years, 40–64 years, 65–79 years, and ≥80 years

FDR-adjusted p-values were calculated using the Benjamini–Hochberg method across medication exposure tests within each panel and outcome. Odds ratios were not estimated when no outcome events occurred among exposed patients. UFR-defined hyposalivation was defined as UFR < 0.1 mL/min, and SFR-defined hyposalivation was defined as SFR < 0.7 mL/min. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate; CI, confidence interval; FDR, false discovery rate

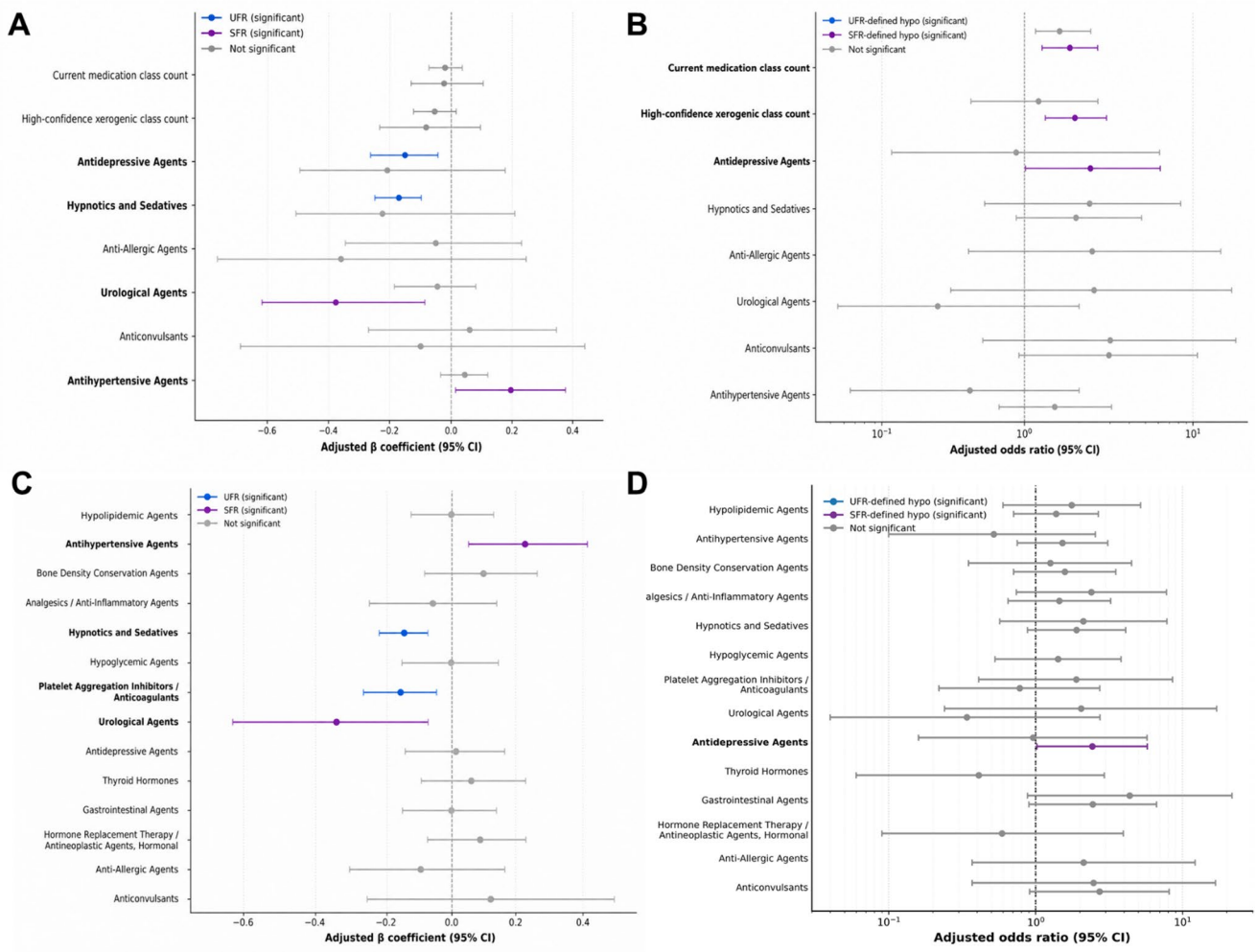

Fig. 2 Regression-based adjusted associations of medication burden and individual medication classes with salivary outcomes. Forest plots show adjusted associations with continuous salivary flow outcomes and flow-rate-defined hyposalivation. (**A**) Adjusted β coefficients for medication burden and the six high-confidence xerogenic medication classes in relation to UFR and SFR. (**B**) Adjusted odds ratios for medication burden and the six high-confidence xerogenic medication classes in relation to UFR-defined and SFR-defined hyposalivation. (**C**) Adjusted β coefficients for the 14 individual medication classes in relation to UFR and SFR. (**D**) Adjusted odds ratios for the 14 individual medication classes in relation to UFR-defined and SFR-defined hyposalivation. Values to the left of zero indicate lower salivary flow, and odds ratios greater than 1 indicate higher odds of hyposalivation. Models were adjusted for age group, female sex, systemic disease category count, and medication burden as appropriate. Bold y-axis labels indicate statistically significant associations. Estimates were not plotted when odds ratios were not estimable because no outcome events occurred among exposed patients. CI, confidence interval; OR, odds ratio; UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate

SFR-defined hyposalivation, the leading predictors were salivary buffer capacity, salivary pH, VAS, age, and current medication class count (Supplementary Table S3).

The SHAP beeswarm plots showed that the main predictive contributions were concentrated among salivary functional markers and age-related variables rather than systemic disease count alone. Salivary buffer capacity was the highest-ranked predictor for both UFR-defined and SFR-defined hyposalivation. Salivary pH also ranked among the top three predictors for both outcomes. Systemic disease category count and high-confidence xerogenic medication class count showed smaller SHAP contributions than salivary buffer capacity, salivary pH, age, and VAS (Fig. 4; Supplementary Table S3).

Discussion

In this retrospective cross-sectional study, objective salivary hypofunction reflected the combined influence of age, sex, xerogenic medication-class exposure, and chairside salivary functional markers. Older age was associated mainly with lower UFR, whereas female sex was associated with lower UFR and SFR. High-confidence xerogenic

Table 4 Incremental machine-learning prediction performance for salivary flow rates and flow-rate-defined hyposalivation

Outcome	Prediction task	Model	R^2	MAE	RMSE	AUROC	AUPRC	Brier score
UFR, mL/min[a]	Regression	Model 1: Demographic model	0.054	0.189	0.249	—	—	—
	Regression	Model 2: Systemic-medication burden model	0.074	0.184	0.247	—	—	—
	Regression	Model 3: Practical oral-systemic model	0.083	0.184	0.245	—	—	—
	Regression	Model 4: Full salivary oral-systemic model	0.216	0.168	0.227	—	—	—
SFR, mL/min[a]	Regression	Model 1: Demographic model	0.012	0.520	0.700	—	—	—
	Regression	Model 2: Systemic-medication burden model	0.016	0.519	0.698	—	—	—
	Regression	Model 3: Practical oral-systemic model	0.026	0.515	0.695	—	—	—
	Regression	Model 4: Full salivary oral-systemic model	0.080	0.494	0.675	—	—	—
UFR-defined hyposalivation[b]	Classification	Model 1: Demographic model	—	—	—	0.468	0.030	0.031
	Classification	Model 2: Systemic-medication burden model	—	—	—	0.497	0.068	0.031
	Classification	Model 3: Practical oral-systemic model	—	—	—	0.489	0.067	0.031
	Classification	Model 4: Full salivary oral-systemic model	—	—	—	0.723	0.099	0.033
SFR-defined hyposalivation[b]	Classification	Model 1: Demographic model	—	—	—	0.608	0.118	0.082
	Classification	Model 2: Systemic-medication burden model	—	—	—	0.586	0.154	0.082
	Classification	Model 3: Practical oral-systemic model	—	—	—	0.594	0.161	0.081
	Classification	Model 4: Full salivary oral-systemic model	—	—	—	0.725	0.301	0.070

Model 1, demographic model = age + sex; Model 2, systemic-medication burden model = Model 1 + systemic disease category count + current medication class count + 6-class high-confidence xerogenic medication class count; Model 3, practical oral-systemic model = Model 2 + visual analog scale, sticky saliva, dental calculus, tongue coating, and halitosis; Model 4, full salivary oral-systemic model = Model 3 + salivary pH and salivary buffer capacity. Superscript letters after outcome names indicate the prediction task and model type: [a] gradient boosting regression for continuous salivary flow outcomes and [b] XGBoost gradient boosting classification for binary hyposalivation outcomes. Model performance was evaluated using cross-validation. For classification tasks, repeated stratified 5-fold cross-validation with five repeats was used, and out-of-fold predicted probabilities were averaged across repeats. Regression performance was assessed using R^2, mean absolute error, and root mean squared error. Classification performance was assessed using AUROC, AUPRC, and Brier score. The 6-class high-confidence xerogenic medication classes included antidepressive agents, hypnotics and sedatives, anti-allergic agents, urological agents, anticonvulsants, and antihypertensive agents. Salivary pH values outside the physiologically plausible range of 5.0–9.0 were treated as missing before model fitting. UFR and SFR were not used as predictors for their corresponding flow-rate-defined hyposalivation outcomes to avoid data leakage. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate; AUROC, area under the receiver operating characteristic curve; AUPRC, area under the precision–recall curve; MAE, mean absolute error; RMSE, root mean squared error

medication-class count was most consistently associated with SFR-defined hyposalivation, whereas systemic disease category count alone showed limited independent association with salivary flow outcomes. In the incremental prediction models, the largest improvement in discrimination occurred after salivary pH and buffer capacity were added. These findings suggest that objective salivary hypofunction should be interpreted through a clinically layered framework that integrates age-associated differences in salivary function, medication-class exposure, and current chair-side salivary functional status rather than relying on chronological age, disease count, or medication count alone.

The age-related pattern was clearer for UFR than for SFR. UFR reflects basal resting secretion rather than stimulus-induced salivary reserve and may be more sensitive to gradual salivary decline [26]. Previous studies have reported age-related increases in xerostomia and salivary hypofunction, although the relative roles of aging, comorbidity, and medication exposure remain difficult to separate [7, 27]. Affoo et al. reported that age-related salivary flow reduction was gland-specific, involving whole saliva and submandibular/sublingual secretion but not parotid or minor gland flow [28]. In the present study, continuous UFR was lower in the older age groups than in younger patients, whereas UFR-defined hyposalivation did not differ clearly across age groups. Some participants aged ≥ 80 years retained relatively high UFR or SFR, reflecting substantial interindividual variability in salivary function among older adults. Systemic disease and medication exposure were also more prevalent in the older age groups, but their adjusted associations with continuous UFR and SFR were limited. This pattern suggests that medication exposure may contribute to salivary hypofunction in selected patients, whereas lower salivary flow in older patients likely reflects a broader combination of glandular reserve, sex, systemic health, medication exposure, and local salivary functional status [26, 29].

Female sex was associated with lower salivary flow in adjusted analyses. This is consistent with register-based data showing that xerostomia diagnoses are more frequent in women than in men [30]. Xerostomia is also commonly reported in peri- and postmenopausal women [31]. The lower salivary flow observed in women may partly reflect their smaller average parotid and submandibular gland sizes, although hormonal changes, menopausal status, autoimmune susceptibility, and differences in medication exposure may also contribute [32–34]. The present data cannot

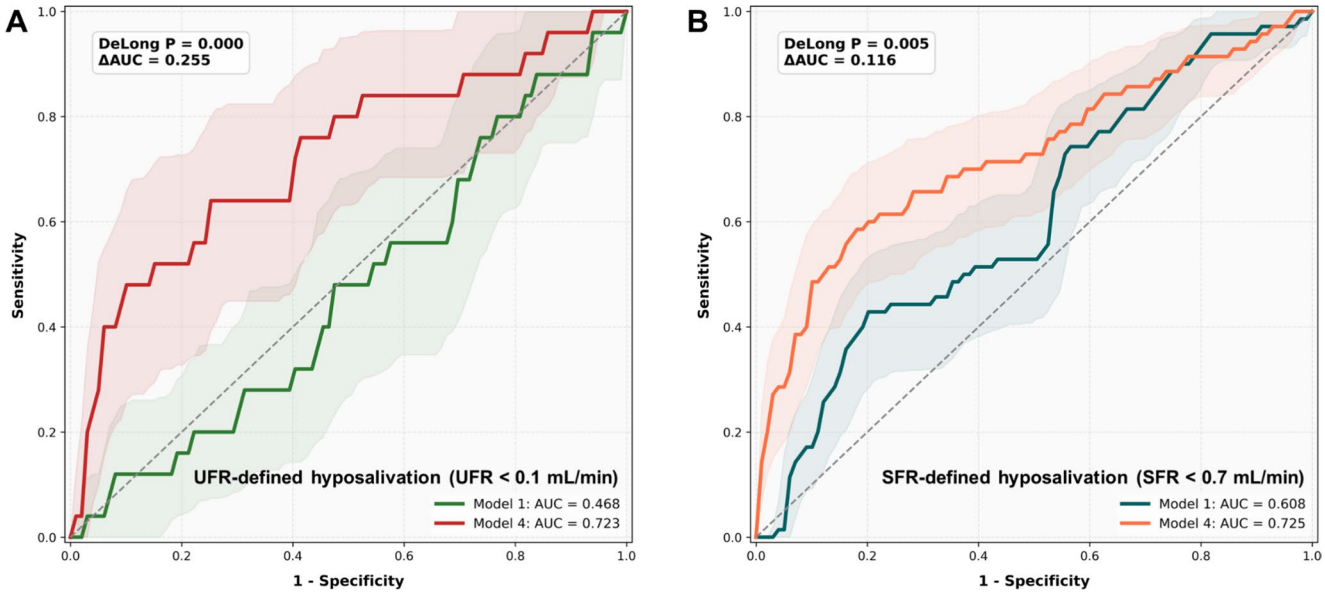

Fig. 3 Incremental machine-learning discrimination for flow-rate-defined hyposalivation. Receiver operating characteristic curves compare the demographic model and the full salivary oral-systemic model for predicting flow-rate-defined hyposalivation. (**A**) UFR-defined hyposalivation. (**B**) SFR-defined hyposalivation. Model 1 included age and sex. Model 4 included demographic variables, systemic disease burden, medication burden, oral clinical variables, and salivary functional variables, including salivary pH and salivary buffer capacity. Shaded areas represent 95% confidence intervals. AUROC values with 95% confidence intervals are shown in the figure. DeLong p-values compare Model 4 with Model 1, and ΔAUROC represents the incremental gain in discrimination. UFR-defined hyposalivation was defined as UFR < 0.1 mL/min, and SFR-defined hyposalivation was defined as SFR < 0.7 mL/min. AUROC, area under the receiver operating characteristic curve; UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate

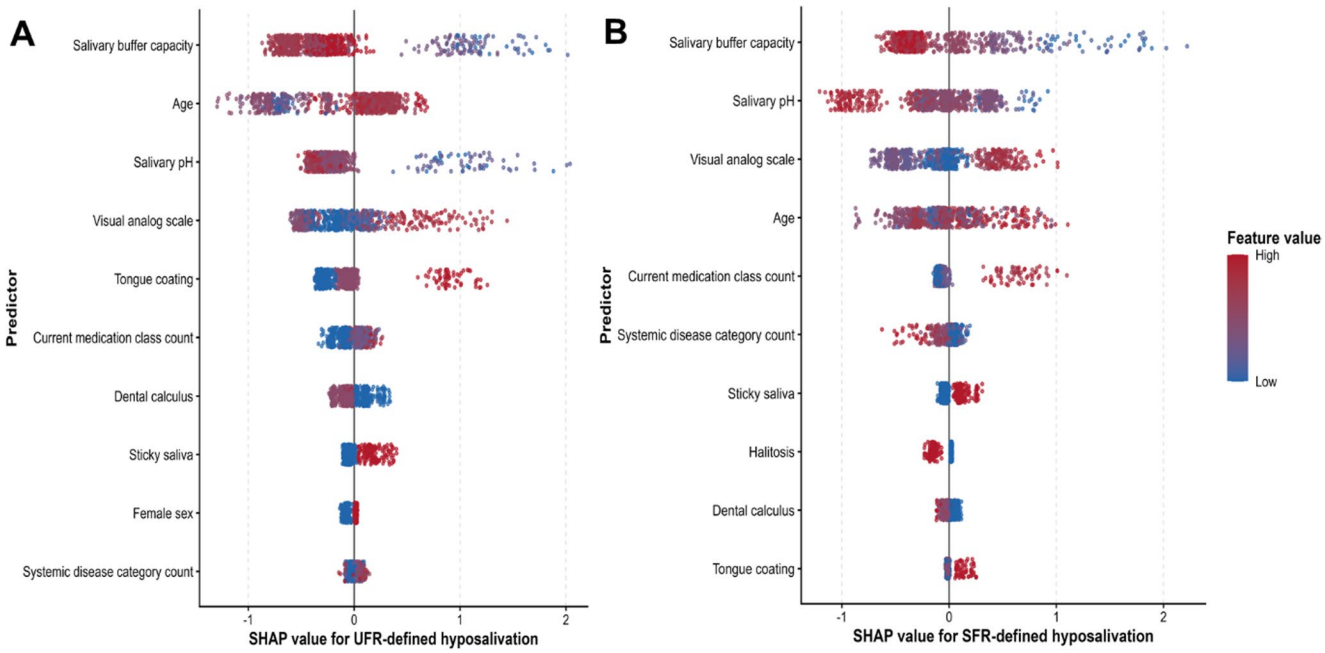

Fig. 4 Shapley additive explanations (SHAP)-based interpretation of full salivary oral-systemic models for flow-rate-defined hyposalivation. SHAP beeswarm plots show the direction and magnitude of each predictor's contribution to the full salivary oral-systemic model output. (**A**) UFR-defined hyposalivation. (**B**) SFR-defined hyposalivation. Each dot represents one participant. The x-axis indicates the SHAP value, with positive values increasing the predicted probability of hyposalivation and negative values decreasing the predicted probability. Dot color represents the feature value, with blue indicating lower values and red indicating higher values. The full salivary oral-systemic model included age, sex, systemic disease category count, current medication class count, high-confidence xerogenic medication class count, visual analog scale, sticky saliva, dental calculus, tongue coating, halitosis, salivary pH, and salivary buffer capacity. UFR, unstimulated salivary flow rate; SFR, stimulated salivary flow rate; SHAP, SHapley Additive exPlanations

determine which mechanism is most important. Still, the findings support the need to account for sex in studies of salivary function.

Systemic disease category count was not consistently associated with UFR or SFR after adjustment. This does not mean that systemic disease is irrelevant. Rather, a simple disease count may not capture the biological burden that affects salivary secretion. Previous studies have linked chronic disease and multimorbidity to xerostomia or impaired salivary function [35, 36]. However, disease count does not reflect severity, duration, inflammatory activity, metabolic control, autonomic dysfunction, treatment intensity, or physiological reserve [37, 38]. This issue may be especially important in elderly and super-elderly individuals, in whom the same number of disease categories can represent very different clinical states [39–42]. Therefore, in older adults, particularly those aged ≥ 80 years, simple counts of systemic diseases may be insufficient for estimating salivary vulnerability unless they are interpreted together with functional reserve [43], medication class exposure, and chair-side salivary findings.

The medication findings support a class-informed assessment rather than a simple medication-count approach. Polypharmacy has been associated with xerostomia and salivary hypofunction in older and medically complex populations [44], but total medication count treats all drugs as equivalent and may obscure class-specific effects [45]. In this study, antidepressive agents and hypnotics/sedatives showed nominal associations with lower UFR, and antidepressive agents showed a nominal association with SFR-defined hyposalivation. These findings are consistent with the known xerogenic potential of psychoactive and autonomic-modulating medications [46, 47]. Urological agents also showed a nominal association with lower SFR, which is biologically plausible because some drugs used for urinary symptoms have anticholinergic properties that can reduce parasympathetic stimulation of salivary glands [10, 11]. The unexpected positive association between antihypertensive agents and SFR should be interpreted cautiously because antihypertensive medications are pharmacologically heterogeneous and the finding may reflect confounding by indication, co-medication patterns, or residual differences in cardiovascular health [48].

High-confidence xerogenic medication class count was most consistently related to SFR-defined hyposalivation. Because the strength of xerogenic evidence differs across drugs and medication classes [9], this variable was designed to focus on medication classes with stronger clinical and biological plausibility. This approach may be more informative than numerical polypharmacy alone, because it reflects xerogenic pharmacologic exposure rather than medication count itself [49, 50].

The machine-learning analysis was used as a complementary risk-stratification layer, not as a replacement for regression modeling or direct salivary flow assessment. Regression models provided adjusted effect estimates for prespecified clinical variables, whereas gradient boosting models evaluated combined predictive patterns across demographic, systemic, medication-related, and oral/salivary variables [51–53]. Despite incorporating systemic disease burden, medication exposure, oral clinical findings, and salivary functional markers, the classification models showed only moderate discrimination, suggesting that salivary production and secretion are influenced by dynamic factors beyond the variables available in this dataset. These may include short-term hydration status, circadian rhythm, psychological state or acute stress at the time of saliva collection, nutritional status, body composition, autonomic function, hormonal status, medication dose and duration, genetic susceptibility, and gland-specific secretory reserve [54–56]. Therefore, the present models are best viewed as tools for risk stratification rather than stand-alone diagnostic models.

SHAP analysis further supported the clinical relevance of chair-side salivary functional markers. Salivary buffer capacity was the leading contributor for both UFR-defined and SFR-defined hyposalivation, and salivary pH also ranked among the top predictors. These markers may reflect current salivary functional status through glandular secretion, buffering reserve, oral microbial ecology, diet, hydration, and mucosal conditions [57, 58]. This finding is consistent with the clinical observation that subjective xerostomia and objective salivary hypofunction do not always overlap [6, 7]. However, SHAP values are model-based contributions and should not be interpreted as causal effects [59].

This study has several limitations. First, the retrospective cross-sectional design does not allow causal inference or temporal assessment of systemic disease, medication exposure, salivary functional markers, and salivary flow outcomes. Second, systemic disease and medication exposure were based on questionnaire-derived information. Medication dose, duration, adherence, and specific active ingredients were not available. Third, systemic disease burden was measured using disease category count, which does not capture disease severity, duration, inflammatory activity, metabolic control, treatment intensity, or physiological reserve. Fourth, this was a single-institution study, and the findings may not generalize to other clinical or community-based populations. Fifth, only 35 patients met the criterion for UFR-defined hyposalivation. Given the relatively small number of events compared with the number of candidate predictors, the binary UFR models may be susceptible to model instability or overfitting despite internal cross-validation. These findings should therefore be interpreted

cautiously. In addition, although the group aged≥80 years was clinically important, its sample size was smaller than that of the other age groups; therefore, estimates for patients aged≥80 years should be interpreted with appropriate caution. Finally, although the machine-learning models were internally evaluated using cross-validation, external validation is needed before clinical use.

Conclusion

In conclusion, objective salivary hypofunction was associated with age, female sex, and selected xerogenic medication exposures, whereas systemic disease and medication counts alone did not fully explain salivary outcomes. Chairside salivary pH and buffer capacity provided the greatest incremental information for risk stratification beyond demographic, systemic disease, and medication variables. These markers should not be interpreted as substitutes for direct salivary flow measurement, but they may serve as practical adjuncts for identifying patients who warrant objective salivary flow assessment, particularly when considered together with age, sex, and xerogenic medication-class exposure.

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Author contributions Y.-H.L. and Y.-K.N. conceived and designed the study. Y.-H.L. contributed to clinical investigation, data collection, dataset curation, clinical interpretation, and drafting of the original manuscript. T.-S.K. contributed to clinical resources and validation. S.K. contributed to medical interpretation of systemic disease and medication-related findings. S.-W.L. contributed to physiological interpretation of salivary function and manuscript review. S.J. and D.-H.K. contributed to dataset curation and performed statistical and machine-learning analyses. S.J. and D.-H.K. implemented the software, validation, and visualization procedures. Y.-K.N. supervised the computational methodology and contributed to project administration. Y.-H.L. and Y.-K.N. supervised the study. All authors contributed to manuscript review and editing, read and approved the final manuscript, and agree to be accountable for the work.

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Data availability The de-identified analysis dataset supporting the findings of this study is publicly available in the GitHub repository: https://github.com/Profyeonheelee/SalivaryFlowRateXerostomiaML.

Code availability Custom Python code used for data preprocessing, statistical analyses, machine-learning modeling, and figure generation is publicly available in the same GitHub repository: https://github.com/Profyeonheelee/SalivaryFlowRateXerostomiaML.

Declarations

Ethics approval and consent to participate This retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines. The study protocol was approved by the Institutional Review Board of Kyung Hee University Dental Hospital, Kyung Hee University (approval number: KH-DT21025). The requirement for informed consent was waived by the Institutional Review Board because of the retrospective nature of the study and the use of pre-existing clinical data.

Consent for publication Not applicable. This study did not include identifiable individual-level information, images, or personal clinical details requiring consent for publication.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Yeon-Hee Lee[1,2] · Seonggwang Jeon[3] · Do-Hoon Kim[3] · Sunyoung Kim[4] · Tae-Seok Kim[2] · Sang-woo Lee[5] · Yung-Kyun Noh[3,6]

✉ Yeon-Hee Lee
omod0209@gmail.com

✉ Yung-Kyun Noh
nohyung@hanyang.ac.kr

Seonggwang Jeon
qq22512@hanyang.ac.kr

Do-Hoon Kim
kik941002@hanyang.ac.kr

Sunyoung Kim
ggutsun@khu.ac.kr

Tae-Seok Kim
taiseok11@naver.com

Sang-woo Lee
goodman23@snu.ac.kr

1 School of Dentistry, Dental Research Institute, Seoul National University, 101, Daehak-ro, Jongro-gu, Seoul 03080, Republic of Korea

2 Department of Orofacial Pain and Oral Medicine, College of Dentistry, Kyung Hee University Dental Hospital, Kyung Hee University, #613 Hoegi-dong, Dongdaemun-gu, Seoul 02447, Republic of Korea

3 Department of Computer Science, Hanyang University, Seoul 04763, Republic of Korea

4 Department of Family Medicine, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, Republic of Korea

5 Department of Physiology, School of Dentistry and Dental Research Institute, Seoul National University, Seoul 03080, Republic of Korea

6 School of Computational Sciences, Korea Institute for Advanced Study (KIAS), Seoul 02455, Republic of Korea