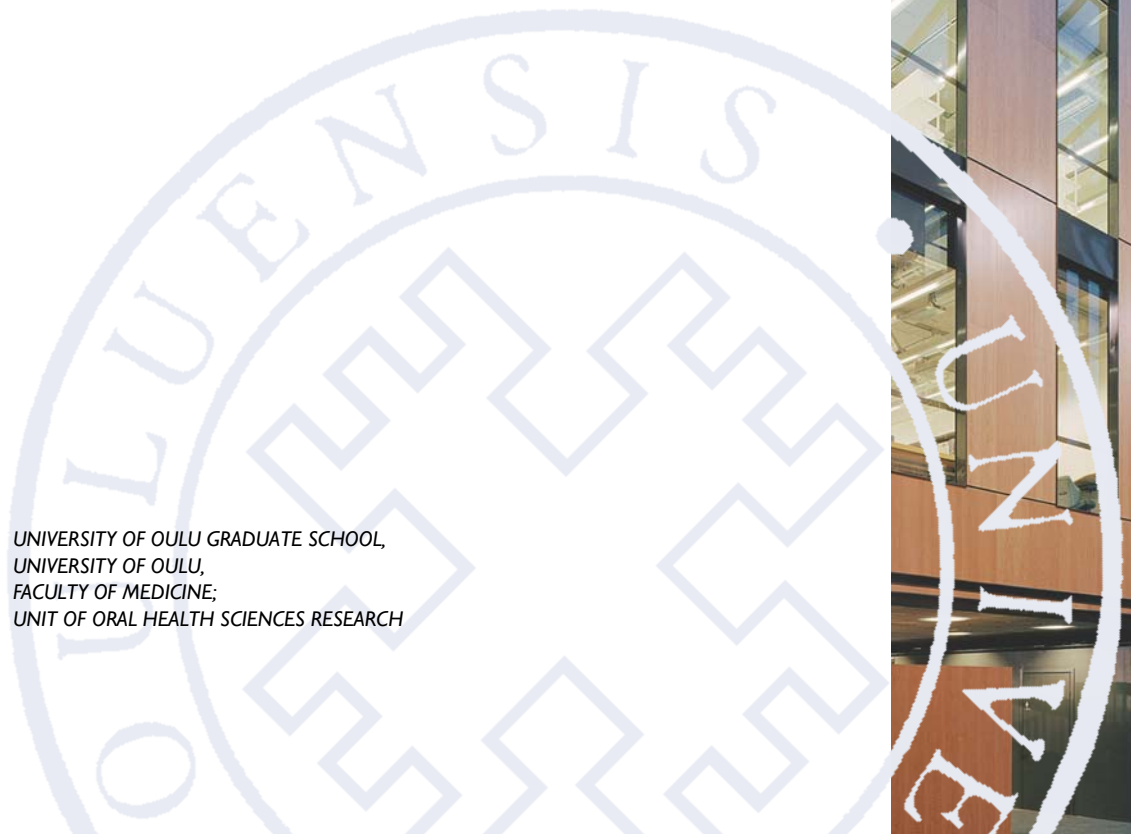


Antti Tiisanoja

SEDATIVE LOAD AND
ORAL HEALTH AMONG
COMMUNITY-DWELLING
OLDER PEOPLE

UNIVERSITY OF OULU GRADUATE SCHOOL,
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
UNIT OF ORAL HEALTH SCIENCES RESEARCH



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ANTTI TIISANOJA

**SEDATIVE LOAD AND ORAL
HEALTH AMONG COMMUNITY-
DWELLING OLDER PEOPLE**

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium F101 of the Faculty of Biochemistry and Molecular Medicine (Aapistie 7), on 19 January 2018, at 12 noon

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Abstract

With the growing proportion of older people and increasing use of drugs in this population, it is important to study how drugs affect oral health among older people. The aim of this thesis was to study whether sedative load, which represents cumulative exposure to drugs with sedative properties, is associated with oral health among community-dwelling older people. The focus was on a dry mouth, oral health behavior, dental caries, and infection in the periodontium. In addition, sedative load and anticholinergic burden were compared.

The present study population was a subpopulation from an intervention study “Geriatric Multidisciplinary Strategy for Good Care of the Elderly”. The study population consisted of 159 community-dwelling, dentate, and non-smoking people aged 75 or older from the city of Kuopio, Finland. Data were collected with interviews, geriatric assessments, and clinical oral examinations. Sedative load was determined by using a previously published method.

The study showed that participants with a sedative load were more likely to have dental caries, but not periodontitis, when compared with participants without a sedative load. Sedative load was associated with decreased stimulated salivary secretion and less strongly with unstimulated salivary secretion but not with xerostomia. The results also showed that sedative load was associated with poor or insufficient oral health behavior. Anticholinergic burden was associated with low unstimulated salivary secretion and xerostomia, but not with low stimulated salivary secretion.

In conclusion, cumulative exposure to drugs with sedative properties was associated with insufficient oral self-care and poor oral health. The results from this study emphasize the fact that older people using drugs with sedative properties require thorough prophylaxis measures and regular dental check-ups because of their high risk of having poor oral health.

Keywords: 75 and over, aged, anticholinergic, dental caries, dry mouth, hyposalivation, independent living, medication, oral hygiene, periodontitis, sedatives, xerostomia

Tiisanoja, Antti, Sedatiivikuorma ja suun terveys kotona asuvilla iäkkäillä henkilöillä.

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Suun terveyden tutkimusyksikkö

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Tiivistelmä

Väestön iäkkäiden henkilöiden osuuden kasvaessa ja heidän lääkkeiden käytön lisääntyessä on tärkeää tutkia, miten lääkkeet vaikuttavat ikääntyneiden suun terveyteen. Tutkimuksen tarkoituksena oli selvittää lääkityksestä aiheutuvan sedatiivikuorman (sedative load) vaikutuksia suun terveyteen kotona asuvilla iäkkäillä henkilöillä. Eritoten tutkimuskohteena oli sedatiivikuorman yhteys kuivaan suuhun, suun terveystyötyymiseen, kariekseen sekä hampaiden tukikudosten sairauteen. Lisäksi tutkittiin antikolinergisen kuorman yhteyttä kuivaan suuhun ja tuloksia verrattiin sedatiivikuormaan.

Tutkimuspopulaatio oli osa geriatrasta Hyvän Hoidon Strategia -interventiotutkimusta (HHS). Populaatio koostui 159 kotona asuvasta 75-vuotiaasta tai sitä vanhemmasta hampaallisesta, eitu-pakoivasta kuopiolaisesta. Tutkimusmateriaali kerättiin haastattelulla, geriatrisella tutkimuksella sekä kliinisellä suun tutkimuksella. Sedatiivikuorma laskettiin käyttäen aiemmin kehitettyä mallia, jossa määritetään kokonaislääkityksestä aiheutuva sedatiivikuorma.

Tutkimus osoitti, että osallistujilla, joilla oli sedatiivikuormaa, oli keskimäärin enemmän kariesta muttei hampaiden tukikudoksen sairautta verrattuna henkilöihin, joilla ei ollut sedatiivikuormaa. Tulokset osoittivat myös, että sedatiivikuorma oli yhteydessä alentuneeseen stimuloitujen syljeneritykseen ja vähemmässä määrin alentuneeseen leposyljeneritykseen, mutta ei kuivan suun tunteeseen. Antikolinerginen kuorma oli yhteydessä alentuneeseen leposyljeneritykseen ja kuivan suun tunteeseen, mutta ei alentuneeseen stimuloitujen syljeneritykseen. Sedatiivikuorma oli yhteydessä puutteelliseen suun terveystyötyymiseen, kuten vähäiseen hammastahnan käyttöön ja suureen plakkimäärään.

Johtopäätöksenä voidaan todeta, että altistuminen väsyttävillä lääkkeillä on yhteydessä puutteelliseen omahoitoon ja huonoon suun terveyteen. Tämän tutkimuksen tulokset korostavat väsyttäviä lääkkeitä käyttävien ikääntyneiden tarvitsevan perusteellisia ennaltaehkäiseviä toimia sekä säännöllisiä suun tutkimuksia, koska heillä on suurentunut riski huonoon suun terveyteen.

Asiasanat: 75 vuotta täyttäneet, antikolinergiset lääkkeet, ikääntyneet, karies, kotona asuvat, kuiva suu, kuivan suun tunne, lääkitykset, parodontiitti, sedatiivit, suuhygienia, vähentynyt syljeneritys

To my grandparents

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5.11.2017

Antti Tiisanoja

Abbreviations

ADS	Anticholinergic Drug Scale
ARS	Anticholinergic Risk Scale
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CGA	Comprehensive Geriatric Assessment
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrAS	Clinician-rated Anticholinergic Scale
DMFT	Decayed Missing Filled Teeth
FCI	Functional Comorbidity Index
GABA	gamma-aminobutyric acid
GeMS	Geriatric Multidisciplinary Strategy
HHS	Hyvän Hoidon Strategia
IADL	Instrumental Activities of Daily Living
MAO	monoamine oxidase
MMSE	Mini-Mental State Examination
OR	odds ratio
SAA	serum anticholinergic activity
SL	sedative load
SNRI	serotonin–norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
RR	relative risk
WHO	World Health Organization

List of original articles

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

- I Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) Sedative load, carious teeth, and infection in the periodontium among community-dwelling older people. *Gerodontology* 34: 13–23
- II Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2016) Sedative load and salivary secretion and xerostomia in community-dwelling older people. *Gerodontology* 33: 117–184
- III Tiisanoja A, Syrjälä AM, Komulainen K, Lampela P, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) Anticholinergic burden and dry mouth among Finnish community-dwelling older adults. *Gerodontology* doi: 10.1111/ger.12304
- IV Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) The association of medications with sedative properties with oral health behavior in community-dwelling older people. *Int J Dent Hyg* doi:10.1111/idh.12285

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1 Introduction

The proportion of older people (defined here as ≥ 65 years) is growing worldwide, but the increase is particularly distinct in developed countries (WHO 2011, Rechel *et al.* 2013). In Finland, the proportion of people aged ≥ 65 years is expected to increase from the current 20 percent to 26 percent by 2030 and the proportion is estimated to grow to 29 percent by 2060 (Official Statistics Finland 2015). This demographic change is causing and will continue to cause challenges for the health care system in the near future. For example, in developed countries multimorbidity is already affecting more than half of the population aged 65 years or older (Marengoni *et al.* 2008, van Oostrom *et al.* 2012, Roberts *et al.* 2015). From the oral health perspective, the increasing number of older people who are retaining their own natural teeth (Kassebaum *et al.* 2014a) will require more oral health care services (Dounis *et al.* 2010, Petersen *et al.* 2010).

Alongside with morbidity, drug use is also increasing with age (Boyd *et al.* 2005), and concurrent use of multiple drugs is common among the older population (Banerjee *et al.* 2011, Sigurdardottir *et al.* 2011). Use of drugs with sedative properties such as hypnotics and antipsychotics, is especially high among older people (Taipale *et al.* 2014, Olfson *et al.* 2015b). Such drugs cause sedation either as a desired therapeutic effect or as an unwanted side effect, and cumulative exposure to these drugs can be measured with the Sedative Load Model (Linjakumpu *et al.* 2003 & 2004).

Biological changes that take place concomitantly with aging cause older people to be at a higher risk of suffering from adverse effects of drugs than younger people (Lavan *et al.* 2016). One of the most common adverse effects of medication, especially with psychotropics and other drugs with sedative properties (Guggenheimer *et al.* 2003, Smith *et al.* 2013), is a dry mouth (Thomson 2015). A dry mouth decreases the quality of life by making eating, speaking, and tasting more difficult (Turner & Ship 2007) and it predisposes people to oral diseases such as dental caries and prosthetic stomatitis (Dawes 2008). Oral diseases such as dental caries (Thomson *et al.* 2002, Maupomé *et al.* 2006) and periodontal diseases (Alani & Seymour 2014) are also related to certain drugs and drug groups.

Because of the growing proportion of the older population and the challenges that come with treating this population, it is important to search for ways to identify people who are at a high risk of having oral health problems. Based on previous knowledge about the detrimental effects of drugs on oral health, one possible method could be assessment of sedative load, which could be used to focus enhanced dental

prophylaxis measures and treatment efforts on those who need them most. Thus, the overall purpose of this thesis was to study the effects of sedative load and, to a lesser extent, of anticholinergic burden on oral health among community-dwelling older people.

2 Review of the literature

2.1 Medication in older population

When discussing about the medication in an older population, two important topics are often raised: concurrent use of multiple drugs and adverse effects of drugs. These two topics are discussed below briefly before the literature review on sedative and anticholinergic drugs.

Polypharmacy

Due to the commonness of morbidity and multimorbidity in the older population, drug use increases with age. When multiple chronic diseases co-occur, treating them with drugs according to guidelines usually leads to polypharmacy (Boyd *et al.* 2005). Despite the common use of this term, there is no clear definition for polypharmacy, but often in the literature the term refers to taking four to five, or more drugs concurrently (Page *et al.* 2010, Steinman and Hanlon 2010). Polypharmacy is common among the older population, varying between 25 and 50 percent worldwide (Junius-Walker *et al.* 2007, Banerjee *et al.* 2011, Sigurdardottir *et al.* 2011).

Polypharmacy can be seen to have two meanings: inappropriate polypharmacy (too many drugs) and appropriate polypharmacy (many drugs) (Aronson 2004). Since polypharmacy does not always lead to poor outcomes, it is becoming more acceptable to prescribe multiple drugs, and in some cases this is even encouraged, especially in patients with multiple chronic conditions (Hughes *et al.* 2014). Appropriate polypharmacy, however, requires a thorough review of the medications taken, good knowledge about the effects of the drugs, monitoring of these effects, and use of only beneficial drugs (Payne *et al.* 2014).

Adverse effects

Older people are more susceptible to adverse effects from drugs than younger people because of the biological changes caused by the aging process, which affect pharmacodynamics and pharmacokinetics (Lavan *et al.* 2016). The use of multiple drugs increases the risk of medication errors (Koper *et al.* 2013), adverse drug effects (Nguyen *et al.* 2006, Bourgeois *et al.* 2010), and drug-drug interactions

(Goldberg *et al.* 1996). Other factors predisposing to the adverse effects of drugs are female gender (Lucas *et al.* 2016), renal dysfunction (Epstein 1996), liver failure or insufficiency (Weersink *et al.* 2016), multimorbidity (Lavan *et al.* 2016), and frailty (Hubbard *et al.* 2013), for example. The most common adverse effect of drugs on the oral cavity is a dry mouth, followed by different mucosal lesions and ulcerations (Scully & Bagan 2004).

2.1.1 Sedation caused by drugs

Sedation can be described as objectively measured decreased psychomotor functioning and a subjective feeling of drowsiness or sleepiness (Bourin *et al.* 2004). Objective measurements of sedation include psychometric tests that focus on different aspects of sensory-motor processing, cognitive skills, concentration, and psychomotor and motor abilities (Hindmarch *et al.* 2009). People may not report feeling sedated even though they show decreased psychomotor functioning in an objective test (Echizenya *et al.* 2007).

Certain drugs such as anxiolytics and hypnotics (benzodiazepines, z-hypnotics, etc.) cause sedation as their main therapeutic effect, while some other drugs cause sedation as an unwanted adverse effect. After the development of atypical antipsychotics and selective serotonin reuptake inhibitors (SSRI), sedation has changed from being an essential part of the therapeutic effect to an undesired adverse effect of antipsychotics and antidepressants (Bourin *et al.* 2004). Especially in diseases or syndromes that impair cognition and psychomotor functioning (severe depression, dementia etc.), additional sedation caused by drugs is detrimental to the patient (Hindmarch 2009).

Multiple pharmacological mechanisms mediate sedation in the central nervous system (CNS). These mechanisms include agonism of benzodiazepine receptors in the gamma-aminobutyric acid (GABA)-A complex (Möhler *et al.* 2002), antagonism of histamine H1 receptors (Turner *et al.* 2006) and μ -opioid receptors (Young-McCaughan *et al.* 2001), antagonism or agonism of $\alpha 1/\alpha 2$ -adrenergic receptors (Reynolds 2004), and blockage of muscarinic receptors (Bourin *et al.* 2004). The same mechanisms are thought to contribute to impaired physical functioning.

2.1.2 Use of drugs with sedative properties

Benzodiazepines and other benzodiazepine-like drugs (z-hypnotics etc.) are the drugs with sedative properties most commonly used among the older population,

and their use ranges between 9 and 12 percent worldwide (Hollingworth & Siskind 2010, Taipale *et al.* 2014, Olfson *et al.* 2015a, Johnson *et al.* 2016). Other drugs with sedative properties commonly used among the older population are antipsychotics (Beck *et al.* 2005, Olfson *et al.* 2015b), antidepressants (Linjakumpu *et al.* 2002, Taipale *et al.* 2014), and opioids (Sakshaug *et al.* 2017, Veal *et al.* 2015).

Concomitant use of multiple drugs with sedative properties is also common in the older population (Linjakumpu *et al.* 2002, Johnell & Fastbom 2009, Veal *et al.* 2015). Benzodiazepines, in particular, are often used alongside with other psychotropic drugs such as antidepressants or antipsychotics (Johnell & Fastbom 2009). It has also been shown that concurrent use of anxiolytics/hypnotics is common alongside with regular opioid analgesics (Veal *et al.* 2015). The above-mentioned drugs may have an accumulative sedative effect, especially in older patients, due to their adverse effects and interactions, or both (Hughes 1998, Pollock 1998).

2.1.3 Sedative Load Model

Determining cumulative exposure to multiple drugs with sedative properties is challenging because these drugs include a variety of different pharmacological groups. Four methods have been developed for assessing cumulative exposure to drugs with sedative properties: the Sedative Load Model (Linjakumpu *et al.* 2003 & 2004), the Sloane Model (Sloane *et al.* 2008), the Drug Burden Index (Hilmer *et al.* 2007), and the CNS Drug Model (Hanlon *et al.* 2009, Wright *et al.* 2009). Of the four models, the Sedative Load Model is the most comprehensive in terms of drugs and drug classes (Taipale *et al.* 2010).

The Sedative Load Model was created by reviewing summaries of the product characteristics of all drugs available in Finland between 1998 and 2001 (Linjakumpu *et al.* 2003 & 2004). The model was updated in 2009 to include drugs that had been brought to the market since the development of the original model (Taipale *et al.* 2011a). All the drugs were classified into one of four groups based on their sedative properties (Linjakumpu *et al.* 2004). The four groups were: 1) primary sedatives; 2) drugs with sedation as a prominent side effect or drugs with a sedating component; 3) drugs with sedation as a potential adverse effect; and 4) drugs with no known sedative effect. Each drug in group one was given a sedative rating of 2 and drugs in group two were given a sedative rating of 1. No sedative rating was assigned to groups three or four. Sedative load was calculated by summing the sedative ratings of all the drugs in the person's drug regimen.

2.1.4 Sedative load in the older population

Since the development of the Sedative Load Model, several studies have used it to measure cumulative exposure to drugs with sedative properties among older populations in different settings (Table 1).

Among community-dwelling Finnish people aged 64 years or more, 35 percent had a sedative load ≥ 1 and 12 percent had a sedative load ≥ 3 (Linjakumpu *et al.* 2004). In a more recent study by Taipale *et al.* (2012), it was shown that among Finns aged 75 years or more, 21 percent had a sedative load of 1–2 and 8 percent had a sedative load ≥ 3 in 2004, and that by 2007 the proportions had increased to 24 percent and 12 percent, respectively. A study by Peklar *et al.* (2015) showed that among an aged, community-dwelling Irish population, 14 percent had a sedative load of 1–2 and 5 percent had a sedative load ≥ 3 . Among community-dwelling Australian men aged 70 or more, 7 percent had a sedative load of 1 and 8 percent had a sedative load ≥ 2 (Gnjidic *et al.* 2014).

Older people living in residential or long-term care facilities have been shown to have higher sedative loads than community-dwelling people. For example, in Finland 85 percent of long-term care residents had a sedative load ≥ 1 and 53 percent had a sedative load ≥ 3 (Taipale *et al.* 2009). In the same study population it was found that sedative load did not differ between people with or without dementia (mean 3.0 vs. 2.7) (Bell *et al.* 2010). In Northern Ireland, 55 percent of people with dementia living in a residential care facility had a sedative load of 1–2 and 12 percent had a sedative load ≥ 3 (Parsons *et al.* 2011). Table 1 presents more detailed information about sedative load in various studies.

Table 1. Distribution of sedative load in various studies.

Study	Country	N	Age	Setting	Distribution of Sedative load
Linjakumpu <i>et al.</i> 2004	Finland	1197	≥ 65 years	Community	35% had a sedative load ≥ 1, 12% had a sedative load ≥ 3
Taipale <i>et al.</i> 2009	Finland	1004	Mean age 81	Institution	85% had a sedative load ≥ 1, 53% had a sedative load ≥ 3
Parsons <i>et al.</i> 2011	Northern Ireland	133	≥ 83 years	Institution	55% had a sedative load of 1–2, 12% had a sedative load ≥ 3
Taipale <i>et al.</i> 2012a	Finland	700	≥ 75 years	Community	In 2004: 21% had a sedative load of 1–2 and 8% had a sedative load ≥ 3 In 2007: 24% had a sedative load of 1–2 and 12% had a sedative load ≥ 3
Gnjidic <i>et al.</i> 2014	Australia	1696 men	≥ 70 years	Community	7% had a sedative load of 1, 8% had a sedative load ≥ 2
Peklar <i>et al.</i> 2015	Ireland	3446	≥ 65 years	Community	14% had a sedative load of 1–2, 5% had a sedative load ≥ 3

2.1.5 Anticholinergic drugs

Anticholinergic drugs usually refer to drugs that can block any of five muscarinic receptors (M1-M5) found in smooth muscle, motor neurons, the heart, or the CNS (Karimi *et al.* 2012). Many commonly used drugs have an affinity to muscarinic receptors (Tune 2001, Chew *et al.* 2008). Because of their anticholinergic effect, certain drugs like atropine are used to treat specific medical conditions. On the other hand, many common drugs (antidepressants, antipsychotics, etc.) also have an anticholinergic effect, which is not related to their therapeutic action and is thus seen as an unwanted adverse effect.

The wide distribution of muscarinic receptors (M1–M5) in the body leads to anticholinergic drugs causing a variety of adverse effects, which can be divided into peripheral and central adverse effects (Wawruch *et al.* 2012). Peripheral adverse effects are, e.g. a dry mouth, urinary retention, blurred vision, constipation; central adverse effects are, e.g. delirium, confusion, drowsiness, and cognitive decline (Gerretsen & Pollock 2011).

Because drugs with anticholinergic properties include different drug groups and because their anticholinergic potency varies, different methods are used to

classify anticholinergic drugs (Kersten & Wyller 2014). These drugs are classified by means of serum anticholinergic activity (SAA), *in vitro* muscarinic receptor affinity (pKi), clinical consensus, or a combination of these methods.

2.1.6 Anticholinergic Drug Scale

Cumulative exposure to anticholinergic drugs can be observed by measuring the anticholinergic burden caused by the drugs used. Several ranked lists have been developed for this purpose, such as the Anticholinergic Drug Scale (ADS) (Carnahan *et al.* 2006), the Anticholinergic Risk Scale (Rudolph *et al.* 2008), and a list compiled by Chew *et al.* (2008). Of the above-mentioned lists, the ADS includes the highest number of drugs with anticholinergic properties (n = 117) and it covers 88 percent of the drugs regularly used in the original Geriatric Multidisciplinary Strategy for Good Care of the Elderly (GeMS) study population (Lampela *et al.* 2013).

The ADS's drug classification is based on expert opinion and the scale has been validated in both institutional (Carnahan *et al.* 2006) and community-dwelling (Ness *et al.* 2006) settings. Drugs were classified into four categories based on their anticholinergic activity (Carnahan *et al.* 2006). The first category (ADS score 3) includes drugs with significant anticholinergic activity, the second category (ADS score 2) includes drugs that are noted to have anticholinergic adverse effects, the third category (ADS score 1) includes drugs with potential anticholinergic activity as evidenced by receptor-binding studies, and the fourth category (ADS score 0) includes drugs with no known anticholinergic activity. Dose adjustments are done for the drugs belonging to categories 1 and 2. The total ADS score for a person is a summation of each drug's ADS score and it represents the anticholinergic burden.

2.1.7 Use of anticholinergic drugs in the older population

The frequency of anticholinergic drug use depends on the method with which anticholinergic drugs are classified (Durán *et al.* 2013). In the following text the focus is on the prevalence of anticholinergic drug use classified by ADS and ADS scores.

The most common drugs with a strong anticholinergic effect (ADS score 3) among the older population are tricyclic antidepressants, such as amitriptyline and doxepine (Han *et al.* 2008, Parkinson *et al.* 2015); first-generation antihistamines, such as diphenhydramine, chlorpheniramine, and hydroxyzine (Marcum *et al.*

2016); antiemetics, such as meclizine; and urinary antispasmodics, such as oxybutynin (Marcum *et al.* 2016). Common drugs with a moderate anticholinergic effect (ADS score 2) are antidepressants paroxetine and nortriptyline (Kersten *et al.* 2013, Marcum *et al.* 2016). The most common drugs with a low anticholinergic effect (ADS score 1) are furosemide, isosorbide mono/dinitrate, prednisolone, and warfarin (Kersten *et al.* 2013, Parkinson *et al.* 2015, Marcum *et al.* 2016).

The use of anticholinergic drugs among the older population varies from 16 (Low *et al.* 2009) to 75 percent (Lampela *et al.* 2013). Explanations for the large variation in the use of anticholinergic drugs can be found in the differences in the drug inclusion criteria (taking account only drugs with ADS ≥ 3), age, co-morbidity, living situation, and the differences in a prescription culture (Table 2). Earlier studies have also shown that an anticholinergic burden is often comprised mostly of drugs with an ADS score of 1 and that concomitant use of multiple anticholinergic drugs is common (Low *et al.* 2009, Chen *et al.* 2010, Kersten *et al.* 2013, Mate *et al.* 2015, Parkinson *et al.* 2015).

Table 2. Distribution of anticholinergic burden in various studies.

Study	Country	N	Age	Setting	Anticholinergic drug use
Han <i>et al.</i> 2008	USA	544 men	≥ 65 years	Community	63% had an ADS score ≥ 1 , mean ADS score 1.3 ± 1.5
Low <i>et al.</i> 2009	Australia	2058	60–64 years	Community	16% had an ADS score ≥ 1
Chen <i>et al.</i> 2010	USA	491	Mean age 75.6 years	Community/ Institution	42% had an ADS score of 1, 8% had an ADS score of 2, 16% had an ADS score ≥ 3 ,
Lampela <i>et al.</i> 2013	Finland	781	≥ 75 years	Community	75% had an ADS score ≥ 1
Kersten <i>et al.</i> 2013	Norway	1101	> 70 years	Institution	21% had an ADS score ≥ 3
Sura <i>et al.</i> 2013	USA	1.56 M	≥ 65 years	Community	60% had an ADS score ≥ 1
Marcum <i>et al.</i> 2016	USA	61,451 women	≥ 65 years	Community	11% had an ADS score ≥ 3
Parkinson <i>et al.</i> 2015	Australia	5560 women	≥ 82 years	Community	43% had an ADS score ≥ 1

2.2 Dry mouth and drugs

A dry mouth can be defined as consisting of two conditions: xerostomia and hyposalivation (Thomson 2015). Xerostomia is a subjective feeling of dryness in the mouth (Fox *et al.* 1987) and hyposalivation is a condition where a person has objectively measured low salivary secretion (either stimulated or unstimulated salivary flow) (Navazesh 1993). These conditions can manifest together but they are not necessarily concurrent (Thomson *et al.* 1999), and only a small portion of people (15%) with a dry mouth have both conditions (Thomson 2015). Xerostomia is likely to occur when the salivary flow rate is lower than the rate of fluid evaporation and fluid absorption in the oral cavity (Dawes 2004). If xerostomia correlates with hyposalivation, then often unstimulated salivary secretion has decreased more than 40 or 50 percent from the normal rate (Dawes 1987, Ship *et al.* 1991).

Based on a review of epidemiological studies, the prevalence of a dry mouth, including both xerostomia and hyposalivation, is around 20 percent among the older population (Orellana *et al.* 2006, Thomson 2014). When observed separately, the prevalence of xerostomia among community-dwelling older people ranges from 17 to 40 percent (Hochberg *et al.* 1998, Andersson *et al.* 2004), and for hyposalivation, prevalence is between 15 and 23 percent (Hochberg *et al.* 1998, Thomson *et al.* 1999).

The most common etiological factors for a dry mouth among older people are drugs and their side effects, or polypharmacy (Wolff *et al.* 2008, Thomson 2015, Villa *et al.* 2015). Other common etiological factors are systemic diseases such as Sjögren's syndrome (Peri *et al.* 2012) and diabetes mellitus (López-Pintor *et al.* 2016), radiotherapy of the head and neck region (Pinna *et al.* 2015), depression (Han *et al.* 2015), and Alzheimer's disease (Rejnefelt *et al.* 2006). Table 3 lists common consequences of a dry mouth.

Table 3. Consequences of a dry mouth.

Component	Description
Saliva	Composition of ions and proteins changes Oral acid neutralization decreases
Oral cavity	Bacterial composition changes Oral clearance of food and microbes decreases Tooth remineralization decreases Oral mucosa lubrication decreases Oral mucosa becomes desiccated and friable
Functional difficulties	Speaking Mastication Swallowing Denture retention
Sensory disturbances	Xerostomia Taste
Oral diseases	Dental caries Candidiasis

Most commonly drugs cause dry mouth by inhibiting acetylcholine binding to muscarinic receptors (M3 and M1) in the salivary glands, which leads to decreasing or even depletion of acinar cell fluid transport (Miranda-Rius *et al.* 2015, Proctor 2016, Villa *et al.* 2016). Another mechanism by which drugs cause a dry mouth is by affecting certain receptors (α 1, β 2, H2 and GABA) directly on acinar cells in the salivary glands (Scully 2003, Villa *et al.* 2016). Concurrent use of multiple drugs can have a synergistic effect on the salivary glands or CNS and thus can cause more severe symptoms of dry mouth (Han *et al.* 2015, Villa *et al.* 2015).

According to drug monographs, over 500 drugs are estimated to cause xerostomia or hyposalivation as an adverse effect (Porter *et al.* 2004, Spolarich 2014). A recently published systematic review (Wolff *et al.* 2017) showed that 106 drugs have strong or moderate proof and 48 drugs have only weak proof of causing xerostomia or hyposalivation. The drugs most often associated with a dry mouth are those with strong anticholinergic activity, such as antipsychotics, urinary antispasmodics, tricyclic antidepressants, sedative hypnotics, opiates, muscle

relaxants, bronchodilators, and diuretics (Guggenheimer *et al.* 2003, Scully 2003, Smith *et al.* 2013). A summary of selective drugs associated with xerostomia or hyposalivation is presented in Table 4.

Table 4. Example list of drugs that cause a dry mouth.

Mechanism that causes a dry mouth	Pharmacological group	Example drugs
Anticholinergic action	Tricyclic antidepressants	Amitriptyline, nortriptyline, clomipramine, imipramine
	Antipsychotics	Phenothiazine, olanzapine, quetiapine, risperidone
	Anti-Parkinson's drugs	Biperiden, amantadine, levodopa, carbidopa
	Muscarinic receptor antagonist	Oxybutynin
	Antispasmodics	Propantheline bromide
	Alpha-receptor antagonists	Tamsulosin, terazosin
	Diuretics	Furosemide, bumetanide, torsemide
	Antihistamine	Loratidine, hydroxyzine, diphenhydramine, cetirizine
	Antiemetics/drugs for vertigo	Scopolamine
	Bronchodilator	Ipratropium bromide, tiotropium bromide
	Atropine and analogs	Atropine, benztropine
Sympathomimetic action	Antidepressants: SSRI, SNRI	Venlafaxine, Duloxetine, mirtazapine, bupropion
	Antihypertensive	Metoprolol, timolol, clonidine, prazosin, terazosin
	Antimigraine agents	Zolmitriptan, rizatriptan
	Bronchodilators	Albuterol, formoterol,
	Skeletal muscle relaxants	Cyclobenzaprine, tizanidine
Synergistic action (Anticholinergic and Sympathomimetic)	Benzodiazepine	Alprazolam, lorazepam, diazepam, triazolam, temazepam
	Nonbenzodiazepine hypnotics	Zolpidem, eszopiclone, zolpiclone
	Opioids	Fentanyl, tramadol, oxycodone
Other	H2 antagonists, proton pump inhibitors	Omeprazole

SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin-norepinephrine reuptake inhibitors.

A dry mouth is associated with a large number of drugs (Nederfors *et al.* 1997, Smidt *et al.* 2010, Liu *et al.* 2012, Villa *et al.* 2016). Early studies by Närhi *et al.* (1992) and Wu & Ship (1993) showed that a large number of drugs is associated with decreased salivary flow in older people. In other studies it has been shown that, among community-dwelling older adults, the risk of xerostomia is higher in participants taking ≥ 3 drugs than in participants taking only one drug (Locker 1995), and that among older home care clients, excessive polypharmacy (taking more than 10 drugs) was found to be associated with xerostomia (Viljakainen *et al.* 2016). In a study done among vulnerable older people, the prevalence of a dry mouth with one drug was shown to be 37 percent, with two drugs, 62 percent, and with three drugs, 78 percent (Liu *et al.* 2012).

Xerostomia and decreased salivary secretion have been shown to be associated with concurrent use of multiple drugs with sedative properties (de Almeida Pdel *et al.* 2008, Hashimoto *et al.* 2012, Okamoto *et al.* 2016). Concomitant use of multiple anticholinergic drugs (Ghezzi 2003, Desoutter *et al.* 2012, Günes *et al.* 2012) and an anticholinergic burden (Rudolph *et al.* 2008, Kersten *et al.* 2013) have also been reported to be associated with a dry mouth.

2.3 Oral health behavior and drugs

Toothbrushing twice a day with fluoride toothpaste is the basis of sufficient oral hygiene for people with natural teeth. Furthermore, because using only a toothbrush is not effective in the interdental region, interdental brushes, dental floss or toothpicks are recommended based on the individual anatomy and need. In addition to sufficient oral self-care, maintaining good oral health also requires healthy diet, absence of smoking, and regular use of dental care services.

There is considerable variation in oral health behavior among older people. In the western countries, the proportion of people who brush their teeth twice a day has increased and it varies between 40 and 97 percent, depending on the population (Claydon 2008). Among the Finnish older population, toothbrushing at least twice a day ranges between 46 and 75 percent (Komulainen *et al.* 2012, Suominen *et al.* 2012). There is also difference in the toothbrushing frequency between genders, women (68%, aged ≥ 75 years) brushing twice a day more often than men (47%, aged ≥ 75 years) (Suominen *et al.* 2012). The use of toothpaste twice a day in adults is surprisingly low, varying between 45 and 85 percent (Christensen *et al.* 2003, Vehkalahti & Knuutila 2004, Tseveenjav *et al.* 2010). Furthermore, regular use of dental care services is generally less frequent among older people than among

younger people (Holm-Pedersen *et al.* 2005), ranging between 50 and 80 percent (Holm-Pedersen *et al.* 2005, Österberg *et al.* 2007, Li *et al.* 2011, Suominen *et al.* 2012).

Poor oral health behavior has been shown to be associated with several socio-demographic and health-related factors, such as low education level (Brothwell *et al.* 2008), poor health and several systemic diseases (Kiyak *et al.* 2005, Scully & Ettinger 2007), functional impairments (Dolan *et al.* 1998), and impaired cognitive functions (Wu *et al.* 2007, Moriya *et al.* 2011). At the moment, knowledge about the effects of drugs on oral health behavior, including toothbrushing, toothpaste use, or utilization of dental care services, is limited.

2.4 Dental caries and drugs

Dental caries begins with an accumulation of bacteria on the tooth surface and formation of dental plaque (Selwitz *et al.* 2007). In matured dental plaque, bacteria such as *Streptococcus* species, for example, use sugars and other fermentable carbohydrates to produce acids on the tooth surface, causing a shift in the balance between remineralization and demineralization towards increased demineralization of the tooth (Takahashi & Nyvad 2008). The progression of dental caries is affected by salivary secretion and saliva composition, consumption of sugars, systemic diseases, and oral hygiene (Selwitz *et al.* 2007).

Dental caries is one of the main causes of orofacial pain, suffering, and disability (Baelum *et al.* 2007). Despite the overall decline of dental caries in industrialized countries (Murray 2011), this reduction has not happened as much in the older population (Selwitz *et al.* 2007, Micheelis 2011, Suominen *et al.* 2012). The worldwide prevalence of dental caries, especially root caries, among the older population ranges between 30 and 60 percent (Suominen-Taipale *et al.* 2004, Gluzman *et al.* 2013, Kassebaum *et al.* 2015).

Drugs are thought to play a role in the development of dental caries in two main ways (Thomson *et al.* 2002). The first is by reducing salivary secretion to a level where the normal buffer capacity of saliva is not sufficient to deal with acid challenges and maintain a balance towards remineralization of dental tissues. The second is by causing a feeling of a dry mouth, xerostomia, which could lead the person to seek relief from the symptoms by chewing hard candies or drinking beverages with a high sugar content or acidity (Thomson *et al.* 2002). Another plausible pathway might be the influence of psychotropic drugs on oral health behavior through alteration of cognition or mood (Vermeeren 2004).

The findings in current literature about the association between drugs and dental caries are uncertain (Table 5). This is due to differences in classification methods, study designs, and small study samples. There are studies which have shown that the number of drugs is associated with dental caries or increased restoration rates (Papas *et al.* 1993, Thomson *et al.* 1995, Fure 2004, Maupomé *et al.* 2006), while others have shown that the number of drugs is not associated with dental caries or increased restoration rates (Saunders & Handelman. 1992, Hawkins *et al.* 1997, Närhi *et al.* 1998, Thomson *et al.* 2002, Janket *et al.* 2003). Regarding specific drug classes, the following drugs and drug groups have been found to be associated with dental caries or higher restoration rates: tricyclic antidepressants, SSRIs, and monoamine oxidase (MAO) inhibitors (Rundegren *et al.* 1985, Thomson *et al.* 1995, Rindal *et al.* 2005); first-generation antipsychotics, such as chlorpromazine, fluopentixol, and haloperidol (Hu *et al.* 2016); antihistamines (Drake *et al.* 1994, Lawrence *et al.* 1995); antiasthma drugs (Bjerkeborsn *et al.* 1987, Thomson *et al.* 2002); and anti-ulcer drugs (Thomson *et al.* 1995) (Table 5).

Table 5. Drugs associated with dental caries.

Study	Country	N	Study design	Drugs and dental caries
Rundegren <i>et al.</i> 1985	Sweden	32	Older adults in the community / Cross sectional	Long-term use of cyclic antidepressants was associated with dental caries prevalence
Bjerkeborsn <i>et al.</i> 1987	Sweden	61	Asthmatic children / Cross sectional	Antiasthma drugs were associated with coronal caries prevalence in children
Papas <i>et al.</i> 1993	USA	120	Older adults in the community / Cross sectional	Xerogenic drugs were associated with an increased risk of dental caries
Drake <i>et al.</i> 1994	USA	605	Older adults in the community / Longitudinal	Antihistamines were associated with coronal caries among white participants in 1.5 years' time
Lawrence <i>et al.</i> 1995	USA	452	Older adults in the community / Longitudinal	Antihistamines were associated with coronal caries among white participants in 3 years' time
Thomson <i>et al.</i> 1995	Australia	848	Older adults in the community / Cross sectional	Antidepressants and antiulcer drugs were associated with root caries, but the number of drugs were not

Study	Country	N	Study design	Drugs and dental caries
Hawkins <i>et al.</i> 1997	Canada	493	Older adults in the community / Cross sectional	The number of drugs was not associated with dental caries
Närhi <i>et al.</i> 1998	Finland	195	Older adults in the community / Cross sectional	The number of drugs was not associated with root caries
Thomson <i>et al.</i> 2002	Australia	848	Older adults in the community / Longitudinal	Antiasthma drugs were associated with dental caries but the number of drugs were not in 5 years' time
Chalmers <i>et al.</i> 2002	Australia	216	Older adults with and without dementia / Longitudinal	Use of neuroleptic drugs was associated with high caries increments
Janket <i>et al.</i> 2003	USA	345	Veterans in the community / Cross sectional	The number of drugs was associated with dental caries non-significantly
Fure 2004	Sweden	102	Older adults in the community / Cross sectional	The number of drugs was associated with dental caries
Rindal <i>et al.</i> 2005	USA	915	Older adults in the community / Cross sectional	Antidepressants and the number of drugs were associated with a high restoration rate
Maupomé <i>et al.</i> 2006	USA	11253	Older adults / Cross sectional	The number of drugs was associated with a high restoration rate
Hu <i>et al.</i> 2016	Taiwan	3610	Newly diagnosed schizophrenia patients / Cohort study	First-generation antipsychotics and antihypertensives were associated with treated dental caries

2.5 Periodontitis and drugs

Periodontitis is a continuous inflammatory process that begins with inflammation of the gingival tissues triggered by pathogenic bacteria. Accumulation of periodontal pathogens (anaerobes, spirochetes, and motile bacteria) causes an influx of inflammatory cells into the periodontal tissues and an increase in the amount of proinflammatory cytokines (Cekici *et al.* 2014). Prostaglandins (PGE2), interleukins (IL-1 β), and tumor necrosis factor-alpha (TNF- α) regulate the inflammatory response, and in periodontal disease they lead to progressive

attachment loss and destruction of the surrounding alveolar bone (Cekici *et al.* 2014).

As with dental caries, periodontal health has also improved in the general population over the past decades (Albandar 2005, Hugoson *et al.* 2008), but the change has been less pronounced among the older population (Thomson *et al.* 2004, Qian *et al.* 2007, Haas *et al.* 2012). The prevalence of periodontitis, measured by deepened periodontal pockets (probing depth \geq 4–5 mm), varies between 60 and 80 percent among people aged \geq 65 years (Micheelis 2011, Suominen *et al.* 2012, Eke *et al.* 2016). With severe periodontitis (probing depth \geq 6 mm) the prevalence varies between countries from 3.6 to 18.7 percent (Kassebaum *et al.* 2014).

Multiple factors influence the progression of periodontal disease: oral health behavior, smoking, stress, anxiety, and systemic conditions such as diabetes and rheumatic diseases (Khan *et al.* 2015). The pathogenesis and also the progression of periodontitis can be affected by a variety of drugs, especially those that interact with immune and inflammatory responses (Alani & Seymour 2014). Because of the complexity of the inflammation process in the periodontal tissue, drugs can have an influence on multiple levels of the inflammatory cascade (Cekici *et al.* 2014). Certain drugs can intensify the periodontal breakdown while others can provide protection against the breakdown (Alani & Seymour 2014). The dosage of drugs is also an important factor, because many immunosuppressive drugs have a narrow therapeutic window related to periodontal health (Alani & Seymour 2014).

The following drug groups have been shown to have either a protective or a detrimental effect on the progression of periodontitis in humans via their direct effects on the inflammatory cascade: tetracyclines (Golub *et al.* 2016), corticosteroids (Renvert *et al.* 2009), non-steroidal anti-inflammatory drugs (NSAIDs) (Vogel *et al.* 1984, Pinho *et al.* 2008), immunosuppressants (Alani & Seymour 2014), statins (Alani & Seymour 2014, de Monès *et al.* 2015), biopharmaceuticals, such as TNF- α blockers (Mayer *et al.* 2009, Ünstün *et al.* 2013), and bisphosphonates (Rocha *et al.* 2001). Additional evidence from animal models has shown that other drugs, for example fluoxetine (Branco-de-Almeida *et al.* 2012, Ortuño *et al.* 2016), tianeptine (Breivik *et al.* 2006), and diazepam (Gomes *et al.* 2013) can also have a protective effect on the progression of periodontitis. These drugs are thought to have a secondary effect on the inflammatory cascade due to their therapeutic effect on depression and anxiety, which can reduce inflammation (Branco-de-Almeida *et al.* 2012, Gomes *et al.* 2013).

2.6 Rationale for the study

With the growing older population and the considerable use of drugs with sedative properties among this population, further studies on the effects of these drugs on oral health are warranted. The review of literature showed that there are limitations in current knowledge about the effects of drugs with sedative properties on oral health and oral health behavior. More evidence is needed on the role of sedative drugs in oral health among older people.

3 Aims of the study

The overall purpose was to study the effects of sedative load on oral health among community-dwelling older people. The purpose was also to study whether an anticholinergic burden is associated with a dry mouth and to compare its effects with sedative load.

More specifically, the aims were to study:

1. If sedative load is associated with dental caries and infection in the periodontium (Study I)
2. If sedative load is associated with salivary secretion and xerostomia (Study II)
3. If anticholinergic burden is associated with salivary secretion and xerostomia (Study III)
4. If sedative load is associated with oral health behavior, including toothbrushing, use of toothpaste, utilization of dental care, and dental plaque (Study IV)

4 Subjects and methods

This study is based on the Geriatric Multidisciplinary Strategy for Good Care of the Elderly (GeMS) study, which was conducted in Kuopio, Eastern Finland, between the years 2004 and 2007. The original GeMS was a longitudinal, population-based study, with the purposes of optimizing medical treatment and medication and improving function or nutrition among community-dwelling older people.

The Comprehensive Geriatric Assessment (CGA) was performed on the participants at the baseline of the study and annually in the following years until 2007. The CGA was done by a multidisciplinary team consisting of three trained nurses, two trained physiotherapists, and two physicians specializing in geriatrics. More detailed information about the original GeMS study can be found in the papers published by Lampela *et al.* 2010, Jyrkkä *et al.* 2011, and Tikkanen *et al.* 2012.

4.1 Study population

The GeMS study population consisted of 1000 randomly selected inhabitants from the city of Kuopio, Finland, who were ≥ 75 years old on the first of November in 2003. A total of 781 participants provided written informed consent to participate in the original study (162 refused, 55 died before the scheduled baseline examination and two moved away). The original study population was divided into an intervention group ($n = 404$) and a control group ($n = 377$). The CGA and clinical oral examinations were done to the participants belonging to the intervention group.

The clinical oral examination was performed on 354 participants (27 refused and 23 died before the oral examination) during the years 2004–2005 and this population became the Oral Health GeMS study population. Oral interventions started after the oral examinations. For this thesis, the study population was further restricted to community-dwelling, dentate, and non-smoking participants. The final study population consisted of 159 participants (112 women and 47 men, mean age 79.3 SD 3.67).

4.2 Data collection

4.2.1 Data collected in the Comprehensive Geriatric Assessment

Information on each participant's socio-demographic factors, health status, and health behavior was obtained from an interview done by two trained nurses. In situations where the participant was unable to answer the questions due to his/her cognitive or other impairment, a close relative or a caregiver provided the information.

Socio-demographic factors

Residential status was marked as community-dwelling if the participant lived alone or with somebody else in their own home or in a surrounding comparable to home living, e.g. a sheltered home. Education level was classified into two categories based on the number of years of formal education: a lower education level being compulsory comprehensive school or less (< 7 years), a higher education level being secondary school or occupational education (≥ 7 years).

Health-related factors

Each participant's general health status was determined by means of cognitive ability, functional capability, and comorbidities in addition to diagnoses of certain diseases.

Cognitive ability was determined by using the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975) screening test, which assesses various cognitive functions (memory, arithmetic, orientation) with a 30-point questionnaire. The maximum score was 30, indicating good cognitive function, and a cut-off value of 24 or less indicated cognitive impairment (Dahl *et al.* 2007).

Functional capability was assessed with the Lawton Instrumental Activities of Daily Living (IADL) scale (Lawton *et al.* 1969). The IADL consists of a questionnaire with eight fields of following daily activities: ability to use a telephone, shop for groceries, prepare food, do housekeeping, do laundry, use transportation, and manage medication and finances. The maximum score of eight meant independence in all of the above-mentioned daily activities and zero meant total dependency. For the purpose of the current study, the IADL was categorized into two groups: 0–6 vs. 7–8.

Comorbidities were determined by using a modified Functional Comorbidity Index (FCI) (Groll *et al.* 2005), which was designed for assessment of physical

function in older people. The modified version of the FCI included 13 conditions: rheumatoid arthritis and other connective tissue disorders, chronic asthma/chronic obstructive pulmonary disease (COPD), depression, Parkinson's disease/multiple sclerosis, osteoporosis, stroke, coronary artery disease, myocardial infarction, heart failure, diabetes mellitus, visual impairment, hearing impairment, and obesity (body mass index >30). Each diagnosis was given a numeric value of 1 and they were summed together; higher index scores indicated higher comorbidity. Information about a specific diagnosis/symptom was obtained from the participants themselves, the medical records of primary health care, Kuopio University Hospital, or data obtained from the Finnish Special Reimbursement Registers maintained by the Social Insurance Institution of Finland.

Drug use

Self-reported drug use was determined by a study nurse during the interview and verified by the examining physician from prescription forms, drug packages, and medical records. The data were collected on average six months before the clinical oral examination. All drugs in use were classified according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization (WHO). The following modifications were made to the ATC because of the calculation of sedative load. 'Atypical antipsychotics' were defined as clozapine, quetiapine, olanzapine, risperidone, ziprasidone, and aripiprazole. 'Conventional antipsychotics' included all other drugs in ATC group N05A excluding lithium. 'Tricyclic antidepressants' included ATC class N06AA, 'SSRIs' included N06Ab class, and 'other antidepressants' included moclobemide and N06AX class.

Sedative load

Cumulative exposure to drugs with sedative properties was determined by using the Sedative Load Model (Linjakumpu *et al.* 2003&2004). The model was formed by categorizing all drugs marketed in Finland between 1998 and 2001 according to their sedative potential. Each drug taken by the participant was categorized into one of the four groups based on their sedative properties, specified in the manufacturers' summaries of product characteristics (Table 6). The categorization of the drugs was based on consensus between a psychogeriatrician, a geriatrician, and a physician specialized in pharmacoepidemiology. The model was updated in 2009 to include

drugs that became available in Finland after the development of the original model (Taipale *et al.* 2011a).

- The first group included primary or first line sedative drugs, such as anxiolytics, hypnotics, conventional antipsychotics, or tricyclic antidepressants
- The second group included drugs with sedation as a prominent side effect or with a sedating component, such as atypical antipsychotics, SSRIs, or antiepileptics
- The third group included drugs with sedation as a potential but rare adverse effect, such as second-generation antihistamines or acetylcholinesterase inhibitors
- The fourth group included all other drugs with no known sedative properties

A sedative rating was appointed to each of the four drug groups based on sedative properties. Drugs in group one were given a rating of 2 and in group two, a rating of 1. Drugs in groups three and four were given a rating of zero. The participant's sedative load was defined by summing the sedative ratings of all regularly used drugs. The following formula was used:

$$\text{Sedative load} = \sum_{k=1}^n SR_k$$

Where n is the number of drugs and SR_k indicates the sedative rating of the drug k .

Sedative load was classified in two ways: three-categorical: a) 0 b) 1–2 (moderate) c) ≥ 3 (high) and two-categorical: No vs. Yes. Use of sedative drugs by different class is presented in Table 7.

Table 6. Sedative rating of different drug classes in the Sedative Load Model.

Drug class	Sedative Load Model rating
Antipsychotics	
Conventional antipsychotics	2
Atypical antipsychotics	1
Anxiolytics and hypnotics	
Benzodiazepines and z-hypnotics (zopiclone.)	2
Other anxiolytics and hypnotics ¹	2
Antidepressants	
Tricyclic antidepressants and non-selective MAO inhibitors	2
SSRIs	1
Second-generation antidepressants	1
Opioids	1
Antiepileptics	1
Antiemetics (metoclopramide, scopolamine)	1
Antispasmodics with psychotropics	1
Centrally acting muscle relaxants	1
Anticholinergic anti-Parkinson drugs	1

¹ Clometiazole, valerian, barbiturates, first-generation antihistamines, buspiron, chloral hydrate.

MAO: monoamine oxidase, SSRIs: selective serotonin reuptake inhibitors.

Table 7. Use of drugs with sedative properties in the study population.

Drug class	Users, % (n)
Antidepressants	
SSRIs	1.9 (3)
Other antidepressants ¹	5.7 (9)
Antipsychotics	
Conventional antipsychotics ²	3.8 (6)
Atypical antipsychotics ³	3.1 (5)
Benzodiazepines and related drugs	
Benzodiazepines	9.4 (15)
Benzodiazepines-related drugs	5.0 (8)
Antiepileptics	1.9 (3)
Opioids	1.9 (3)

SSRIs: selective serotonin reuptake inhibitors.

¹ Including mianserin, mirtazapine, venlafaxine, moclobemide, trazodone.

² Including all the drugs in ATC group N05A excluding lithium.

³ Clozapine, quetiapine, olanzapine, risperidone, ziprasidone, and aripiprazole.

Anticholinergic Drug Scale

Carnahan's Anticholinergic Drug Scale (ADS) (Carnahan *et al.* 2006) was used to determine the anticholinergic burden caused by the drugs used. This scale was earlier referred to as the Clinician-rated Anticholinergic Scale (CrAS) modified version. The ADS is based on a combination of a literature review of drugs marked as having anticholinergic effects and an expert consensus of three geriatric psychiatrists who independently rated the anticholinergic effects of each drug (Carnahan *et al.* 2006). It includes 536 drugs, of which 117 have anticholinergic activity and the remaining 419 are classified as having no anticholinergic activity. The ADS has been validated in both institutional (Carnahan *et al.* 2006) and community-dwelling settings (Ness *et al.* 2006). Drugs are classified into four score categories based on their anticholinergic activity.

- The first category (ADS score 3) includes drugs with significant anticholinergic activity (e.g. amitriptyline, brompheniramine, or oxybutynin)
- The second category (ADS score 2) includes drugs which are sometimes noted to have anticholinergic adverse effects, usually with excessive doses (e.g. carbamazepine, cyproheptadine, or disopyramide)

- The third category (ADS score 1) includes drugs with potential anticholinergic activity as evidenced by receptor-binding studies (e.g. furosemide, digoxin, or captopril)
- The fourth category (ADS score 0) includes drugs with no known anticholinergic activity

Dose adjustments were done for the drugs in the first (ADS 3) and second category (ADS 2). Because all of the drugs do not have special dosing recommendations for geriatric patients, the total daily dose of the drug was compared with its maximum recommended daily dose. The participant's total ADS score was determined by summing the anticholinergic scores of all the drugs. This summation represents the anticholinergic burden caused by the drugs used. The ADS was categorized into three groups: a) 0, b) 1–2 (moderate) and c) ≥ 3 (high). The distribution of anticholinergic drugs in the study population is presented in Table 8.

Table 8. Use of drugs with anticholinergic activity (ADS) in the study population.

Anticholinergic activity	Users, % (n)
ADS score 1	
Isosorbide (mono-/dinitrate)	23 (37)
Furosemide (+ triamterene) ¹	12 (19)
Warfarin	11 (17)
Digoxin	5 (8)
Diltiazem	3 (5)
Dipyridamole	3 (5)
Prednisolone	3 (5)
Temazepam	2.5 (4)
Nifedipine	2.5 (4)
ADS score 2	
Ranitidine	1.2 (2)
ADS score 3	
Thioridazine	1.2 (2)
Amitriptyline	1.2 (2)
Oxybutynin	1.2 (2)

¹ In Finland triamterene is only available in combination with furosemide.

4.2.2 Data collected in the clinical oral examination

The clinical oral examinations and interviews were carried out in 2004 and 2005 in a primary care setting at a dental clinic of the municipal health center of Kuopio or at the participant's home. Both intra- and extra-oral examinations were performed on a standard dental unit equipped with a gauze pad, a WHO color-coded periodontal probe, and a mouth mirror. The home visits were performed in a similar fashion, with the exception of a different light source (a headlamp or a flashlight) and a lack of dental chair.

The clinical oral examinations were carried out by two experienced dentists who were standardized by examining seven participants together before the survey. The examiners worked in adjacent rooms, allowing them to consult with each other when needed. Furthermore, specific workshops for the dental team were held before and during the study to resolve possible problems. Due to the length of the clinical examination (one hour) and the high age of the participants, no repeated or parallel examinations were carried out.

Oral health behavior interview

Information about the participant's oral health behavior was attained from an interview done by a dentist during the clinical oral examination. In the interview, the participants were asked about their use and presence of removable dentures, frequency of tooth and denture brushing, use of toothpaste and a denture cleaning agent, use of sugary products, and utilization of dental care services.

Oral health behavior-related factors were mostly used as dichotomous variables. Toothbrushing frequency was classified as brushing at least twice a day *vs.* less frequently. Use of toothpaste was classified as using it at least twice a day *vs.* more seldom. Dental visits were classified as regular (annually or less frequent) *vs.* only symptom-based or never.

Salivary flow rate measurements and subjective feeling of a dry mouth

Both unstimulated and stimulated salivary secretion samples were collected using the draining method (Navazesh 1993) before the clinical oral examination. The participants were asked to refrain from eating or drinking one hour before the salivary sample collection. Participants with removable dentures provided the unstimulated salivary sample without dentures and the stimulated sample with dentures. The

participants were asked to sit straight and bend their head slightly forward during the saliva sample collection. After swallowing, passively drooled saliva was collected into a centrifuge tube for five minutes. For the stimulated salivary secretion sample, the participants were asked to chew on a piece of paraffin wax capsule for 30 seconds and then swallow or spit the saliva. After clearing the mouth, the participants kept chewing the paraffin capsule for five minutes and their saliva was drained into a glass centrifuge tube. The unstimulated salivary secretion was categorized into two groups according to literature: < 0.1 ml/min (low) vs. ≥ 0.1 ml/min (normal) and the stimulated salivary secretion was classified using two cut-off values: < 0.7 ml/min (low) vs. ≥ 0.7 ml/min (normal) and < 1.0 ml/min (low) vs. ≥ 1.0 ml/min (normal) (Heintze *et al.* 1983, Pedersen *et al.* 2002, Flink *et al.* 2008).

During the clinical oral examination the participants were asked about their subjective feeling of a dry mouth (xerostomia). The measurement of xerostomia was based on a single-item approach with the question “How often does your mouth feel dry?” (Thomson *et al.* 1993), and it was categorized into two categories based on the frequency of the feeling: not at all or occasional feeling of a dry mouth vs. often feeling of a dry mouth.

Clinical oral measurements

The clinical oral examination was based on visual and tactile inspections. Radiographs were taken only if they were indicated for dental treatment. The examination was started by asking the participants whether they had any pain or discomfort in their mouth.

The status of the teeth and periodontium was documented for each dentate participant. The participants were defined as dentate if they had at least one clinically visible tooth or dental radix. The presence of dental plaque was determined from the buccal and palatal surfaces of each tooth by visual examination after light drying.

Classification of dental caries was based on a restorative treatment need, which was determined with visual and tactile examinations of each surface of each tooth. Dental caries was recorded as crown caries (the lesion reached the dentin layer on the clinical crown), root caries (the root surface was softened), crown and root caries, or decayed dental root. The tooth was considered carious if one of these criteria was met on any surface of the tooth.

The presence of gingival infection was based only on visual examination of redness and/or edema on the buccal and/or lingual/palatal gingiva of each tooth. Periodontal pockets and depths were probed (WHO periodontal probe) on the

distopalatal/distolingual and mesiobuccal surfaces of each tooth. The number of teeth with periodontal pockets 4 mm deep or deeper was used to measure the extent of periodontal infection. The presence of dental calculus (both supra- and subgingival calculus) was defined during the periodontal probing.

Use of variables as outcomes in the articles

In the first article, the outcome variables were the number of carious teeth and the number of teeth with deepened periodontal pockets (≥ 4 mm). In the second and third articles, both unstimulated and stimulated salivary secretion and xerostomia were used as outcome variables. In the fourth article, oral health behavior, consisting of the frequency of toothbrushing, use of toothpaste, the regularity of dental visits, and the number of teeth with dental plaque, was used as the outcome variable.

4.3 Statistical methods

Logistic regression models were used in articles I and III to estimate odds ratios (OR) with 95% confidence intervals (CI) for dichotomical outcome variables. In articles II and III, Poisson multivariate regression model was used to estimate relative risk (RR) with 95% CI for continuous outcome variables. In article IV, Poisson multivariate regression model with a robust error variance was used to estimate RR for dichotomical outcome variables.

The selection of potential confounding variables was based on the literature. Covariates for the models were chosen if they were associated with the outcome variables in unadjusted models and were unequally distributed in the categories of the explanatory variables. The statistical analyses were done using SPSS 22.0 statistical software for Windows (SPSS, Chicago Ill. USA).

4.4 Ethics of the study

The participants took part in this study voluntarily. Before the study enrollment, written informed consent was obtained from all the study participants or their relatives. The GeMS study protocol was approved in the Research Ethics Committee of the Hospital District of Northern Savo and the University of Kuopio, as required by Finnish legislation.

Participants who had difficulty with communication or memory were accompanied by a family member or a caregiver to the appointments for the

examinations. A family member or close caregiver of the participant was also present during the dentist's home visit. Written information about the main findings of the clinical oral examination was given to all the participants. Standard dental care, including relief from oral pain and restorative, prosthetic, or surgical treatment, was offered to the participants when necessary.

5 Results

In this study population, the mean age of the participants was 80.6 years and 70 percent of the participants were women. Regarding their general health, over one-third of the participants (36%) had high comorbidity ($FCI \geq 3$), 23 percent had lowered physical functioning (IADL 0–6), and 16 percent had impaired cognition ($MMSE \leq 24$).

The mean number of drugs used in the study population was 5.96. Twenty-eight percent of the participants used at least one drug with sedative properties and almost half of the participants (48%) used at least one drug with anticholinergic properties (Table 9). The most commonly used sedative drug group was benzodiazepine and related drugs, with 14 percent of the participants using them.

Table 9. Basic descriptive statistics of the study population.

Characteristics	Study population
N	159
Socio-demographic factors	
Age (mean \pm SD)	79.3 \pm 3.67
\geq 85 years, %	11
Gender, proportion of women, %	70
Education \geq 7 years, %	55
Health-related factors	
Diabetes, %	12
Rheumatoid diseases, %	11
BMI \geq 30, %	20
FCI \geq 3 (high comorbidity), %	36
IADL 0–6 (lowered physical functioning), %	23
MMSE (mean \pm SD)	27 \pm 3.9
MMSE \leq 24 (impaired cognition), %	16
Total number of drugs (mean \pm SD)	6.0 \pm 3.8
Users of benzodiazepines and z-drugs ¹ , %	14
Users of anticholinergic drugs, %	48
Sedative load, %	
0	72
1–2	20
\geq 3	8
Anticholinergic Drug Scale, %	
0	52
1–2	35
\geq 3	13

¹ Zopiclone, zolpidem, zalepon.

BMI: Body Mass Index, FCI: Functional Comorbidity Index, IADL: Instrumental Activity of Daily Living, MMSE: Mini-Mental State Examination.

The mean number of teeth was 14.7, and 59 percent of the participants had teeth with deepened periodontal pockets (\geq 4 mm) and 47 percent had dental caries. Xerostomia was a common complaint; 50 percent of the participants reported having a feeling of a dry mouth and 21 percent reported that it occurred often. Lowered unstimulated salivary secretion affected 29 percent of the participants and lowered stimulated salivary secretion affected 32 percent of the participants.

Oral health behavior also varied in the study population; 84 percent of the participants brushed their teeth at least twice a day, but only 48 percent used

toothpaste twice a day. Regular dental visits were made by 58 percent of the participants (Table 10).

Table 10. Oral health-related factors of the study population.

Characteristics	Study population
N	159
Number of teeth, mean \pm SD	14.7 \pm 8.2
Removable dentures, %	57
Oral health behavior	
Toothbrushing \geq 2 a day, %	84
Use of toothpaste \geq 2 a day, %	48
\geq 1 a day, %	78
Inter-dental cleaning at least once a day, %	17
Regular dental visits, %	58
Dental plaque, %	82
Dental calculus, %	77
Oral diseases	
Gingivitis (at least one tooth), %	50
Carious teeth, %	47
Deepened periodontal pockets (\geq 4 mm), %	59
Self-reported xerostomia, %	50
Unstimulated salivary flow \leq 0.1 ml/min (lowered), %	29 ¹
Stimulated salivary flow \leq 1.0 ml/min (lowered), %	32 ²
Stimulated salivary flow \leq 0.7 ml/min (lowered), %	18 ²

¹ 5 people missing, ² 7 people missing.

5.1 Association of sedative load with dental caries and infection in the periodontium

The distribution of the number of teeth with caries and deepened periodontal pockets is presented in Figure 1 (Study I). The proportion of participants who had no dental caries varied in the different sedative load groups (SL 0: 54%; SL 1–2: 45% and \geq 3: 51%). The proportions of participants who had no teeth with deepened periodontal pockets in the categorized sedative load groups were: 0: 40%; 1–2: 45% and \geq 3: 42% (Table 11).

Table 11. Oral health-related factors in different categories of sedative load.

Characteristics	SL 0	SL 1–2	SL \geq 3
N	115	31	12
Number of teeth, mean \pm SD	15 \pm 8.0	13.6 \pm 8.2	12.3 \pm 9.3
Removable dentures, %	56	61	58
Oral health behavior			
Toothbrushing \geq 2 a day, %	84	84	75
Use of toothpaste \geq 2 a day, %	52	42	25
Inter-dental cleaning at least once a day, %	18	10	25
Regular dental visits, %	60	55	42
Dental plaque, %	83	81	83
Dental calculus, %	79	74	67
Oral diseases			
Gingivitis, %	68	77	58
Dental caries, %	46	55	49
Deepened periodontal pockets (\geq 4 mm), %	60	55	58
Self-reported xerostomia (often), %	19	23	33
Unstimulated salivary flow < 0.1ml/min (low), %*	22	48	55
Stimulated salivary flow < 1.0 ml/min (low), %*	25	45	70
Stimulated salivary flow < 0.7 ml/min (low), %*	12	32	50

* 7 people missing.

Poisson regression models for dental caries were adjusted for age, gender, education, co-morbidities (FCI), physical functioning (IADL), cognitive function (MMSE), diabetes, rheumatoid diseases, and total number of drugs. These analyses showed that participants with a moderate (1–2) or high sedative load (\geq 3) had a higher likelihood of having carious teeth (RR: 1.8, CI: 1.2–2.6 and RR: 2.4, CI: 1.4–4.1, respectively) than participants without a sedative load. Additional adjustments for toothbrushing, use of toothpaste, use of anticholinergic drugs, or dental plaque essentially did not change the risk estimates (Models 2–4, Table 12).

There was an inverse association between sedative load and the number of teeth with deepened periodontal pockets after adjusting for confounding factors. In fact, participants with a high sedative load (\geq 3) had a low likelihood of deepened periodontal pockets (RR: 0.5, CI: 0.3–0.9) compared with participants without a sedative load. Additional adjustments for toothbrushing, use of toothpaste, dental plaque, or use of anticholinergic drugs did not have an essential effect on the risk estimates (Models 2–4, Table 12).

The total number of drugs was found to be non-consistently associated with dental caries and teeth with deepened periodontal pockets (Table 12).

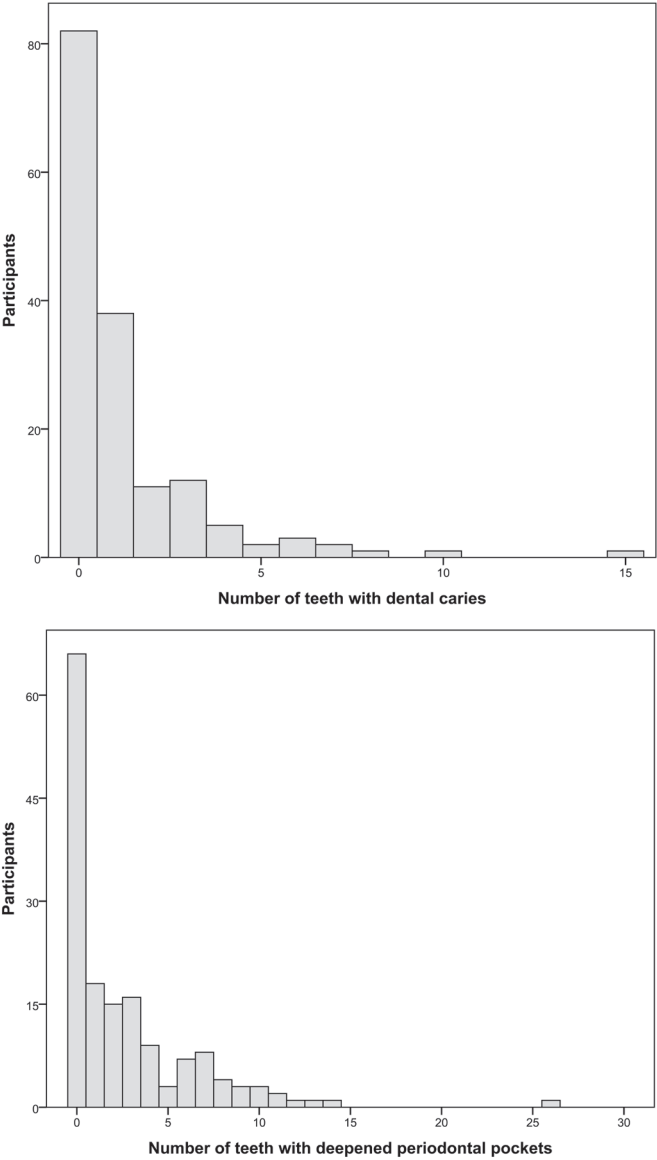


Fig. 1. Distribution of dental caries and deepened periodontal pockets in the study population (Study I, published by permission of Wiley).

Table 12. Associations between sedative load and number of drugs and carious teeth and the number of teeth with deepened periodontal pockets (Study I, published by permission of Wiley).

Sedative Load	Number of carious teeth RR (95% CI)	Number of teeth with periodontal pockets (≥ 4 mm) RR (95% CI)
Model 1 ¹		
0	1.0	1.0
1–2	1.8 (1.2–2.6)	0.9 (0.7–1.2)
≥ 3	2.4 (1.4–4.1)	0.5 (0.3–0.9)
continuous	1.21 (1.06–1.38)	0.92 (0.82–1.00)
Model 2 ¹⁺²		
0	1.0	1.0
1–2	1.5 (1.0–2.3)	0.9 (0.7–1.2)
≥ 3	1.4 (0.8–2.8)	0.5 (0.3–0.9)
continuous	1.09 (0.94–1.27)	0.91 (0.82–1.01)
Model 3 ²⁺³		
0	1.0	1.0
1–2	1.8 (1.2–2.6)	0.9 (0.7–1.1)
≥ 3	2.4 (1.4–4.1)	0.5 (0.3–0.8)
continuous	1.21 (1.05–1.38)	0.89 (0.79–0.98)
Model 4 ¹⁺⁴		
0	1.0	1.0
1–2	1.9 (1.3–2.8)	0.9 (0.6–1.1)
≥ 3	3.0 (1.7–5.2)	0.5 (0.3–0.8)
continuous	1.27 (1.10–1.45)	0.87 (0.78–0.97)
Model 5 ¹⁺⁵		
0	1.0	
1–2	1.9 (1.3–2.8)	
≥ 3	2.9 (1.8–4.7)	
continuous	1.29 (1.14–1.45)	
Total number of drugs ¹⁺⁶		
0–3	1.0	1.0
4–6	0.9 (0.6–1.4)	1.3 (0.9–1.6)
7–9	1.9 (1.2–3.1)	1.0 (0.7–1.4)
≥ 10	1.1 (0.6–2.0)	1.6 (1.1–2.4)
continuous	1.04 (0.99–1.09)	1.02 (0.99–1.06)

¹ Adjusted for age, gender, education, Functional Comorbidity Index, Mini-Mental State Examination, Instrumental Activity of Daily Living, diabetes, and rheumatoid diseases; the number of teeth was used as an offset variable. Dental caries was also adjusted for the total number of drugs.

² Additional adjustment for toothbrushing and use of toothpaste.

³ Additional adjustment for dental plaque.

⁴ Additional adjustment for the Anticholinergic Drug Scale.

⁵ Adjusted without the total number of drugs.

⁶ Additional adjustment for sedative load.

5.2 Association of sedative load with salivary secretion and xerostomia

The effects of sedative load on salivary flow and xerostomia were studied in 152 participants from whom salivary secretions were measured (Study II). It was found that both low stimulated and low unstimulated salivary secretions were more common among participants with a high (≥ 3) and a moderate (1–2) sedative load than among participants without a sedative load. Xerostomia was also more common among participants with either a high or a moderate sedative load than in participants without a sedative load (Table 11).

After adjusting for confounding factors (age, gender, education, diabetes, and rheumatoid diseases), logistic regression models showed that participants with a high sedative load (≥ 3) were more likely to have low stimulated salivary secretion (< 0.7 ml/min) (OR: 11, CI: 2.2–59) compared with participants without a sedative load. With a continuous sedative load, the odds ratio was 1.84 (CI: 1.19–2.82). Additional adjustments for the total number of drugs and the Anticholinergic Drug Scale (ADS) caused only slight variation in the odds ratios (Model 2&3, Table 13). When a higher cut-off value (< 1.0 ml/min) for stimulated salivary flow was used, the odds ratios were lower (Table 13).

Participants with either a moderate (1–2) or a high sedative load (≥ 3) were also more likely to have low unstimulated salivary secretion (< 0.1 ml/min) (OR: 2.7, CI: 1.0–7.4 and OR: 4.5, CI: 1.0–20; respectively) compared with those without a sedative load. When a continuous sedative load was used the odds ratio was 1.51 (CI: 1.05–2.17). Additional adjustments for the total number of drugs and the Anticholinergic Drug Scale attenuated the odds ratios only slightly (Model 2&3, Table 13).

Analyses with the total number of drugs as an explanatory variable showed that the association between the number of drugs and hyposalivation was weaker than the association between sedative load and hyposalivation (Table 13). The categorized total number of drugs was associated strongly, although statistically non-significantly, with xerostomia. On the other hand, the continuous number of drugs was statistically associated with xerostomia (OR: 1.16, CI: 1.02–1.33).

Table 13. Associations of sedative load and number of drugs with salivary secretion and xerostomia (Study II, published by permission of Wiley).

Sedative load	Stimulated salivary flow (< 0.7 ml/min) OR (95% CI)	Stimulated salivary flow (< 1.0 ml/min) OR (95% CI)	Unstimulated salivary flow (< 0.1 ml/min) OR (95% CI)	Xerostomia OR (95% CI)
Model 1¹				
0	1.0	1.0	1.0	1.0
1–2	2.4 (0.6–8.6)	1.2 (0.4–3.3)	2.7 (1.0–7.4)	0.7 (0.2–2.3)
≥ 3	11 (2.2–59)	4.8 (0.9–24)	4.5 (1.0–20)	2.5 (0.7–1.5)
continuous	1.84 (1.19–2.83)	1.29 (0.90–1.86)	1.51 (1.05–2.17)	1.04 (0.72–1.51)
Model 2²				
0	1.0	1.0	1.0	1.0
1–2	2.0 (0.5–7.7)	1.2 (0.4–3.3)	2.5 (0.9–7.0)	0.4 (0.1–1.6)
≥ 3	11 (2.2–53)	4.8 (0.9–24)	3.9 (0.8–18)	1.5 (0.3–7.4)
continuous	1.73 (1.09–2.74)	1.38 (0.92–2.05)	1.43 (0.97–2.11)	0.89 (0.60–1.32)
Model 3³				
0	1.0	1.0	1.0	1.0
1–2	2.4 (0.6–9.2)	1.0 (0.3–3.0)	1.8 (0.6–5.3)	0.3 (0.06–1.3)
≥ 3	11 (2.0–66)	3.8 (0.7–21)	2.5 (0.5–12)	1.1 (0.2–5.9)
continuous	2.28 (1.34–3.89)	1.24 (0.84–1.84)	1.35 (0.89–2.03)	0.87 (0.59–1.28)
Number of drugs⁴				
0–3	1.0	1.0	1.0	1.0
4–6	0.7 (0.1–3.9)	0.8 (0.3–2.3)	1.1 (0.3–3.5)	1.1 (0.3–4.5)
7–9	1.2 (0.2–6.7)	1.3 (0.4–4.6)	2.3 (0.6–8.1)	3.8 (0.9–16)
≥ 10	1.9 (0.4–9.6)	0.8 (0.2–2.8)	1.6 (0.4–5.8)	4.3 (0.9–19)
continuous	1.10 (0.96–1.27)	0.99 (0.88–1.11)	1.08 (0.95–1.22)	1.16 (1.02–1.33)

¹ Adjusted for age, gender, education, diabetes, and rheumatoid diseases.

² Adjusted for age, gender, education, diabetes, rheumatoid diseases, and total number of drugs.

³ Adjusted for age, gender, education, diabetes, rheumatoid diseases, and the Anticholinergic Drug Scale.

⁴ Adjusted for age, gender, education, diabetes, rheumatoid diseases, and sedative load.

5.3 Association of anticholinergic burden with salivary secretion and xerostomia

In Study III, the focus was on the association between anticholinergic burden, measured by the Anticholinergic Drug Scale (ADS), and salivary secretion and xerostomia. Lowered unstimulated and stimulated salivary secretions affected 64 percent and 55 percent (respectively) of the participants with a high anticholinergic burden ($ADS \geq 3$). Fifty-five percent of the participants with a high anticholinergic burden often had the feeling of a dry mouth (Table 14).

Table 14. Salivary secretion and xerostomia and their distribution in different categories of the Anticholinergic Drug Scale.

Variable	Anticholinergic Drug Scale		
	0	1–2	≥ 3
N	77	53	22
Self-reported xerostomia (often), n (%)	8 (10)	13 (25)	12 (55)
Unstimulated salivary flow < 0.1 ml/min, n (%)	16 (21)	15 (33)	14 (64)
Stimulated salivary flow < 1.0 ml/min, n (%)	19 (25)	19 (36)	12 (55)

The participants with a high anticholinergic burden ($ADS \geq 3$) were more likely to have xerostomia (RR: 3.2; CI: 1.4–6.9) than the participants without an anticholinergic burden after adjustments for confounding factors. For a continuous ADS the relative risk was 1.20 (1.06–1.37). Further adjustments for the total number of drugs or sedative load caused a slight variation in the risk estimates (Model 2&3, Table 15).

Study III showed that the participants with a high anticholinergic burden ($ADS \geq 3$) were more likely to have lowered unstimulated salivary secretion (RR: 2.3, CI: 1.2–4.4) than the participants without an anticholinergic burden. When a continuous ADS was used the relative risk was 1.22 (1.10–1.34). Additional adjustments essentially did not change the risk estimates (Model 2&3, Table 15).

Anticholinergic burden had a weaker association with low stimulated salivary flow than with xerostomia or low unstimulated salivary flow (Table 15).

Table 15. Association of the Anticholinergic Drug Scale with lowered unstimulated salivary secretion, stimulated salivary secretion, and xerostomia (Study IV, published by permission of Wiley).

ADS	Xerostomia RR (95% CI)	Unstimulated salivary flow (< 0.1 ml/min) RR (95% CI)	Stimulated salivary flow (< 0.7 ml/min) RR (95% CI)	Stimulated salivary flow (< 1.0 ml/min) RR (95% CI)
Model 1 ¹				
0	1.0	1.0	1.0	1.0
1–2	1.3 (0.6–2.9)	1.1 (0.6–2.1)	0.5 (0.2–1.2)	1.2 (0.7–2.1)
≥ 3	3.2 (1.4–6.9)	2.3 (1.2–4.4)	1.1 (0.4–2.7)	1.50 (0.8–2.8)
continuous	1.20 (1.06–1.37)	1.22 (1.10–1.34)	1.09 (0.91–1.29)	1.09 (0.98–1.20)
Model 2 ²				
0	1.0	1.0	1.0	1.0
1–2	1.4 (0.6–3.1)	1.0 (0.5–2.1)	0.3 (0.2–0.8)	1.2 (0.6–2.1)
≥ 3	3.8 (1.5–9.9)	2.0 (1.0–4.2)	0.6 (0.2–1.6)	1.4 (0.7–2.8)
continuous	1.24 (1.04–1.47)	1.19 (1.07–1.34)	1.00 (0.82–1.22)	1.08 (0.97–1.19)
Model 3 ³				
0	1.0	1.0	1.0	1.0
1–3	1.3 (0.6–3.0)	1.0 (0.5–2.0)	0.3 (0.1–0.8)	1.2 (0.6–2.1)
≥ 3	3.5 (1.6–7.6)	2.0 (1.0–4.0)	0.6 (0.2–1.4)	1.4 (0.8–2.7)
continuous	1.21 (1.06–1.37)	1.19 (1.09–1.32)	1.02 (0.83–1.25)	1.08 (0.98–1.19)

¹ Adjusted for age, gender, education, diabetes, rheumatoid disease, and Functional Comorbidity Index.

² Adjusted for age, gender, education, diabetes, rheumatoid disease, Functional Comorbidity Index, and total number of drugs.

³ Adjusted for age, gender, education, diabetes, rheumatoid disease, Functional Comorbidity Index, and sedative load.

5.4 Association of sedative load with oral health behavior

Oral health behavior was measured in this study by means of toothbrushing, use of toothpaste, dental visits, and the number of teeth with dental plaque (Study IV). For this study, sedative load was categorized into two groups: No vs. Yes.

All the models were adjusted for age, gender, education, co-morbidity (FCI), and the total number of drugs. The analyses showed that participants with a sedative load were more likely to have insufficient oral hygiene in terms of using toothpaste less than twice a day (OR 3.3, CI: 1.4–8.1) and having teeth with dental plaque (RR: 1.2, CI: 1.0–1.4) compared with participants without a sedative load. Additional adjustments for the cognitive function (MMSE) and physical

functioning (IADL) changed the risk estimates only slightly (Model 2&3, Table 16).

Table 16. Association between sedative load and oral health behavior (Study III, published by permission of Wiley).

Sedative load	Toothbrushing (less than twice a day) OR (95% CI)	Toothpaste (less than twice a day) OR (95% CI)	Dental visits (non-regular visits) OR (95% CI)	Number of teeth with dental plaque RR (95% CI)
Model 1 ¹				
No	1.0	1.0	1.0	1.0
Yes	1.7 (0.6–4.9)	3.3 (1.4–8.1)	2.3 (0.9–5.3)	1.2 (1.0–1.4)
continuous	1.16 (0.78–1.71)	1.72 (1.19–2.48)	1.34 (0.97–1.84)	1.08 (1.02–1.14)
Model 2 ²				
No	1.0	1.0	1.0	1.0
Yes	1.5 (0.5–4.5)	2.9 (1.2–7.2)	1.9 (0.8–4.5)	1.1 (0.9–1.3)
continuous	1.11 (0.74–1.67)	1.62 (1.12–2.34)	1.26 (0.91–1.74)	1.04 (0.98–1.09)
Model 3 ³				
No	1.0	1.0	1.0	1.0
Yes	1.7 (0.6–5.1)	3.0 (1.2–7.6)	2.2 (0.9–5.3)	1.1 (1.0–1.3)
continuous	1.12 (0.73–1.69)	1.65 (1.12–2.44)	1.30 (0.93–1.83)	1.04 (0.98–1.10)

¹ Adjusted for age, gender, education, Functional Comorbidity Index, and total number of drugs.

² Adjusted for age, gender, education, Functional Comorbidity Index, total number of drugs, and Mini-Mental State Examination.

³ Adjusted for age, gender, education, Functional Comorbidity Index, total number of drugs, and Instrumental Activities of Daily Living.

6 Discussion

6.1 Main findings and their significance

6.1.1 *Dental caries and infection in the periodontium*

The main findings of Study I were that sedative load was associated with an increased likelihood of dental caries and a lowered likelihood of periodontitis. Further adjustments for the total number of drugs, the ADS, and variables describing oral hygiene did not change the results essentially, indicating that the effects of sedative load are independent of these factors.

The result regarding sedative load and dental caries concurs with some previous studies (Rundegren *et al.* 1985, Lawrence *et al.* 1995, Thomson *et al.* 1995, Rindal *et al.* 2005) that have shown an association between drugs with sedative properties and a higher prevalence of dental caries or a higher restoration rate. On the other hand, other studies have reported that there is no association between drugs with sedative properties and dental caries (Hawkins *et al.* 1997, Närhi *et al.* 1998, Thomson *et al.* 2002, Janket *et al.* 2003). The reason for these contradicting findings is unclear, but in many cases this discrepancy in the results can be explained by the different classifications of dental caries and drugs, study designs, or chance.

The finding that sedative load was inversely associated with infection in the periodontium is to some extent in line with earlier studies. These studies have shown that certain drugs are associated with periodontitis, but the focus has mainly been on drugs with a direct pharmacological effect on the inflammatory cascade (Pinho *et al.* 2008, Alani & Seymour 2014, Golub *et al.* 2016). Interestingly, animal models have shown that certain drugs (antidepressants or sedatives), which are not thought to directly influence the inflammatory cascade, can have a protective effect on the progression of periodontal infection by reducing stress-related cytokines via the hypothalamic–pituitary–adrenal axis (Gomes *et al.* 2013, Ortuño *et al.* 2016).

The most likely mechanism explaining the association between sedative load and the increased risk of dental caries and the decreased risk of periodontitis is medication-induced hyposalivation. The results from Study II support this assumption by showing that sedative load was associated with hyposalivation. Decreased salivary secretion changes the intraoral pH to more acidic (Bardow *et al.* 2001), which in turn causes a transition in the composition of dental plaque to more cariogenic with elevated numbers of lactobacilli and mutans streptococci

(Almståhl & Wikström 1999/2005). While decreased salivary secretion creates favorable conditions for cariogenic bacteria, the condition is opposite for periodontal pathogens such as *Fusobacterium nucleatum* (Bradshaw & Marsh 1998) or *Aggregatibacter actinomycetemcomitans* (Haase *et al.* 2006), which favor a neutral or alkaline pH. On the other hand, a recent study by Belstrøm *et al.* (2016) found no difference in the cariogenic bacterial composition of the saliva of participants with severe hyposalivation when compared with participants with normal salivation.

Hyposalivation decreases the buffer capacity of saliva by reducing saliva secretion and its buffering compounds such as bicarbonate, phosphate, and proteins (Ravald & List 1998). When saliva cannot neutralize the acid challenge sufficiently, the balance on the tooth surface moves towards demineralization (Takahashi & Nyvad 2008). Because hyposalivation is also associated with reduction in the salivary output of bicarbonate, sodium, potassium, calcium, and phosphate (Almståhl & Wikström 2003), it may lead to decreased calculus formation and thus reduce the risk of periodontitis.

Another mechanism that could explain the findings is the changes in oral health behavior related to the sedative effects of drugs. Study IV showed that sedative load was associated with poor or insufficient oral health behavior and this can be seen, to some extent, to support the result of Study I. The dilemma with this explanation is the fact that both dental caries and periodontitis are plaque-related conditions (Selwitz *et al.* 2007, Khan *et al.* 2015). If the association would be solely explained by poor oral hygiene, one would not expect an inverse association between sedative load and periodontal pocketing. Thus, it can be speculated that there might be a synergistic effect between poor oral health behavior and drugs with sedative properties in the development of dental caries, and at the same time certain drugs with sedative properties could protect the periodontium against the bacterial irritation and periodontal breakdown (Yaron *et al.* 1999, Branco-de-Almeida *et al.* 2012, Gomes *et al.* 2013).

6.1.2 Dry mouth

In Studies II and III, both sedative load and anticholinergic burden were associated with different aspects of a dry mouth. Sedative load was strongly associated with low stimulated salivary secretion, whereas a high anticholinergic burden was strongly associated with low unstimulated salivary secretion and xerostomia.

These findings are by no means surprising, since previous studies have shown that drugs with sedative properties (Guggenheimer *et al.* 2003, Smith *et al.* 2013,

Spolarich 2014) and an anticholinergic burden (Rudolph *et al.* 2008, Kersten *et al.* 2013) are both associated with hyposalivation and xerostomia. Concurrent use of multiple sedative drugs (antipsychotics, sedatives, and antidepressants) (de Almeida Pdel *et al.* 2008, Hashimoto *et al.* 2012, Okamoto *et al.* 2016) and the use of multiple anticholinergic drugs (Ghezzi 2003, Desoutter *et al.* 2012, Günes *et al.* 2012) are also associated with a dry mouth.

When comparing the results of this study (Study II and III) with previous findings, one must take into account some differences between the studies. Earlier studies used different methods to classify the use of drugs with sedative properties (de Almeida Pdel *et al.* 2008, Hashimoto *et al.* 2012, Okamoto *et al.* 2016), anticholinergic burden (Rudolph *et al.* 2008, Kersten *et al.* 2013), and the anticholinergic potential of drugs (Ghezzi 2003, Desoutter *et al.* 2012, Günes *et al.* 2012). There is also variation in how hyposalivation and xerostomia were assessed. Some earlier studies used only either salivary secretion (Hunter *et al.* 1995, Wolff *et al.* 2008, Kersten *et al.* 2013) or xerostomia (Ghezzi 2003, Rudolph *et al.* 2008, Günes *et al.* 2012, Hashimoto *et al.* 2012) as an outcome variable. Only the studies by Desoutter *et al.* (2012), de Almeida Pdel *et al.* (2008a), and Okamoto *et al.* (2016) used combinations of stimulated/unstimulated salivary secretion or oral moisture and xerostomia as outcome variables.

The study by de Almeida Pdel *et al.* (2008) showed that simultaneous use of SSRIs and benzodiazepines was associated with a more severe decrease in stimulated salivary secretion and xerostomia compared with monotherapy with SSRIs. Concurrent use of multiple antipsychotic or anxiolytic drugs among schizophrenia patients was associated with decreased oral moisture (Okamoto *et al.* 2016) and xerostomia (Hashimoto *et al.* 2012). Kersten *et al.* (2013) used the same ADS as in Study III to investigate the association between anticholinergic burden and unstimulated salivary secretion, while Rudolph *et al.* (2008) used the Anticholinergic Risk Scale (ARS) to measure anticholinergic burden when investigating anticholinergic burden and xerostomia. Studies by Günes *et al.* (2012), Desoutter *et al.* (2012), and Ghezzi (2003) used expert compiled lists, a pharmaceutical database, or literature such as Martindale and Theriaque to determine anticholinergic drugs, and all three reported a positive association between anticholinergic drugs and a dry mouth.

The lack of an association between sedative load and xerostomia is not unexpected, since xerostomia and hyposalivation often occur separately from each other (Thomson *et al.* 1999). In this population, sedative load was more strongly associated with stimulated salivary secretion than with unstimulated salivary

secretion. This might also explain why it was not associated with xerostomia; also earlier studies have suggested that decreased unstimulated salivary secretion is more sensitive in relation to xerostomia than decreased stimulated salivary secretion (Dawes 1987, Wang *et al.* 1998). While stimulated salivary secretion represents the functional capacity of the salivary glands (Valdez & Fox 1993), unstimulated salivary secretion indicates more the general situation in the mouth (Han *et al.* 2015). These above-mentioned facts also provide an explanation for the strong association between anticholinergic burden and unstimulated salivary secretion and xerostomia. Furthermore, diuretic furosemide constituted a large proportion of the ADS scores of the participants (Table 7), and it has been associated with unstimulated salivary secretion and xerostomia (Nederfors *et al.* 2004). Most likely the association between anticholinergic burden and xerostomia is mediated by changes in the composition of saliva to be more viscous (Wang *et al.* 1998).

Both sedative load and anticholinergic burden showed dose-dependency with outcome variables. An explanation for this could be the fact that the participants with a high sedative load or anticholinergic burden were using more drugs with profound sedative (SL 2 & 3) and anticholinergic (ADS score 2 & 3) properties, which have a strong effect on salivary secretion or are prone to cause xerostomia. The dose-dependency of anticholinergic burden was more profound than that of sedative load, and this might be due to the dose adjustments. The participants with a high anticholinergic burden had a higher dosage of drugs, and this might have caused an additive effect on a dry mouth.

Contrary to previous studies (Ostberg *et al.* 1992, Wu and Ship 1993, Nederfors *et al.* 1997, Fure 2004, Smidt *et al.* 2010, Viljakainen *et al.* 2016) the results of Studies II and III suggest that the total number of drugs by itself is not an essential risk factor for hyposalivation or xerostomia. The total number of drugs was inconsistently associated with a dry mouth, and when the multivariate models for either sedative load or anticholinergic burden were adjusted for the number of drugs, the risk estimates changed only slightly. These results indicate that both sedative load and anticholinergic burden are risk factors for a dry mouth, independent of the total number of drugs. This supports the self-evident conception that the type or class of drugs is a more important factor than the number of drugs itself when studying the effects of drugs on a dry mouth.

The results from the additional analyses showed that sedative load and anticholinergic burden were associated with a dry mouth independently from each other. Based on the risk estimates from Study III, anticholinergic burden appeared to have stronger association with unstimulated salivary secretion and xerostomia when

compared with sedative load, which was more strongly associated with stimulated salivary flow. Explanations for these findings can be found from differences in the drug groups included in the sedative load and anticholinergic burden and in their different effects on salivary secretion. For example, benzodiazepines, which contributed a large portion of the sedative load, have been previously reported to be associated with low stimulated salivary secretion (de Almeida *et al.* 2008) and furosemide, which contributed a large portion of the anticholinergic burden, has been reported to be associated with low unstimulated salivary secretion and xerostomia (Nederfors *et al.* 2004). Thus, it can be speculated that anticholinergic drugs have a more direct effect on the salivary glands and on the composition of saliva via an inhibition of local muscarinic receptors, while the sedative properties of the drugs have more of an impact on stimulated salivary secretion through the central nervous system.

6.1.3 Oral health behavior

The results of Study IV showed that sedative load was associated with poor oral health behavior and insufficient oral hygiene due to less frequent use of toothpaste and a higher amount of dental plaque. The results also suggest that sedative load was associated with less frequent toothbrushing and irregular dental visits.

The most plausible explanations for the findings of Study IV could be the deteriorating effect of drugs with sedative properties on functional capacity (Taipale *et al.* 2011b) and cognitive function (Blazer *et al.* 2000, Fox *et al.* 2011, Desplenter *et al.* 2012). Other plausible mediating factors, although to a lesser extent, could be lowered muscle strength (Taipale *et al.* 2012b) and mobility (Gnjidic *et al.* 2014). All the above-mentioned factors have been previously shown to be associated with poor oral hygiene (Moriya *et al.* 2011, Chen *et al.* 2015) or irregular utilization of dental care services (Hoad-Reddick *et al.* 1987, Dolan *et al.* 1998, Naorungroj *et al.* 2013).

The role of functional capacity and cognitive function as mediating factors in the association between sedative load and poor oral health behavior was supported by the observation that the participants with a sedative load had lower functional capacity and decreased cognitive function than the participants without a sedative load. On the other hand, adjustments for cognitive function (MMSE) and physical functioning (IADL) caused only minor attenuations of the risk estimates for sedative load.

The latter suggests that sedative load is a fairly independent determinant of oral health behavior and it is reasonable to consider the use of drugs with sedative properties as an indicator for poor oral health behavior among older people.

6.2 Discussion about methods

6.2.1 Study population and sample size

The GeMS study population was randomly drawn from inhabitants aged 75 or older living in Kuopio, representing nine percent of the age group in the city. The study population was homogenous in terms of age, ethnic background, and place of residence. The participation rate for people who completed the oral health study was fairly low, 56 percent, which is about the same level as in other longitudinal studies among this age group (Newman 2010).

The bias caused by non-participation was difficult to assess because only limited information about the non-participants was available due to privacy protection legislation. However, it is known that the main reasons for non-participation were poor general health and the absence of natural teeth.

People living in an institutional setting were excluded from this study population because they typically have greater use of drugs with sedative properties, different indications for drug use, and more complex medical conditions than people living in a community setting (Van Rensbergen & Nawrot 2010, Haasum *et al.* 2012). The current study population was further restricted to non-smoking, dentate participants, which meant that the remaining number of participants was relatively small ($n = 159$). These restrictions meant that the generalizability of the findings decreased, but on the other hand, it also meant that the validity of the study increased.

6.2.2 Measurements

The data were collected by the same multiprofessional team, including two dentists, two dental nurses, one dental hygienist, two medical doctors (specializing in geriatrics), two physiotherapists, three nurses, and one nutritionist, throughout the whole GeMS study, excluding one of the physicians who left after a few months. This stability of researchers and examiners over the study period increased the reliability of the clinical measurements. Two study dentists trained together and written instructions were formulated for the study.

One-fourth of the Oral Health GeMS participants preferred a home visit by the dentist (Komulainen *et al.* 2012) and their clinical oral examination was also carried out at home. Sixty-one percent of the participants that were examined at home were edentulous, meaning that the overall underestimation of dental diseases related to

home examination was small. However, the more demanding circumstances during the home examination might have resulted in less precise detection of oral diseases in the dentate participants.

All the studies in this thesis are cross-sectional in design, which makes it difficult to determine the temporal sequence between outcome variables and explanatory variables. This means, for example, that it is impossible to draw any conclusions about the caries increment or the development of periodontitis. Another limitation is that drugs with sedative properties might have been selectively prescribed to participants who are at higher risk for oral health problems, such as those with mental disorders or multimorbidities.

There was, on average, a six-month time interval between the collection of medical data and the clinical oral examinations, and this should be taken into account when interpreting the results of the studies. Yet, it is not unreasonable to assume that the time interval did not change the results because of its short duration, and because medication for chronic diseases is relatively permanent (Marcum *et al.* 2017) and oral diseases are quite stable (Thomson *et al.* 2004).

Dry mouth

A dry mouth was determined by means of three factors: both unstimulated and stimulated salivary flows and xerostomia. This comprehensive approach is thought to be the most adequate method of describing a dry mouth (Thomson 2015).

The measurement of xerostomia was based on a single-item approach with the question “How often does your mouth feel dry?” (Thomson *et al.* 1993). This global item approach does not consider all the aspects of xerostomia as do more thorough questionnaires, such as the Xerostomia Inventory (Villa *et al.* 2015), and thus it might have caused underestimation of xerostomia.

The salivary secretion measurements were based on the “draining” method (Navazesh & Christensen 1982), which has been proven to be a valid method for measuring salivary secretion (Villa *et al.* 2015). Salivary secretions were not measured at the same time of day, which might have caused some measurement errors, although most likely not a systematic error. The cut-off values for unstimulated salivary secretion (≤ 0.1 ml/min) and stimulated salivary secretion (≤ 0.7 ml/min and ≤ 1.0 ml/min) are based on the previous literature (Heintze *et al.* 1983, Pedersen *et al.* 2002, Flink *et al.* 2008). The two cut-off values for stimulated salivary flow were used because both of them have also been used in the earlier studies and thus the current findings are more comparable.

Aging has not been taken into account for the salivary flow cut-off values, even though a recent meta-analysis (Affoo *et al.* 2015) showed that aging decreases the whole salivary secretion (both unstimulated and stimulated) in healthy people. On the other hand, this adjustment might not be necessary, because the current cut-off values for salivary flow already depict the necessary level of salivary secretion needed to maintain oral health (Aliko *et al.* 2015, Dawes *et al.* 2015).

Oral health behavior

In Study III, oral health behavior was assessed using four variables that describe different aspects of oral health behavior and they included both subjective (questions about oral hygiene and dental visits) and objective measures (the number of teeth with dental plaque). The level of oral hygiene was determined during the clinical oral examination by observing the amount of dental plaque on the teeth. The number of teeth with dental plaque is a more objective variable for oral hygiene than the subjective variables, which do not provide information about the success of oral hygiene practices. Thus, these four variables are partly complementary to each other and this method of describing oral health behavior can be considered to increase the credibility of the findings.

Dental caries

The recording of dental caries was based on the need for restorative treatment and the registration was done at the tooth level. This robust method was used because of the time limitation in the clinical oral examination and because the Oral Health GeMS study was designed as an intervention study with the focus on clinical parameters and individual treatment need. This registration method differs from the ones generally used in epidemiological studies: for dental caries the commonly used methods are DMFT and ICDAS (WHO 2013).

Because dental caries was registered at the tooth level and not on the surface level, it has most likely caused underestimation of dental caries. Additionally, no bitewing radiographs were taken and caries detection was based only on visual-tactile examination, which may have also lead to underdetection of caries lesions (Ewoldsen & Koka 2010).

Periodontitis

The registration of periodontal condition was based on the presence of deepened (≥ 4 mm) periodontal pockets and was done on the tooth level. The same restrictions influenced the registration of periodontal condition as with dental caries, such as the home visits and the time limitation during the oral examination.

In epidemiological studies, periodontal condition is usually recorded by a combination of probing depth and attachment loss (O'Sullivan *et al.* 2011, Kassebaum *et al.* 2014b), which is in line with the classification of periodontitis from the American Academy of Periodontology (Armitage 1999, American Academy of Periodontology 2015). Because only probing depth was used as the recording method, it might have underestimated the extent or severity of periodontal disease.

In Study I, the robustness of the recording methods for both dental caries and periodontal condition might have caused attenuation in the associations between sedative load and outcome variables. This fact should be taken into consideration when interpreting the findings of that particular study.

Instrumental activities of daily living

Daily functional capacity was determined by using the IADL questionnaire. There is no widely accepted cut-off values for the IADL in the literature, and often the cut-off values are chosen according to the purpose of a particular study. In the present study, the cut-off value of IADL 6 was chosen because it represents already some level of difficulty in daily living. The same cut-off value has also been used earlier in dental research (Komulainen *et al.* 2012).

6.2.3 Controlling for confounding factors

All the multivariate models were controlled for confounding factors such as age, gender, education, diseases known to be associated with both oral health and oral hygiene (diabetes, rheumatoid diseases), total number of drugs, and other comorbidities (FCI). The selection of additional potential confounding variables was done for each outcome variable separately based on its association with the outcome variables and its distribution in the categories of explanatory variables. With dental caries and periodontal condition, for example, additional adjustments were done for toothbrushing, use of toothpaste, use of anticholinergic drugs, or the amount of dental plaque; with a dry mouth they were done for total number of

drugs, ADS or SL; and with oral health behavior additional adjustments were done for MMSE and IALD.

In Study IV, the first set of models was not adjusted for MMSE or IADL because the assumption was that they mediate, at least partly, the association between sedative load and oral health behavior. In order to explore more thoroughly the roles of cognitive function and functional capacity in the association between sedative load and oral health behavior, the second and third sets of models were adjusted for MMSE and IADL, respectively.

Because causal models can be complex, it is difficult to specify the actual effects of the explanatory variable and confounding variables. For example, impaired cognition and low functional capacity could pre-exist or be the cause for a sedative load, they could mediate the sedative effects, or they could cause confounding in the relation between sedative load and oral health behavior. Interpretation of the findings from Study IV depends on the underlying causal model. Moreover, it should be kept in mind that adjusting for mediating factors causes bias (Schisterman *et al.* 2009).

Despite all efforts, the possibility of residual confounding cannot be totally excluded with using statistical methods. For a dry mouth, possible residual confounding factors could be stress (Hugo *et al.* 2008) or anxiety (Bergdahl 2000), but because of the lack of appropriate data, these factors could not be taken into account. Other factors related to a dry mouth, such as depression, Parkinson's disease, HIV, Hepatitis C, or radiotherapy of head and neck region, were rare in this study. There might also be some shared underlying reasons for taking medications and for oral diseases that cannot be totally controlled by using statistical methods. These partially controlled or uncontrolled factors could be related to poor general or psychological health.

6.2.4 Sedative load

The Sedative Load Model is a comprehensive measurement of drugs with sedative properties, which has been shown to be adequate among older people (Linjakumpu *et al.* 2003 & 2004). In 2009 the model was updated to include new drugs that had been brought to the market after the development of the original model (Taipale *et al.* 2011a). The Sedative Load Model took into account the use of multiple drugs with sedative properties and also included drugs for somatic diseases (Taipale *et al.* 2010). Thus, the model can be considered suitable and comprehensive in terms of drug use by the GeMS study population.

When-required drugs were not included in the Sedative Load Model, because the specific frequency of use was not known or it was infrequent (max. four times a week). Inclusion of these drugs could have led to overestimation of the sedative effect of the drugs.

One limitation of the model is that it does not take into account the dosage of drugs. The presence of a dose-response association is commonly accepted as evidence of adverse drug reactions (Naranjo *et al.* 1981). On the other hand, there is no evidence from clinical trials of an appropriate dosage of sedative drugs for older people (Hilmer *et al.* 2012), and this can be problematic when choosing the “reference dose” for metrics measuring the cumulative medication burden. Furthermore, the doses of the drug might vary between different indications.

Another limitation of the Sedative Load Model is that the drug groups include intra-class variation in sedative potential. For example, SSRIs, which are commonly seen as non-sedating, have high intra-class variation in their capacity to cause impairment in cognitive and psychomotor processing (Hindmarch 2009). Similar variation in sedative potential can also be seen in conventional and atypical antipsychotics.

6.2.5 Anticholinergic Drug Scale

There is no standardized rating scale for measuring the anticholinergic burden, and discrepancies exist in the ratings of drugs between the metrics (Salahudeen *et al.* 2015). The ADS has been shown to be a valid measure for the anticholinergic burden of drugs among older people (Carnahan *et al.* 2006, Ness *et al.* 2006, Naples *et al.* 2015). The scale includes 117 drugs with known anticholinergic activity, which is more than in the other metrics, such as the Anticholinergic Risk Scale (49 drugs) (Rudolph *et al.* 2008) or the Anticholinergic Cognitive Burden Scale (88 drugs) (Boustani *et al.* 2008).

The final ADS score of the drug is based on the median values of ratings given by each of three geriatric psychiatrists on an expert panel (Carnahan *et al.* 2006). The subjective rating of anticholinergic activity relied mostly on the panel’s knowledge of adverse effects associated with anticholinergic drugs and the inclusion and ranking of the drugs were heavily influenced by subjective decisions (Salahudeen *et al.* 2015).

The fact that the ADS, to some extent, takes into account the dosage of anticholinergic drugs can also be seen as a strength, because it is commonly accepted that the dose-response relation is proof of adverse drug reactions

(Naranjo *et al.* 1981). On the other hand, drug dosage has not been shown to have a significant effect on serum anticholinergic activity (Carnahan *et al.* 2006) or clinical parameters, such as depression or physical functioning (Mate *et al.* 2015).

6.2.6 Intervention in the GeMS study

The original GeMS study included interventions in medical treatment and medication, health counseling and managing care services, nutritional counseling, and physical and mobility improvement. The general health-related interventions, such as a medication review and physical activity guidance, started in 2004 and they continued to be carried out on parallel with the clinical oral examinations. Although some of the interventions (not the oral interventions) started earlier than the oral health examinations, these interventions had no effect or had only a miniscule effect on the clinical oral examinations. For example, the medication review required more than one appointment with the doctor and changes in the drug dosages were made carefully (benzodiazepines, etc. require a gradual lowering of the dose). General health-related interventions were given to all participants of the Oral Health GeMS study, although based on individual need.

After the clinical oral examinations at the baseline, the Oral Health GeMS study population was further divided into an oral health intervention group and an oral health control group. The oral health intervention group was given individually tailored personal guidance on dental/denture hygiene, use of fluoride and xylitol, etc. based on the personal needs of the participant. These interventions were given after the clinical oral examination, meaning that they had no effect on the results.

6.3 Implications of the findings

Based on the findings of the study, the following clinical suggestions can be made regarding oral health and dental prophylaxis. Firstly, in order to identify those who suffer from hyposalivation or xerostomia, salivary secretion should be measured and an interview concerning xerostomia should be done to older people taking multiple drugs with sedative properties or anticholinergic activity. Secondly, sufficient guidance should be given about how to appropriately cope with symptoms of a dry mouth, such as drinking water or using saliva substitutes to relieve the symptoms and avoiding sugary juices and pastilles. It is also important to maintain the salivary gland function as high as possible with regular mealtimes and by eating food that requires chewing. Furthermore, the findings stress the importance of providing

oral hygiene guidance for older people taking sedative drugs. Instructions should be given on proper toothbrushing and interdental cleaning techniques and the importance of using fluoride toothpaste. Because of the increased risk for dental caries, older people require thorough prophylaxis measures, such as additional fluoride, i.e. high-concentrate fluoride toothpaste or fluoride varnishes, and regular oral examinations by a dentist and oral hygienist visits.

The current findings also imply that dentists should more often and easily work together or consult physicians and pharmacists, when treating patients with multiple drugs. Drug utilization review, often done by a pharmacist, and suggested changes into the drug regiment, can provide solutions or at least relieve adverse-effects and symptoms caused by drugs in the oral cavity. Dentists can provide important knowledge directly for primary physicians about the harmful effects of medication on patient's oral health and with this knowledge; physicians can adjust the medication accordingly if possible. By working together, these health care professionals can improve patients' oral health, quality of care and quality of life.

Scientifically, the thesis provides new evidence on how to study the effects of drugs on oral health. Sedative load appeared to be a more coherent and precise variable related to oral health than was the total number of drugs. Also, the Anticholinergic Drug Scale proved to be a precise measure for assessing the adverse effects of anticholinergic drugs. In future research where the study focus is on the adverse effects of medication, instead of using the total number of drugs, either sedative load or anticholinergic burden could be used instead. Possible interesting topics for future studies could be the effect of anticholinergic burden on oral diseases, such as dental caries and periodontal diseases, or the effect of sedative load on tempomandibular disorders, for example.

7 Summary

Both sedative load and anticholinergic burden appeared to be independent of each other and they affected different aspects of dry mouth. Based on these results it can be concluded that sedative load has more effect on stimulated salivary secretion, whereas anticholinergic burden has more impact on unstimulated salivary secretion and xerostomia.

In this study, sedative load was shown to be associated with poor oral health behavior and insufficient oral hygiene. Thus, sedative load can be interpreted as an indicator for poor oral health behavior.

Sedative load is associated with dental caries but not with periodontal diseases. The above-mentioned findings support this conception by showing that sedative load predisposes people to circumstances where the risk of dental caries is increased.

In conclusion, the findings of this study provide evidence that community-dwelling older people with a sedative load have poorer oral health than those without a sedative load. Furthermore, the results show that sedative load is an independent risk for poor oral health.

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Original publications

- I Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) Sedative load, carious teeth, and infection in the periodontium among community-dwelling older people. *Gerodontology* 34: 13–23.
- II Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2016) Sedative load and salivary secretion and xerostomia in community-dwelling older people. *Gerodontology* 33: 117–184
- III Tiisanoja A, Syrjälä AM, Komulainen K, Lampela P, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) Anticholinergic burden and dry mouth among Finnish community-dwelling older adults. *Gerodontology* DOI:10.1111/ger.12304
- IV Tiisanoja A, Syrjälä AM, Komulainen K, Hartikainen S, Taipale H, Knuuttila M, Ylöstalo P (2017) The association of medications with sedative properties with oral health behavior in community-dwelling older people. *Int J Dent Hyg* DOI:10.1111/idh.12285

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- I428. Salokorpi, Niina (2017) Treatment of craniosynostoses
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- I441. Huhtaniska, Sanna (2018) The association between antipsychotic and benzodiazepine use with brain morphology and its changes in schizophrenia
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- I443. Keto, Jaana (2018) The middle-aged smoker in health care : Primary health care use, cardiovascular risk factors, and physician's help in quitting

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