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# High anticholinergic burden and hyposalivation and xerostomia in the elderly

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**ABSTRACT**

**Objective:** The aim was to study the association between high anticholinergic burden and hyposalivation and xerostomia among older people.

**Background:** Anticholinergic drugs have been shown to cause xerostomia and hyposalivation. Yet there are few studies on the association between anticholinergic burden and hyposalivation and xerostomia in the elderly.

**Material and Methods:** The study population consisted of community-dwelling older people ($n = 321$, mean age 81.6 years) from the Oral health GeMS study. Participants provided salivary samples and xerostomia was determined with a questionnaire. The baseline data were collected by interviews, oral clinical examinations and from patient records. Each participant's anticholinergic burden was determined by eight anticholinergic scales. Poisson regression models with robust error variance were used to estimate relative risks (RR) with a 95% confidence interval (CI).

**Results:** RRs of high anticholinergic burden in anticholinergic scales for xerostomia (multiple symptoms) ranged from 1.02 to 1.68; for low unstimulated salivary flow ($\leq$0.1 mL/min) from 1.47 to 1.67; and for low stimulated salivary flow ($\leq$0.7 mL/min) from 0.99 to 2.07. A high anticholinergic burden according to seven out of eight scales was associated ($p < .05$) with hyposalivation or xerostomia.

**Conclusions:** A high anticholinergic burden was associated more strongly with hyposalivation (both unstimulated and stimulated) than with xerostomia.

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## Introduction

Anticholinergic drugs block muscarine receptors $M_1$-$M_5$. These drugs are widely used for various conditions such as respiratory disorders, allergies, psychiatric disorders such as depression, urinary incontinence, cardiovascular diseases, and mydriasis. In most cases, anticholinergic properties are unwanted adverse effects. These can be divided into central effects such as confusion, falls, disorientation, delirium and cognitive impairment, and peripheral effects such as urinary retention, constipation, and dryness in the eyes and mouth [1,2]. High age, polypharmacy, high dose, declined cognitive function and variability in an individual's pharmacokinetics and dynamics have been found to be risk factors for the adverse effects of anticholinergic drugs [3–5].

Anticholinergic burden refers to the overall effect of taking multiple drugs with anticholinergic properties [6]. Several anticholinergic rating scales have been developed to assess total anticholinergic burden. These scales include a list of drugs and score these drugs by their anticholinergic potency. These scores can be summed up and thereby they represent an individual's total anticholinergic burden. The burden is often categorized according to the risk level for adverse anticholinergic effects: none, moderate, or high [7]. Due to a lack of a commonly established method to quantify anticholinergic burden, it is recommended to use multiple scales in research [8].

In the older population, both an objectively measured low salivary secretion (hyposalivation) and a subjective feeling of dry mouth (xerostomia) are common conditions [9]. These conditions predispose people to poor oral health by increasing the risk for oral diseases, including dental caries [10]. Common causes for dry mouth are iatrogenic (drugs, radiation) and psychogenic (depression, anxiety) factors, general diseases (Sjögren's syndrome, Parkinson's disease), and dehydration [11,12]. Among older people, the main causes for dry mouth are thought to be aging, use of drugs, and polypharmacy (five or more drugs daily) [13,14]. More than 400 drugs (including anticholinergic drugs) have been considered to affect salivary secretion and a recent systematic review reported that 106 substances had at least moderate evidence of causing hyposalivation or xerostomia [5,15]. The mechanism by which anticholinergic drugs cause hyposalivation and

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xerostomia is by blocking muscarine receptors in the salivary glands [16].

As the use of drugs with anticholinergic potency is common among older people, it is important to study these drugs using anticholinergic scales. Subsequently, the aim of this study was to investigate whether a high anticholinergic burden, measured with various anticholinergic scales, is associated with hyposalivation and xerostomia in the older population.

## Material and methods

The study used baseline data from the Oral Health Geriatric Multidisciplinary Strategy for the Good Care of the Elderly study (Oral Health GeMS study), which is a part of a larger parent GeMS study. The parent GeMS study is a population-based study conducted in Kuopio, Finland, during 2004-2007. GeMS study has been described in detail in previous studies [17,18]. In summary, the parent GeMS study consists of 1,000 randomly selected participants 75 years of age or older who were living in the city of Kuopio on the first of November 2003. Participants of the parent study were randomized into an intervention group ($n = 500$) and a control group ($n = 500$). The intervention group underwent comprehensive geriatric assessments (CGA) that were carried out by a multidisciplinary team (two physiotherapists, two nurses and two physicians). The CGA included interviews, assessment of drug usage, clinical examinations and blood tests. Data on the drug use of the participants were collected by interviews (self-reported drug usage) and it was verified from participants' prescriptions, drug packages and medical records. Information was also gathered from the medical records of community health centres, home care services, local hospitals and Kuopio University Hospital.

Participants of the intervention group were invited for further clinical oral examinations. The total number of participants of the Oral Health GeMS study who went through comprehensive geriatric and oral health assessments was 354 out of 500 persons. Oral health assessments were carried out for these participants by two dentists during the years 2004-2005. Oral health assessments included interviews, clinical oral examinations and saliva flow rate measurements performed in the primary care settings of the Social and Health Centre of Kuopio or the participant's house. Dentists performed home visits if the participant preferred a house call or was unable to visit the local dental clinic. Oral clinical examinations were performed in a dental unit using basic dental appliances, e.g. a dental mirror and periodontal probe, and a gauze pad. On home visits, the dental unit was not available, and a headlight and flashlight were used as the source of the light. For this study, the study population was restricted to community-dwelling people whose salivary secretion was measured, a total of 321 patients (92 men, 229 women, mean age 81.6 SD 4.6).

To calibrate the dentists, the first seven examinations were carried out together. Due to the participants' high age and the length of the oral examination, examinations were not repeated.

Participation in this study was voluntary and all subjects or their relatives gave written informed consent before entering the study. The study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo and the University of Kuopio as required by Finnish legislation.

### Outcome variables

The outcome variables were whole salivary flow rates, both stimulated (SWSFR) and unstimulated (UWSFR), and xerostomia.

Both unstimulated and stimulated whole salivary flow collections were made using the draining method [19]. In this method, participants were asked to refrain from beverages and eating 1h before the salivary flow rate measurement. In unstimulated whole salivary flow sample collections, participants were asked to sit straight and comfortably and tilt their head slightly forward. After that, they were asked to empty their mouths and let saliva drain passively for five minutes into a centrifuge tube. To stimulate salivary flow, participants were asked to chew a piece of paraffin capsule for 30 s and then empty their mouths. After that, they were asked to continue chewing the paraffin capsule for five minutes and simultaneously drain their saliva into the centrifuge tube. The collection of unstimulated saliva was performed without removable dentures and stimulated saliva with removable dentures. Samples in the centrifuge tubes were analyzed and flow rates were calculated in milliliters per minute (mL/min).

The UWSFR and SWSFR were categorized into two groups based on cut-off values presented in the literature [20]. Cut-off values and groups were $\leq$0.1 mL/min (low) and $>$ 0.1 mL/min (normal) for UWSFR. For SWSFR cut-off values were $\leq$0.7 mL/min (low) and $>$ 0.7 mL/min (normal). Also, an additional cut-off value for low SWSFR was used ($\leq$1.0 mL/min). SWSFR could not be collected from 21 participants and UWSFR from 15 participants. Both were missing from 14 participants.

The xerostomia was assessed with an interview by a dentist during the clinical oral examination. Altogether four individual xerostomia questions were used: ' Do you experience difficulties in speaking due to oral dryness?'; 'Can you eat dry bread/cookies without drinking water simultaneously?'; 'Do you have to relieve oral dryness during daytime or at night?'; and ' your mouth dry?'. Answers for the questions were either yes or no. Xerostomia was assessed using both a single-item approach (each question individually) and a multi-item approach (combined answers). In the multi-item approach, each yes-answer to a xerostomia question was given a numeric value of one and these values were then summed (score ranging from 0 to 4).

### Explanatory variables

In this study, eight anticholinergic rating scales were used as explanatory variables and for determining participants' anticholinergic burden. The anticholinergic rating scales were

the following: Anticholinergic Activity Scale (AAS) [21], Anticholinergic Burden Classification (ABC) [22], Anticholinergic Cognitive Burden (ACB) [23], Anticholinergic Risk Scale (ARS) [2], Anticholinergic Load Scale (ALS) [24], Chew's Scale [25], Clinician-Rated Anticholinergic Scale (CrAS) [26] and Durán's scale (Durán's) [1].

The anticholinergic rating scales are designed to estimate anticholinergic exposure by grading the anticholinergic drugs being taken [7]. The drugs are further ranked into groups based on the drug's anticholinergic potency, and the patient's anticholinergic burden is estimated as a sum of the rankings of the drugs being taken. The scales differ from each other by scoring criteria and scoring range [27]. In this study, all of the selected anticholinergic rating scales except two used a 4-point ranking (0 to 3). The AAS and Chew's scale used a 5-point ranking (0 to 4). The scoring of different drugs is based on expert opinions, laboratory measures, literature or pre-existing published anticholinergic scales, or a combination of these. More details of the anticholinergic rating scales used in this study can be seen in Table 1.

### Other variables/potential confounding variables

Data on potential confounders of the association between the anticholinergic burden of drugs and salivary secretion and xerostomia were collected through interviews with patients at comprehensive geriatric assessments, oral examinations and review of medical records. Potential confounders of this study were age, gender, smoking (current vs. former/never), number of drugs being taken regularly, functional comorbidity index (FCI) and presence of removable dentures (full or partial dentures).

A modified version of the Functional Comorbidity Index (FCI) was used to determine common comorbidities [28]. This modified version of the FCI includes 13 different medical conditions: rheumatoid arthritis and osteoarthritis, chronic asthma/chronic obstructive pulmonary disease (COPD), coronary artery disease, depression, diabetes mellitus (type I and II), Parkinson's disease/multiple sclerosis, osteoporosis, stroke, myocardial infarction, heart failure, visual impairment, hearing impairment and obesity (BMI $>$ 30). Each of the above-mentioned medical conditions was given a numeric value of 1 and they were summed up with the maximum value being 13.

### Statistical methods

In this study, Poisson regression models with robust error variance were used to estimate relative risk (RR) with a 95% confidence interval (CI) for dichotomous variables. RRs and their 95% CIs for continuous outcomes (the number of symptoms of xerostomia) were estimated using Poisson regression models. All the models were adjusted for age, gender, smoking, FCI, number of drugs taken regularly, and removable dentures. Statistical analyses were done using IBM SPSS 24.0 software for Windows (SPSS Inc., USA).

**Table 1.** Details of the anticholinergic rating scales used.

| Anticholinergic rating scale | Number of drugs with AA ecognized (*n*) | Rating scale | Rating basis | Validation |
|---|---|---|---|---|
| Anticholinergic Activity Scale (AAS) | 99 | 0–4 | Pre-existing anticholinergic rating scale (Chew's scale) and expert opinions | Cognitive function |
| Anticholinergic Burden Classification (ABC) | 27 | 0–3 | Serum anticholinergic activity and expert opinions | Cognitive function |
| Anticholinergic Cognitive Burden (ACB) | 88 | 0–3 | A systematic review of the drugs with anticholinergic properties and expert opinions | Mortality, delirium, cognitive function and physical function |
| Anticholinergic Risk Scale (ARS) | 49 | 0— | Literature review and expert opinions | Falls, hospitalization, mortality, delirium, cognitive and physical function |
| Anticholinergic Loading Scale (ALS) | 49 | 0–3 | Pre-existing published anticholinergic rating scales (ABC, ARS, Chew's scale, CrAS) and expert opinions | Psychomotor speed and cognitive function |
| Chew's Scale (Chew) | 22 | 0–4 | A radioreceptor assay and expert opinions | Physical function, anticholinergic activity *in vitro* |
| Clinician-Rated Anticholinergic Scale (CrAS) | 60 | 0–3 | Laboratory data, pre-existing published anticholinergic rating scale and expert opinions | Delirium, cognitive and physical function |
| Durán's scale (Durán's) | 100 | 0–3 | Pre-existing published anticholinergic rating scales (AAS, ABC, ACL, ADS, ARS, Chew's scale and CrAS) | – |

AA: Anticholinergic Activity.

**Table 2.** Statistics of the study population according to high anticholinergic burden in different anticholinergic scales.

| | Population | Duran ≥2 | ABC ≥3 | ACB ≥3 | ARS ≥3 | ALS ≥3 | CrAs ≥3 | AAS ≥4 | Chew ≥4 |
|---|---|---|---|---|---|---|---|---|---|
| *N* | 321 | 33 | 67 | 45 | 19 | 26 | 25 | 23 | 27 |
| Age (avg.) | 81.6 | 82.3 | 83.8 | 82.2 | 80.8 | 82.9 | 82.0 | 81.8 | 82.9 |
| Woman, *n* (%) | 229 (71) | 28 (85) | 50 (75) | 36 (80) | 16 (84) | 21 (81) | 22 (88) | 21 (91) | 23 (85) |
| Smoking, *n* (%) | 13 (4.0) | 2 (6.1) | 6 (9.0) | 2 (4.4) | 1 (5.3) | 0 | 0 | 1 (4.3) | 1 (3.7) |
| Rheumatic diseases, *n* (%) | 21 (6.5) | 2 (6.1) | 4 (6.5) | 2 (4.4) | 0 (0) | 1 (4.0) | 1 (4.0) | 2 (9.0) | 2 (7.4) |
| Diabetes, *n* (%) | 45 (14) | 6 (18) | 18 (27) | 10 (22) | 5 (26) | 7 (27) | 3 (12) | 6 (26) | 5 (19) |
| Coronary hearth disease, *n* (%) | 136 (42) | 17 (53) | 42 (65) | 26 (58) | 8 (42) | 17 (68) | 13 (54) | 12 (55) | 13 (50) |
| Chronic hearth failure, *n* (%) | 56 (17) | 5 (15) | 40 (61) | 18 (40) | 3 (16) | 7 (27) | 4 (16) | 5 (22) | 4 (15) |
| Asthma, *n* (%) | 29 (9.0) | 4 (12) | 9 (14) | 6 (14) | 2 (11) | 4 (15) | 3 (13) | 1 (4.3) | 2 (7.4) |
| Parkinson's disease, *n* (%) | 5 (1.6) | 0 (0) | 2 (3.0) | 0 (0) | 2 (11) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| BMI > 30, *n* (%) | 78 (24) | 8 (24) | 2 (3.0) | 13 (29) | 9 (47) | 7 (27) | 4 (16) | 8 (35) | 5 (19) |
| FCI (avg.) | 2.40 | 2.79 | 3.57 | 3.13 | 3.00 | 3.38 | 2.68 | 2.87 | 2.74 |
| Number of drugs, (avg) | 6.12 | 9.15 | 9.00 | 8.91 | 8.21 | 10.7 | 9.04 | 8.91 | 9.11 |
| Removable dentures, *n* (%) | 247 (77) | 28 (85) | 55 (82) | 34 (76) | 16 (84) | 22 (85) | 22 (88) | 18 (78) | 23 (85) |
| Low UWSFR (≤ 0.1 mL/min), *n* (%) | 124 (39) | 22 (71) | 37 (56) | 28 (67) | 12 (67) | 19 (79) | 17 (71) | 17 (77) | 19 (76) |
| Low SWSFR (≤ 1.0 mL/min), *n* (%) | 95 (32) | 17 (56) | 30 (49) | 18 (45) | 11 (61) | 16 (67) | 11 (46) | 13 (59) | 14 (56) |
| Low SWSFR (≤ 0.7 mL/min), *n* (%) | 63 (20) | 14 (45) | 21 (34) | 13 (33) | 9 (50) | 14 (58) | 8 (33) | 10 (46) | 11 (44) |
| Xerostomia multivariate (avg.) | 0.84 | 1.25 | 1.17 | 1.26 | 1.56 | 1.28 | 1.08 | 1.41 | 1.26 |
| Feeling of dry mouth, *n* (%) | 56 (17) | 8 (24) | 19 (28) | 12 (27) | 4 (21) | 7 (27) | 5 (20) | 7 (30) | 8 (27) |
| Troubles in speaking, *n* (%) | 66 (20) | 11 (33) | 19 (28) | 13 (29) | 8 (42) | 9 (35) | 7 (28) | 8 (35) | 9 (33) |
| Mouth moistening, *n* (%) | 113 (35) | 15 (46) | 29 (43) | 22 (49) | 12 (63) | 12 (46) | 11 (44) | 12 (52) | 12 (44) |
| Unable to eat dry foods, *n* (%) | 29 (9.0) | 6 (18) | 9 (13) | 7 (16) | 4 (21) | 4 (15) | 4 (16) | 4 (17) | 5 (19) |

BMI: Body Mass Index; UWSFR: Unstimulated Whole Salivary Flow Rate; SWSFR: Stimulated Whole Salivary Flow Rate; FCI: Functional Comorbidity Index; Duran: Durán's scale; ABC: Anticholinergic Burden Classification; ACB: Anticholinergic Cognitive Burden; ARS: Anticholinergic Risk Scale; ALS: Anticholinergic Load Scale; CrAs: Clinician-Rated Anticholinergic Scale; AAS: Anticholinergic Activity Scale; Chew:Chew's scale; Xerostomia multivariate; each yes-answer to a xerostomia question was given a numeric value of one and these values were then summed (score ranging from 0 to 4).

**Table 3.** Adjusted associations between anticholinergic scales and hyposalivation and xerostomia.

| Scale | Low UWSFR (≤ 0.1ml/min) | Low SWSFR (≤ 0.7ml/min) | Xerostomia multivariate | Feeling of dry mouth | Trouble speaking | Mouth moistening | Unable to eat dry foods |
|---|---|---|---|---|---|---|---|
| Duran ≥2 | 1.45 (1.06–2.03)* | 1.63 (0.99–2.70) | 1.32 (0.91–1.90) | 0.95 (0.44–2.02) | 1.53 (0.83–2.79) | 1.11 (0.71–1.73) | 2.57 (1.06–6.22)* |
| ABC ≥3 | 1.33 (0.97–1.82) | 1.39 (0.84–2.29) | 1.02 (0.75–1.39) | 1.20 (0.68–2.11) | 1.04 (0.59–1.84) | 0.91 (0.62–1.30) | 1.23 (0.49–3.13) |
| ACB ≥3 | 1.54 (1.13–2.09)* | 1.14 (0.66–1.98) | 1.20 (0.87–1.65) | 1.01 (0.58–1.76) | 1.14 (0.65–2.02) | 1.18 (0.82–1.68) | 1.93 (0.77–4.80) |
| ARS ≥3 | 1.39 (0.93–2.08) | 2.07 (1.22–3.50)* | 1.68 (1.12–2.52)* | 0.84 (0.35–2.02) | 1.93 (1.02–3.65)* | 1.67 (1.11–2.49)* | 3.21 (1.208.56)* |
| ALS ≥3 | 1.67 (1.19–2.36)* | 2.01 (1.23–3.52)* | 1.13 (0.74–1.72) | 0.78 (0.33–1.86) | 1.37 (0.66–2.83) | 0.96 (0.59–1.58) | 2.06 (0.67–6.34) |
| CrAs ≥3 | 1.47 (1.03–2.08)* | 0.99 (0.49–2.01) | 1.10 (0.72–1.68) | 0.77 (0.31–1.93) | 1.16 (0.57–2.37) | 1.03 (0.64–1.65) | 2.29 (0.80–6.52) |
| AAS ≥4 | 1.60 (1.17–2.20)* | 1.57 (0.90–2.73) | 1.41 (0.95–2.10) | 1.11 (0.54–2.29) | 1.47 (0.74–2.94) | 1.29 (0.83–1.99) | 2.43 (0.86–6.92) |
| Chew ≥4 | 1.61 (1.19–2.18)* | 1.61 (0.96–2.71) | 1.31 (0.89–1.929 | 1.35 (0.70–2.63) | 1.43 (0.78–2.64) | 1.04 (0.65–1.68) | 2.38 (0.91–6.22) |

UWSFR: Unstimulated Whole Salivary Flow Rate; SWSFR: Stimulated Whole Salivary Flow Rate; FCI:Functional Comorbidity Index; Duran: Durán's scale; ABC: Anticholinergic Burden Classification; ACB:Anticholinergic Cognitive Burden; ARS: Anticholinergic Risk Scale; ALS: Anticholinergic Load Scale; CrAs: Clinician-Rated Anticholinergic Scale; AAS: Anticholinergic Activity Scale; Chew: Chew's scale.
Data presented as adjusted relative risks (RR) with 95% confidence intervals (95% CI).
Adjusted for age, gender, smoking, FCI, number of drugs and removable dentures.
*$p$-value <.05.

## Results

Table 2 shows the basic characteristics of the study population. Participants' mean age ($n = 321$) was 81.6 years and the majority of them were women (71.3%). One-third of the participants had low UWSFR (≤0.1 mL/min) and one-fifth had low SWSFR (≤0.7 mL/min), whereas the presence of different symptoms of xerostomia varied from 9% (unable to eat dry foods) to 35% (mouth moistening).

The majority of the participants had at least one removable denture (76.9%). Participants using full dentures had a lower unstimulated salivary flow rate than those who had their own natural teeth and partial dentures ($p < .05$). Other variables did not essentially differ between participants' denture status. Approximately one-third of the participants (27.7%) had a high anticholinergic burden in at least one or more of the anticholinergic rating scales. Participants with a high anticholinergic burden used more drugs (avg. 8.8 vs. 5.1) and were older (83.4 years vs. 80.9 years) than those without or with a lower anticholinergic burden.

Unadjusted results of regression models are shown in a supplemental file (online) and adjusted results in Table 3. After adjusting for confounding factors (age, gender, smoking, FCI and removable dentures), the results showed that the participants with a high anticholinergic burden according to Duran ≥2, ACB ≥3, ALS ≥3, CrAS ≥3, AAS ≥4 and Chew ≥4 were more likely to have low UWSFR (≤0.1 mL/min) compared to participants without anticholinergic burden. The risk estimates varied between 1.45 and 1.67 (95% CI 1.03–2.36). In addition, participants with a high anticholinergic burden according to ALS (ALS ≥3) and ARS (ARS ≥3) were more likely to have low SWSFR (≤0.7 mL/min; RR: 2.01, 95% CI 1.23–3.52; RR: 2.07, 95% CI 1.22–3.50, respectively) compared to participants without an anticholinergic burden (Table 3). With respect to low SWSFR, the risk estimates for other scales varied between 0.99 and 1.61. Additional analyses using a higher cut-off point for low SWSFR (≤1.0. mL/min) did not cause major changes in risk estimates (results not shown).

The results showed that participants with a high anticholinergic burden according to ARS (ARS ≥3) were more

likely to have multiple xerostomia symptoms (RR: 1.68, 95% CI 1.12–2.52) compared to participants without an anticholinergic burden. Also, they were more likely to have single xerostomia symptoms such as trouble with speaking (RR: 1.93 95% CI 1.02–3.65), need to moisten their mouth (RR: 1.67 95% CI 1.11–2.49) and unable to eat dry foods (RR: 3.21 95% CI 1.20–8.56). The risk estimates of multiple xerostomia symptoms for the rest of the scales varied between 1.02 and 1.41 and were not statistically significant at the *p*-value level of 0.05. With single xerostomia symptoms, the risk estimates varied greatly between the anticholinergic scales (Table 3).

## Discussion

The aim of this study was to investigate whether a high anticholinergic burden, measured with various anticholinergic scales—is associated with hyposalivation and xerostomia among older people. Although there was some variation between the scales, the overall finding was that a high anticholinergic burden was associated with hyposalivation and xerostomia. The anticholinergic rating scales showed a stronger association with hyposalivation (either unstimulated or stimulated salivary flow) than with xerostomia and the strength of the association was dependent on the scale.

The findings are in line with previous studies, which have shown associations between either an anticholinergic burden [2,29,30] or the use of drugs with anticholinergic activity [31–33] and hyposalivation and xerostomia. However, direct comparisons with the earlier studies are challenging due to differences in the study population, assessment of anticholinergic burden or anticholinergic potency, and definition and measurement of hyposalivation and xerostomia. Nevertheless, despite the differences, the findings of the present study further strengthen the hypothesis that anticholinergic burden is associated with hyposalivation and xerostomia.

All eight scales were associated with either xerostomia or hyposalivation and seven of them were associated statistically significantly. The concordance between scales can be explained by the fact that although there are differences in the scales, the ranking of strong anticholinergic drugs does not vary much between the anticholinergic scales. On the other hand, it has been reported that the variation between scales in a mild anticholinergic burden is greater [6,27,34]. As an example of the variation, a commonly used beta blocker drug, metoprolol, has a ranking of zero or one depending on the scale used. Furthermore, only three scales (CrAs, ACB and Chew's scale) include metoprolol on the listing, whereas other scales do not.

The association between the anticholinergic scales with the low stimulated whole salivary flow was on average somewhat weaker than with low unstimulated whole salivary flow. This is in line with previous studies that have shown that in drug-induced hyposalivation, unstimulated whole salivary flow is usually notably decreased whereas stimulated whole salivary flow values can be within a normal range [35,36]. However, in these data, the differences in strength were fairly small.

With xerostomia, only one scale (ARS) was significantly associated. This lack of association may be a result of the subjective definition of xerostomia and the fact that salivary flow usually decreases before the feeling of dry mouth [37,38]. The overall agreement is that xerostomia usually occurs in a later phase when the unstimulated whole salivary flow decreases by about 50%. However, it is worth mentioning that xerostomia can even occur in patients with normal salivary secretion whereas patients with the very low salivary flow do not necessarily experience xerostomia [12,37].

### *Strengths and limitations*

A major strength of this study was that anticholinergic burden was measured using several, yet somewhat different anticholinergic scales. Of those scales, six have been validated with various clinical outcomes [6]. Therefore, the use of multiple anticholinergic scales is important for the validity of the study and this approach has been suggested in a number of previous studies [7,8,27,39]. The inherent limitations of the study relate to the characteristics of the scales, for example, differences between how they identify and include drugs and how they rank them, especially weaker anticholinergic drugs. For example, the AAS scale contains 99 different drugs with anticholinergic properties whereas ABC contains only 27. Further, the aforementioned AAS and ABC rank drugs differently (0–4 *vs.* 0–3) and their validations differ as well (Table 1). The anticholinergic scales that were used in this study have been developed in different countries (Norway, France, USA, Australia, Ecuador) with their own medication prescription guidelines, which might provide some explanation for the variation in the scales' drug inclusions and rankings. To reduce the above-mentioned limitations, only the high anticholinergic burden was taken into account and multiple scales were used concurrently. This approach also increased the comparability with other studies.

When studying high anticholinergic burden, it must be taken into account that none of the scales are adjusted for dose or take into account other factors like age-related changes in pharmacokinetics and dynamics or individual variability in the effects of drugs [6,34]. Anticholinergic scales are based on the assumption that the effects of different drugs are additive in a linear way [27]. This means, for example, that a similar anticholinergic burden (according to the same anticholinergic scale) with three anticholinergic drugs versus with four anticholinergic drugs might not have a similar cumulative effect. Instead of additive effects, it is also possible that the effect of different drugs may be synergistic [5]. Despite these shortcomings, the anticholinergic burden is considered to be a valid method to measure the risk of anticholinergic adverse effects.

It should be noted that the anticholinergic scales were mostly developed to detect the risk of severe adverse reactions of anticholinergic drugs, such as delirium, falls, and decreased cognitive or physical function. However, it can be expected that this has not influenced much the current

results, due to the fact that dry mouth is likely to occur already with drugs with weak anticholinergic effects [30].

The effects of other—non-anticholinergic—drugs on hyposalivation or xerostomia were further studied by performing complementary analyses (data not shown). The analyses were adjusted for a number of drugs that were not included in any of the used anticholinergic scales but have high evidence of causing hyposalivation or xerostomia [15]. These drugs included alendronate (13 users), gabapentin (three users), tiotropium (three users), thiazides (three users), verapamil (five users), and zopiclone/zopidem (29 users). Furthermore, commonly used antihypertensives, enalapril and lisiprinol (28 users), with moderate evidence of causing the dry mouth were also included in the analyses. The results of the complementary analyses did not differ from the results from analyses using a number of regularly used drugs as a covariate.

The fact that data are from 2007 can be considered as a limitation as treatment guidelines for geriatric patients have since then been updated and this has also led to some changes in drug use among older people. On the other hand, the main sources of anticholinergic burden are psychiatric medications and still after 15 years, more or less the same drugs and drug groups are recommended and used for psychiatric diseases (for example selective serotonin reuptake inhibitors). Altogether, despite some changes in treatment guidelines, *i.e.* prescribing less anticholinergic drugs, the anticholinergic burden as a risk for oral diseases remains relevant.

The outcome variables used for hyposalivation and xerostomia can also be seen as strengths of the study. Hyposalivation was assessed from both unstimulated and stimulated salivary flow measurements by using the draining method, which has been proven to be a reliable method [19,20]. Saliva samples were not collected at the same time of the day, which might have caused some biasing effect on the results due to the circadian rhythms and changes in salivary flow rates [40]. Some of the oral examinations were carried out during home visits but this was unlikely to have any major effect on salivary flow rate measurements.

Previous studies have also suggested that incorporating both hyposalivation and xerostomia into a study is beneficial due to the close nature of these variables [42]. This approach made it possible to study the associations between anticholinergic burden and salivary flow rate and xerostomia independently. Xerostomia was assessed with both a single and also multi-item approach, which is not a validated questionnare, such as Xerostomia Inventory [41], but rather a simple representation of multiple simultaneous xerostomic symptoms. This can be considered as a weakness of this study.

Potential confounders in this study were age, gender, smoking, number of drugs being taken regularly, comorbidity (FCI), and use of removable dentures; and these were controlled for in the analyses. Despite the quite extensive control of potential confounders, it is possible that all the potential confounders were not taken into account. For example, anxiety, stress, diet, nutrition, alcohol consumption, amount of physical exercise and radiotherapy on the neck and head region were not used as covariates in the models, although they have been proven to be related to hyposalivation or xerostomia [38]. But, considering the study population, their role can be expected to be small.

Concordance between dentists and repeatability of measurements within dentists was not possible to assess because oral examinations were performed only once. This can be considered as a limitation of this study but this was unlikely to have had any major effect on the results. Nevertheless, the strength of the data collection was that the dentists were calibrated before the actual data collection by performing the first seven examinations in cooperation. This increases the consistency of the measurements.

Due to the fact that the results of this study did not show large differences between the anticholinergic scales and due to the lack of a universal golden standard for anticholinergic scales, no recommendation in favour of any scale can be made. Instead, the authors recommend using any of the seven anticholinergic scales associated with dry mouth until enough evidence exists to indicate which of the scales is the most suitable for assessing the risk of dry mouth.

From a clinical perspective, the study strengthens the notion that it is advisable to avoid prescribing excessively anticholinergic drugs to older people because of the increased risk of adverse effects. Patients taking anticholinergic drugs should be seen as a risk group for poor oral health (due to a dry mouth) and thus, they should receive extensive prophylaxis measures against oral diseases.

## Conclusion

High anticholinergic burden appeared to be associated more strongly with hyposalivation (both unstimulated and stimulated) than with xerostomia among community-dwelling older people. The strength of the associations was dependent on anticholinergic scales.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

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