Thesis for doctoral degree

Association of periodontitis and tobacco use with autoimmune diseases and its radiologic diagnostic challenges with chronic rhinosinusitis

Anna Julkunen-Iivari

Department of Oral and Maxillofacial Diseases
University of Helsinki and Helsinki University Hospital
Helsinki, Finland

and

Department of Dental Medicine
Karolinska Institutet
Stockholm, Sweden

ACADEMIC DISSERTATION

To be presented,
with the permission of the Faculty of Medicine, University of Helsinki,
for public examination in Lecture Hall 2,
Biomedicum Helsinki, Haartmaninkatu 8, Helsinki,
on 15th of January 2021, at 13.

Helsinki 2020

Supervisors
Professor Jukka H. Meurman
Department of Oral and
Maxillofacial Diseases,
University of Helsinki and
Helsinki University Hospital
Helsinki, Finland

and

Docent Anna Maria Heikkinen
Department of Oral and
Maxillofacial Diseases,
University of Helsinki and
Helsinki University Hospital
Helsinki, Finland

and

Docent Sanna Toppila-Salmi
Haartman Institute,
University of Helsinki
Skin and Allergy Hospital
University of Helsinki and
Helsinki University Hospital
Helsinki, Finland

With collaboration
Professor Birgitta Söder
Department of Dental Medicine
Karolinska Institutet
Stockholm, Sweden

Reviewers
Professor Sisko Huumonen
Institute of Dentistry
University of Eastern Finland
Kuopio, Finland

and

Docent Merja Laine
Department of General Practice and
Primary Health Care
University of Helsinki and Helsinki
University Hospital
Helsinki, Finland

Opponent
Professor Päivi Mäntylä
Institute of Dentistry
University of Eastern Finland
Kuopio, Finland

FINDOS doctoral program, University of Helsinki
The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

ISBN 978-951-51-6913-6 (nid.)
ISBN 978-951-51-6914-3 (PDF)

http://ethesis.helsinki.fi/

Unigrafia, Helsinki 2020

I am among those who think that
science has great beauty

– Marie Curie

TABLE OF CONTENTS

ABBREVIATIONS

A.a.	Aggregatibacter actinomycetemcomitans
AARDA	American autoimmune related diseases association
ALARA	As low as reasonable achievable
aMMP	Active matrix metalloproteinase
Anti-BP180	Bullous pemphigoid 180 antibodies
BAFF	B-cell activating factor
BOP	Bleeding on probing, gingival bleeding
CBCT	Cone beam computed tomography
CI	Calculus index
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CT	Computed tomography
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ENT	Ear, nose, throat
GI	Gingival index
HbA1c	Glycated hemoglobin A1c
HIV	Human immunodeficiency virus
HUH	Helsinki University Hospital
ICD	International statistical classification of diseases and related health problems
Ig	Immunoglobulin
IL	Interleukins
LM	Lund-Mackay
MMP	Matrix metalloproteinase
MSCT	Multi slice computed tomography
OMC	Osteomeatal complex
P.g.	Porphyromonas gingivalis
P.i.	Prevotella intermedia
P.n.	Prevotella nigrescens
PI	Plaque index
PTG	Panoramic radiographic

RA	Rheumatoid arthritis
T.d.	Treponema denticola
T.f.	Tannerella forsythia
TIMP	Tissue inhibitors of MPPs
TNF	Tumor necrosis factors
UI	Uncertainty interval
WHO	World Health Organization

ABSTRACT

Chronic periodontitis is an inflammatory disease requiring treatment. Smoking is a significant risk factor for periodontal diseases and many others, including autoimmune diseases and chronic rhinosinusitis. Periodontitis can lead to periodontal-endodontic lesions and may cause chronic rhinosinusitis. To make the right treatment plan for these chronic diseases, diagnosing anatomical structures and pathological signs from radiographs is highly important.

This series of investigations focused on several research questions. How does chronic periodontitis associate with autoimmune and autoimmune-related diseases? How does tobacco-product use affect periodontal health? Is tobacco-product use associated with lower education level and mortality? And what kinds of radiologic challenges can be expected when diagnosing radiological signs of periodontitis and anatomical structures in chronic rhinosinusitis patients.

Altogether 1 676 randomly selected subjects in Stockholm County, Sweden, joined this study in 1985 and they were followed-up for 30 years for mortality (Studies I and II). Their tobacco use habits and the data from oral examination were recorded at baseline. The Swedish national health registers recorded their hospital and open health-care admissions (World Health Organization [WHO] International statistical classification of diseases and related health problems [ICD] 7, 9 and 10 codes). All subjects were classified into groups: "subjects with autoimmune disease" and "subjects without autoimmune diseases" (Study I); and "current tobacco product users" and "non-users" (Study II). Associations between the diagnosed autoimmune disease and the oral-health variables (Study I), periodontal health parameters, current use of tobacco products, education level and age of death were analyzed (Study II). In study III, the imaging data for 59 randomly selected patients in Helsinki University Hospital, Finland, was used. Radiographical signs of local dentoalveolar bone loss and apical radiolucency were analyzed blinded and inter-imaging accuracy was calculated from computed tomography scans (CT) and panoramic radiographic scans (PTG). Study IV employed the CT data of 57 chronic rhinosinusitis patients from Tampere University Hospital, Finland, to analyze the reproducibility of the Lund-Mackay (LM) scores and 43 other anatomical structures between three professional observers. SPSS was used for all analyses.

From the data, 50 patients with diagnosed autoimmune diseases were detected. The plaque index (PI) was significantly higher in the autoimmune disease group compared to non-autoimmune group (≥ median 35 (70%) vs < median 872 (54%), *P*-value = .030). No statistical difference was found in other

periodontal health parameters or use of tobacco products between the groups (Study I). Current tobacco users had poorer periodontal health than non-users. Use of tobacco products associated with higher plaque-, calculus- and gingival-index scores compared to non-users ($P < .001$). They were also more likely to present with deepened periodontal pockets (5 mm) ($P < .001$) and missing teeth ($P = .010$) compared with non-users. Tobacco users had lower education level compared with non-users ($P < .001$), but tobacco-product use did not associate with premature death (Study II). In general, inter-observer agreement in CT and PTG scans with the three other professional observers compared to the oral radiologist was from poor (kappa -0.054) to moderate (kappa 0.455). Based oral-radiologist records, inter-imaging accuracy was moderate (kappa 0.565) to very good (kappa 0.908) (Study III). Between three observers, inter-observer agreement regarding the structures in CT scans was generally moderate by Cohen's kappa coefficient. Poor reproducibility was observed in the certain surgically important structures, like optic nerve and anterior ethmoidal artery (Study IV).

Patients with a higher PI, which characterizes poor oral hygiene, were more likely to develop autoimmune diseases in the long run. Current use of tobacco products has a negative impact on periodontal health parameters and reinforces the perception that tobacco products are risk factors for periodontal diseases. Tobacco-product users are typically less educated than non-users, although, tobacco-product use may not associate with premature death. There is a great variation between professional observers in diagnosing signs of local dentoalveolar bone loss and periapical radiolucency from PTG and CT scans, and anatomical structures in sinus CT scans, which indicates multi-professional consultation before final treatment plan. To diagnose local horizontal bone loss, PTG is as reliable as CT, but not for vertical bone loss or periapical radiolucency.

TIIVISTELMÄ

Krooninen parodontiitti on tulehdussairaus, joka tulee hoitaa. Tupakointi on huomattava riskitekijä ienkudossairauksille ja monille muille, kuten autoimmuunisairauksille ja kroonisille nenänsivuontelotulehduksille (rinosinuiitti). Parodontiitti voi syvän ientaskun kautta saada aikaan apikaaliparodontiitin, joka taas voi johtaa krooniseen poskiontelotulehdukseen ja levitä muihin nenän sivuonteloihin. Jotta näihin kroonisiin sairauksiin voidaan tehdä oikea hoitopäätös, anatomisten rakenteiden ja patologisten löydösten tunnistaminen röntgenkuvien avulla on erityisen tärkeää.

Näiden osatutkimusten tavoite on havaita, kuinka krooninen parodontiitti assosioituu autoimmuunisairauksien ja autoimmuunin kaltaisten sairauksien kanssa, kuinka tupakkatuotteet vaikuttavat ienkudossairauksiin, assosioiko tupakkatuotteet koulutustason ja kuolleisuuden kanssa, ja minkälaisia radiologisia diagnostisia eroavaisuuksia parodontiitin ja kroonisten rinosinutiitin anatomisten rakenteiden havaitsemisessa voi olla.

Osatöissä I ja II satunnaisesti valittu tutkimusjoukko, joka sisältää 1 676 henkilöä Tukholman alueelta, Ruotsista, osallistui tutkimukseen vuonna 1985 ja heidän sairausdiagnoosejaan ja kuolinikäänsä seurattiin 30 vuoden ajan. Heille tehtiin suunterveyden tutkimus ja heidän tupakointitottumuksensa kirjattiin lähtötilanteessa. Ruotsin valtion terveysrekisteri sisälsi heidän sairaala- ja avoimen terveydenhuollon tietonsa, jotka sisälsivät ICD-7, -9, -10 diagnoosit. Kaikki tutkittavat henkilöt jaettiin ryhmiin: “autoimmuunipotilaat” ja ”ei-autoimmuunipotilaat” (osatyö II). Autoimmuunisairauksien ja suun terveyden parametrien yhteydet analysoitiin (osatyö I). Muuttujien, kuten ienkudossairauksien parametrien, tupakointitottumusten, koulutustason ja kuoliniän välinen yhteys analysoitiin (osatyö II). III osatyössä käytettiin satunnaisesti valikoidun 59 potilaan röntgenkuvadataa Helsingin ja Uudenmaan sairaanhoitopiirin tietokannasta. Neljä eri katsojaa tulkitsivat panoraamaröntgenkuvista (PTG) sekä tietokonetomografiakuvista (TT) röntgenologista patologiaa (vertikaalinen ja horisontaalinen luukato ja periapikaalinen luukato). IV osatyössä käytettiin Tampereen yliopistollisen sairaalan 57 kroonisen rinosinuiititittipotilaan TT kuvia. Kolme katsojaa tulkitsivat kuvien anatomisia rakenteita (Lund-Mackay [LM] ja 43 muuta anatomista rakennetta) ja katsojien vastausten yhteneväisyys analysoitiin. Kaikkien tutkimusten analyysit suoritettiin SPSS ohjelmalla.

Yhteensä datan 50 potilaalla oli diagnosoitu autoimmuunisairaus. Autoimmuunipotilaiden ryhmässä havaittiin korkeampi plakki-indeksi verrattuna ei-autoimmuunisairaiden ryhmään (≥ mediaani 35 (70%) vs < mediaani 872

(54%), *P*-arvo= .030). Merkittävää eroa ei löydetty muissa iensairauksien parametreissa tai tupakoinnissa näiden kahden ryhmän välillä (osatyö I). Nykyisillä tupakkatuotteiden (nuuska ja poltettava tupakka) käyttäjillä oli merkittävästi huonompi ienkudosten terveys verrattuna ei-käyttäjiin. Tupakkatuotteiden käyttö assosioitui korkeampaan plakki-, hammaskivi-, ja ienverenvuotoindekseihin, syventyneihin ientaskuihin (5 mm) sekä puuttuviin hampaisiin verrattuna ei-käyttäjiin (*P*< .001). Tupakkatuotteiden käyttäjät olivat vähemmän koulutettuja kuin ei-käyttäjät (*P*< .001). Tutkimuksessamme tupakkatuotteiden käyttö ei kuitenkaan liittynyt ennenaikaiseen kuolemaan (osatyö II). Yleisesti kolmen tulkitsijan yhteneväisyys suuradiologin kanssa TT ja PTG kuvien röntgenologisen patologian tulkinnassa oli huonosta (kappa -0.054) kohtalaiseen (kappa 0.455). Suuradiologin tulkitsemien löydösten perusteella laskettu kuvienvälinen tarkkuus TT ja PTG kuvien välillä oli kohtalaisesta (kappa 0.565) erittäin hyvään (0.908) (osatyö III). Yleisesti kolmen katsojan yhteneväisyys rinosinuiittipotilaiden TT kuvista oli kohtalainen Cohenin kappa kertoimella. Huono yhteneväisyys havaittiin joissakin leikkausalueen kriittisissä anatomisissa rakenteissa, kuten näköhermossa ja etummainen etmoidaali valtimossa (osatyö IV).

Henkilölle, jolla on huonoa suuhygieniaa kuvaava korkea plakki-indeksi, todennäköisemmin kehittyy autoimmuunisairaus pitkällä aikavälillä. Nykyisellä tupakkatuotteiden käytöllä on huonontava vaikutus ienkudoksen terveyteen ja se on riskitekijä ienkudossairauksille. Tupakkatuotteita käyttävillä on alempi koulutustaso kuin ei-käyttävillä. Kuitenkaan tupakkatuotteiden käyttö ei välttämättä ole yhteydessä ennenaikaiseen kuolemaan. Röntgenkuvien tulkitsijoiden välillä on paljon vaihtelevuutta, kun tulkitaan alveoliluukatoa ja periapikaalista luukatoa tai anatomisia rakenteita nenänsivuonteloiden TT kuvista, jonka vuoksi moniammatillinen yhteistyö ja konsultaatio ennen lopullista hoitopäätöstä on suositeltavaa. Horisontaalisen luukadon diagnostiikassa PTG on yhtä luotettava kuvausmenetelmä kuin TT, muttei vertikaalisessa ja periapikaalisessa luukadossa.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications:

Study I: Julkunen A.; Heikkinen A.M.; Söder B.; Söder P.-Ö.; Toppila-Salmi S.; Meurman J.H. Autoimmune Diseases and Oral Health: 30-Year Follow-Up of a Swedish Cohort. Dent J (Basel). 2017;6(1):1. doi:10.3390/dj6010001

Study II: Julkunen-Iivari, A.; Heikkinen, A.M.; Räisänen, I.T.; Ruokonen, H.; Meurman, J.H.; Toppila-Salmi, S.; Söder, P.-Ö.; Söder, B. Tobacco Products, Periodontal Health and Education Level: Cohort Study from Sweden. Dent. J. 2020,8,90

Study III: Julkunen-Iivari, A.; Apajalahti S.; Saat R.; Heikkinen A.M.; Meurman J.H.; Toppila-Salmi S. Inter-observer Agreement and Inter-imaging Accuracy in Sinus Computed Tomography Scans and Panoramic Radiography on Signs of Local Dentoalveolar Bone Loss and Periapical Radiolucency. Submitted.

Study IV: Julkunen A.; Terna E.; Numminen J.; Markkola A.; Dastidar P.; Karjalainen M.; Huhtala H.; Rautiainen M.; Meurman J.H.; Toppila-Salmi S. Inter-observer agreement of paranasal sinus computed tomography scans. Acta Otolaryngol. 2017;137(6):611–617. doi:10.1080/00016489.2016.1262552

Original publications and Tables are reprinted with the permission of the publisher.

1 INTRODUCTION

Periodontitis is a multifactorial inflammatory disease where supportive connective and bone tissues around the teeth may destruct (Nibali et al. 2013, World Health Organization 2020). Periodontitis is caused by host response induced by bacterial accumulation around the teeth, so good daily oral hygiene is the key factor in preventing and controlling the disease (Graves et al. 2000, World Health Organization 2020). Periodontitis causes the upregulation of a number of chemokines and cytokines that mediate the many systemic effects of the disease (Pihlstrom et al. 2005). Periodontitis associates with various different chronic diseases like rheumatoid arthritis (RA), Diabetes Mellitus (DM), osteoporosis and Alzheimer's disease (Araujo et al., Berthelot and Le Goff 2010, Esfahanian et al. 2012, Sonnenschein and Meyle 2015).

A rare pathological stage, where the body's own immune response attacks healthy tissues, leads to autoimmune diseases. The pathomechanisms of autoimmunity are multifactorial and mostly unknown, but there is a strong association between autoimmunity and viral, bacterial and other microbial infections. (Damoiseaux and Tervaert 2002, Kivity et al. 2009, Galli et al. 2012) Pathogens affect the strictly regulated stability and functionality of tissues where the immune system plays a role, and autoimmunity reactions may follow (Ercolini and Miller 2009).

Smoking is a significant health risk for many chronic systemic diseases, such as atherosclerosis and chronic obstructive pulmonary disease (Whisnant et al. 1990, Yanbaeva et al. 2007, Arnson et al. 2010, Kiriyama et al. 2020). Smoking affects periodontal health negatively, increasing attachment loss, visible plaque index (PI), root calculus, deepened periodontal pockets and bleeding on probing (Heikkinen et al. 2008, Genco and Borgnakke 2013, Boulaamaim et al. 2020). The effects of smoking may show in the oral cavity, for instance as oral cancer, tooth loss and periodontal disease (Heikkinen et al. 2008, Warnakulasuriya et al. 2010). Smokeless tobacco (snuff) may be associated with localized gingival recession, leukoplakia and clinical attachment loss (Natvig Norderhaug I. et al. 2005, Katuri et al. 2016).

Chronic rhinosinusitis (CRS) is a common, multifactorial and variable inflammatory disease that has autoinflammatory characteristics, although it is not classified as autoimmune disease (Benninger 2003, Lefrancois et al. 2016, Fokkens et al. 2020). The mechanisms of CRS are not fully understood, however approximately 10% of maxillary sinusitis has an odontogenic etiology (Maillet et al. 2011). After the failure of medical treatment, the severity of CRS and the

putative need for surgery is assessed based on clinical findings and imaging (Fokkens et al. 2020).

In CRS, CT scans are the imaging modality of choice confirming the extent of pathology and the need for surgery (Fokkens et al. 2020). To diagnose periodontal diseases, intra- or extraoral radiographs are needed in addition to clinical examination (Persson et al. 2003, Corbet et al. 2009). Diagnosing anatomical structures or signs of pathology from radiographs is subjective for every clinical observer and sometimes there is lack of inter-observer agreement, which results in different treatment plans (Groth et al. 2009, Shahzad et al. 2018, Al Kasab et al. 2019).

The focus of this series of investigations was to study how periodontitis associates with autoimmune and autoimmune-related diseases; how the use of tobacco products associates with periodontal health, education level and mortality; and what kind of radiologic challenges can be expected when diagnosing radiological signs of alveolar bone destruction or sinonasal anatomical structures.

2 REVIEW OF THE LITERATURE

2.1 PERIODONTAL DISEASE

Periodontitis is a long-term multifactorial inflammatory disease that leads to loss of periodontal tooth-support (Graves et al. 2000, Matuliene et al. 2008, Papapanou et al. 2018). Previously, periodontitis was subdivided into four categories: chronic and aggressive periodontitis, periodontitis as a manifestation of systemic disease, necrotizing periodontal diseases and periodontal abscess (Armitage 1999). In 2018, Papapanou et al. presented a new classification for periodontitis based on stages defined by severity (Table 1), complexity (Table 2) and extent and distribution. In this classification, periodontitis stages are divided into stage I, II, III and IV. They classified periodontitis also into grades, which reflect biologic features of the disease, including evidence of/ risk for fast progression, anticipated treatment response, and impact on systemic health (Table 3). Grades can be used as an indicator of the speed of progression of periodontal disease. (Papapanou et al. 2018)

Table 1. Classification of periodontitis based on severity

	Clinical attachment loss*	Bone loss in radiographs	Tooth loss due to periodontitis
Stage I	1-2mm	Coronal third (<15%)	No
Stage II	3-4mm	Coronal third (15-33%)	No
Stage III	5mm	Extending to middle or apical third of the root	4 teeth
Stage IV	5mm	Extending to middle or apical third of the root	5 teeth

* at site of greatest loss

Table modified from Papapanou et al. (2018)

Table 2. Classification of periodontitis based on complexity

	Local changes
Stage I	Probing depth ≤4mm, mostly horizontal bone loss
Stage II	Probing depth ≤5mm, mostly horizontal bone loss
Stage III	Additionally to stage II: probing depth ≥6mm, vertical bone loss ≥3mm, Furcation Class II or III, moderate ridge defect
Stage IV	Additionally to stage III: need for rehabilitation due to masticatory dysfunction, occlusal trauma (tooth mobility ≥2 degree), severe ridge defect, bite collapse, less that 10 opposing pairs of teeth remaining

Table modified from Papapanou et al. (2018)

Table 3. Classification of periodontitis based on grades

	Over 5 years evidence (alveolar bone loss or clinical attachment loss)	Percentage bone loss/ age	Phenotype	Tobacco smoker	Diabetes mellitus (DM)
Grade A[A]	No loss	<0.25	Burdensome biofilm, low level of periodontal destruction	Non-smoker	Normo-glycemic
Grade B[B]	<2mm	0.25–1.0	Periodontal destruction commensurate with amount of biofilm	Smoker <10 cigarettes per day	Diagnosed DM, HbA1c <7.0%
Grade C[C]	≥2mm	>1.0	Periodontal destruction exceeds, periods of fast progression and/ or early onset disease	Smoker ≥10 cigarettes per day	Diagnosed DM, HbA1c ≥7.0%

[A] Slow rate of progression, [B] Moderate rate of progression, [C] Rapid rate of progression, DM= Diabetes Mellitus, HbA1c= Glycated hemoglobin A1c.

Table modified from Papapanou et al. (2018)

2.1.1 PATHOGENESIS

The invading bacteria and its metabolic products stimulate the destructive inflammatory cascade in periodontium. The host's innate, inflammatory and adaptive immune response defends against microbial attack (Graves et al. 2000). These pathogens may also be present in healthy periodontium, however (Zarco et al. 2012).

The innate immune system is activated, leading to an excess of cytokines and inflammatory mediators, such as prostaglandins, chemokines, interleukins (IL) and tumor necrosis factors (TNF)—especially IL-1, IL-6, TNF-α. This leads to the release of matrix metalloproteinases (MMPs) (Graves et al. 2000, Sorsa et al. 2020).

Periodontitis is a polymicrobial disease where certain indicator bacteria, however, have been useful in research and diagnosis. Porphyromonas gingivalis (P.g.), Tannerella forsythia (T.f.) and Treponema denticola (T.d.) constitutes the "red complex", which expresses progressing periodontitis (Rocas et al. 2001, Holt and Ebersole 2005, Chen et al. 2005). Aggregatibacter actinomycetemcomitans (A.a), Prevotella intermedia (P.i.) and Prevotella nigrescens (P.n.) periodontal-disease-indicator bacteria are also less virulent (Lie et al. 2001, Chen et al. 2005). Chen et al. (2005) suggest that P.g., T.d. and A.a. are found in deep periodontal pockets more frequently than in shallow ones (Chen et al. 2005).

In periodontium heterotypic communities of organisms, which construct polymicrobial synergy, interference of tissue homeostasis leads to a regular immune response. Even a small amount of virulent pathogens increase community pathogenicity and leads to a dysbiotic community, which impairs immune control (Lamont and Hajishengallis 2015). A dysbiotic community leads to the infiltration of characteristic cytokines and inflammatory mediators to periodontal tissue, which results in tissue destruction (Graves et al. 2000).

2.1.2 RISK FACTORS

Lifestyle, environmental and genetic factors contribute to the development of periodontal diseases (Silva et al. 2015). This section will focus on lifestyle and environmental factors (Table 4).

Table 4. Risk factors for periodontal diseases

Lifestyle	Environmental
Tobacco	Age
Snuff	Being male sex
Alcohol	Lower socioeconomic status
Bad oral hygiene habits	Chronic systemic disease

2.1.2.1 Periodontal diseases, tobacco products and alcohol

Smoking tobacco is one well-known critical risk factor for periodontal diseases both in adolescents and in adults (Heikkinen et al. 2008, Genco and Borgnakke 2013, Boulaamaim et al. 2020). Several longitudinal studies have reported the risk of periodontal-disease progression for smokers and non-smokers (Bergstrom 2004, Airila-Mansson et al. 2005). Smokers are three- to six-times more likely than non-smokers to develop periodontal disease (Barbour et al. 1997). Smoking increases density of infection, which increases risk for periodontitis (Arcavi and Benowitz 2004). The amount of cigarette consumption (dose-effect) and pack-years of smoking associates with the severity of periodontal disease (Martinez-Canut et al. 1995). Smoking increases periodontal bone loss compared to non-smokers (Martinez-Canut et al. 1995, Bergstrom 2004, Airila-Mansson et al. 2005). Mullally et al. (1999) suggests that in early-onset periodontitis alveolar bone loss is more severe in maxillary arch compared to the lower arch (Mullally et al. 1999).

Use of smokeless tobacco (snuff) as a risk factor for periodontal diseases has been controversial (Bergstrom et al. 2006, Hugoson and Rolandsson 2011, Katuri et al. 2016). Katuri et al. (2016) showed that smokeless tobacco users had more

clinical attachment loss compared to smokers (Katuri et al. 2016). Some studies reported that use of snuff is not a risk for periodontal diseases (Bergstrom et al. 2006, Hugoson and Rolandsson 2011).

Cigarettes and snuff contain nicotine and other cytotoxic substances, which enter to the blood stream via the oral cavity, cause vasoconstriction and impair the immune-system function (Barbour et al. 1997, Gautam et al. 2011). Smoking inhibits granulocyte function, which weakens host defense (Soder et al. 2002). Smoking also affects angiogenesis-related proteins, impairing angiogenesis and periodontal homeostasis (Yilmaz Sastim et al. 2020). No clear association has been found between smoking and periodontal-pathogens growth. However, bacteria, such as P.g., are adapting to complex environmental changes, which ensures growth and survival within the host (Jiang et al. 2020).

Alcohol use as a risk factor for periodontal diseases has also been controversial. Sankaranarayanan et al. (2019) found no association between alcohol use and deepened periodontal pockets in their cross-sectional study. (Sankaranarayanan et al. 2019) Nonetheless, in a recent meta-analysis study, Wang et al. (2016) suggests that alcohol consumption is associated with increased risk for periodontitis (Wang et al. 2016a).

2.1.2.2 Periodontal diseases, age, gender and socioeconomic status

There are different hypotheses to explain the association between advancing age and periodontal tissue destruction. With the “cumulative” hypothesis, increased periodontal-tissue destruction can be explained by the longitudinal exposure to the effects of periodontal diseases. In turn, with the “age-related susceptibility” hypothesis, advancing age increases the risk to periodontitis by a disturbance in immune-system regulation (Hajishengallis 2010).

Being of male sex has been a significant risk factor for periodontal diseases assessed by prevalence, extent and severity. There seems to be no genetic factor to explain this difference between sexes, but rather a consequence of lifestyle (Genco and Borgnakke 2013). Men can have even 50% higher prevalence of periodontitis compared to women (Eke et al. 2015).

Lower socioeconomic status (i.e. education, income, poverty-income ratio) associates with poorer periodontal health (Borrell and Crawford 2012). A recent cross-sectional study on an adult population found a significant correlation between low educational level, low social class and a higher prevalence of deepened periodontal pockets (Almerich-Silla et al. 2017). Low socioeconomic status may lead to stress and increases allostatic load (Baum et al. 1999, Borrell and Crawford 2012). Subjects with lower education level may smoke tobacco for a longer period compared to subjects with higher socioeconomic status, which

may lead to periodontitis and financial stress as well (Siahpush et al. 2005). Stress can lead to behaviors that can harm periodontal health, such as poor oral hygiene and a higher amount of plaque, increased smoking, less dental visits, and harmful eating habits (Genco and Borgnakke 2013).

2.1.2.3 Effects from biofilm on periodontal health

Dental plaque, a structurally- and functionally-organized biofilm, has a diverse microbial composition that, in health, remains relatively stable over time (microbial homeostasis). Oral biofilm plays a key role in the etiology of oral diseases including periodontitis (Marsh et al. 2015). Preventing treatment and self-education are highly important in plaque control and periodontal disease prevention (Axelsson et al. 2004).

2.1.2.4 Chronic systemic diseases as risk factors to periodontal diseases

Considerable evidence shows that several chronic systemic diseases are risk factors for periodontal diseases, yet the risk is often bidirectional. In this section, chronic systemic diseases that may be considered as risk factors for periodontitis are presented.

One of those diseases is DM. Type I diabetes and type II diabetes increases the prevalence, severity, extent, progression, and possibly the incidence of periodontal disease (Genco and Borgnakke 2013). Insulin resistance appears to mediate the relationship between obesity and periodontal disease. Obesity, on the other hand, is a significant predictor of periodontal disease (Genco et al. 2005). Cardiovascular disease is also a chronic disease, which has been proposed to be a risk factor for periodontitis, although currently there is limited scientific evidence (Sanz et al. 2020).

Esfahanian et al. (2012) suggest that osteoporosis and low systemic bone-mineral-density is a risk factor for periodontal-disease progression (Esfahanian et al. 2012). In their two-year longitudinal study, Payne et al. (1999) showed the alveolar bone height and density changes in osteoporotic/osteopenic women, compared with women with normal lumbar-spine bone-mineral-density, while estrogen deficiency was associated. The authors of the study made the conclusion that osteoporosis/osteopenia and estrogen deficiency are risk factors for loss of alveolar bone density in post-menopausal women with a periodontitis background (Payne et al. 1999).

Alzheimer's disease is bidirectional with periodontitis. Inflammation is common for both diseases but the exact mechanism and cross-link between

chronic periodontitis and Alzheimer's are not so well known (Rong et al. 2020, Sadrameli et al. 2020). Periodontal pathogens, like P.g., are one suggested association between periodontitis and Alzheimer's (Sadrameli et al. 2020). Araujo et al. (2020) also found a link between periodontitis and Alzheimer's disease, but not between periodontitis and oral health-related quality of life. (Araujo et al. 2020)

Rheumatoid arthritis is suggested to be one of the chronic diseases that is a bidirectional risk factor with periodontitis (Mercado et al. 2001). RA and periodontitis both have common aspects in pathogenesis, where an inflammatory triggering factor and changed or impaired host immune defense and involvement of genetic and lifestyle factors are related (Araujo et al., Mercado et al. 2001). RA medication can trigger reduced saliva flow and lead to hyposalivation, which impairs oral health (Torres et al. 2016).

Human immunodeficiency virus (HIV) may also be one risk factor for periodontitis via immunosuppression (Barr et al. 1992). Instead, Aichelmann-Reidy et al. (2010) suggests that HIV itself may not be related to periodontitis, but that subjects with HIV or with high-risk behavior associated with HIV smoke more, which may lead to periodontal bone loss (Aichelmann-Reidy et al. 2010).

2.1.2.5 Smoking as a risk factor for autoimmune diseases

Smoking is related to pathogenesis of certain autoimmune diseases by triggering the development of autoantibodies and misbalancing the immune system (Perricone et al. 2016). Smoking is linked to development and outcome of RA (Hutchinson et al. 2001, Kallberg et al. 2011, Perricone et al. 2016). One hypothesis, which has been proposed on the effect of smoking, is that smoking accelerates citrullination of peptides, which leads to activation of RA susceptibility genes and leads to the onset of RA (Kallberg et al. 2011, Perricone et al. 2016). DM has also been linked to tobacco smoking. One suggested hypothesis is that smoking associates with differential deoxyribonucleic acid (DNA) methylation of the risk genes of DM (Ligthart et al. 2016). Will et al. (2001) reported that rate of DM increases for both genders as frequency of smoking increases (Will et al. 2001).

2.1.3 EPIDEMIOLOGY

In their systemic review, Kassebaum et al. (2014) found that chronic periodontitis is the sixth-most prevalent disease. Results of the study are shown in Figure 1. Between the years 1990 and 2010, the age-standardized prevalence of this

condition globally in the entire population was 11.2% (95% Uncertainty interval [UI]: 10.4%–11.9% in 1990 and 10.5%–12.0% in 2010). Age-standardized prevalence in Western Europe, including Sweden and Finland, was 9.8% (95% UI: 8.9%-10.7%) in 1990 and 9.4% (95% UI: 8.6%-10.3%) in 2010. No significant differences were found between men and women with severe chronic periodontitis, but the prevalence increased with age, reaching its peak at 40 years-of-age, and staying stable at higher ages (Kassebaum et al. 2014).

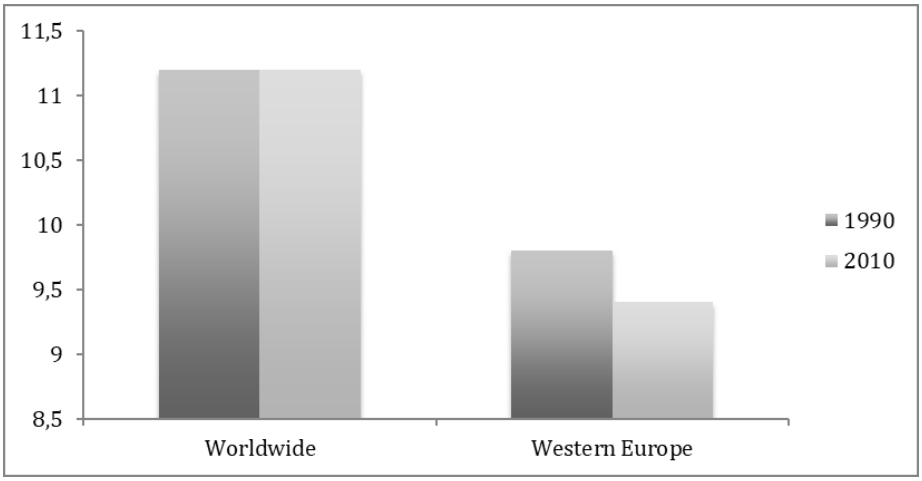

Figure 1. Chronic periodontitis. Prevalence of chronic periodontitis worldwide and in Western Europe in 1990 and 2010 according to Kassebaum et al. (2014).

In a prospective longitudinal study on periodontal bone height changes in a Swedish population, Hugoson & Laurell (2000) reported findings from their random sample of 1 000 individuals. The study finally included 429 dentate individuals, aged 15–60 years at baseline in 1973, and they received full mouth examination, which included plague and gingivitis scores and bone-height measurements from full mouth intra-oral radiographs. After a 17-year follow-up from the age of 30 years, about 80% of the study population had one or more sites with bone loss of at least 10% (Hugoson and Laurell 2000).

2.1.4 DIAGNOSTICS

2.1.4.1 Clinical

When diagnosing periodontal diseases, anamnesis (age, smoking habits, oral care habits, other than oral diseases, medication, and previous dental care) and clinical examination, based on the patient´s symptoms and clinical signs, are

highly important. Evaluation of clinical signs includes the color, shape, texture and bleeding on probing of the gingival tissue (Armitage 2004, Highfield 2009). Clinicians should record the findings from all teeth for: amount and location of plaque, probing depths (> 3mm), calculus, furcation lesions, mobility of the teeth, teeth loss, and bleeding on probing (Armitage 2004).

Biomarkers for diagnosing periodontitis from saliva and gingival crevicular fluid have been intensively studied. The currently known biomarkers from inflamed periodontal tissue include IL-1b, -6, -8, -18, TNF-α, MMP-8, -9, and tissue inhibitors of MPPs (TIMP)-1 (Kaufman and Lamster 2000, Miller et al. 2006, Sorsa et al. 2020). Matrix metalloproteinase-8 (MMP-8) is one of the most studied of these. Active MMP-8 (aMMP-8) levels rise in oral fluids when periodontal disease is in the active phase. In fact, the presence of MMP-8 antibodies can be used to prediction of the progression of periodontitis during the maintenance phase. Sorsa et al. (2020) suggests that the aMMP-8 mouthrinse point-of-care chairside test could be used as the staging and grading biomarker in the new classification system of periodontitis. Occasionally, histopathology, microbiology or serology are also needed for the diagnosis (Highfield 2009).

2.1.4.2 Radiographs

The evidence from intra- or extraoral radiological images supports diagnosing periodontal diseases. Periodontitis manifests, for instance, as diffuse bone margin, vertical alveolar bone loss or horizontal alveolar bone loss (Corbet et al. 2009, Papapanou et al. 2018). Nevertheless Corbet et al. (2009) suggests that in chronic periodontitis radiographs are not required for the establishment of a diagnosis (Corbet et al. 2009).

2.1.4.2.1 Inter-observer agreement in radiographs

Inter-observer agreement in different radiological imaging modalities has been studied with varying results. Studies from inter-observer agreement in oral radiography scans are less common than radiography scans from other anatomical structures.

Croft el al. (2020) found excellent inter-observer agreement between three observers in whole-body magnetic resonance imaging in reporting symptomatic myeloma patients (Croft et al. 2020). Lam et al. (2019) studied inter-observer agreement in ultrasound images of 460 indeterminate thyroid nodules between three observers. Agreements were between fair to very good in different areas (Lam et al. 2019). Al Kasab et al. (2019) investigated inter-observer agreement, between three neuroradiologists, in CT angiography to identify intercranial

aneurysm growth in phantoms. The detection rate in one dimension was nearly 60% and in all dimensions just over 10%, which shows significant variability (Al Kasab et al. 2019).

Shahzad et al. (2018) found fair agreement (kappa 0.3–0.5) in determining the appearance of mental foramen in PTG scans between four observers (Shahzad et al. 2018). Tewary et al. (2011) showed that inter-observer agreement of periapical radiographs is varied and interpretation is subjective. They found inter-observer agreement to be fair (kappa 0.2–0.4) between six trained observers (Tewary et al. 2011). In a recent 2020 study. inter-observer agreement of alveolar bone level from bitewing and panoramic radiographs between three observers was evaluated. The mean intra-class correlation coefficient for bitewings was 0.85, and for PTG was 0.66. (Hellen-Halme et al. 2020)

2.1.4.2.2 Diagnostic challenges in periodontitis

There are some radiologic diagnostic challenges when diagnosing periodontal diseases because changes in radiographs are not visible until the periodontal tissue destruction has already happened (Corbet et al. 2009). Radiographic imaging angle and two-dimensionality can make diagnostic challenging, and sometimes three-dimensionality is required for the diagnosis (Corbet et al. 2009, Assiri et al. 2020). For example, an estimation of bone loss on bucco-lingual sides of alveolar bone is more reliable with three-dimensional scans than with two-dimensional (Assiri et al. 2020). Due to inter-imaging accuracy variations, it is important to select the right imaging method, where benefits are higher than disadvantages (Corbet et al. 2009).

If periodontal disease is in its active phase, it is unreliable to diagnose with radiographs alone. Due to these radiologic diagnostic problems, clinical diagnosis is highly important. However, there are challenges also in clinical diagnosis if a patient smokes (reduced gum bleeding), has chronic systemic diseases that affect oral mucosa, or has medication, like cyclosporine, which causes hypertrophy of the gums (Highfield 2009). Diagnostic challenge is also variation in inter-observer agreement, which can lead to different treatment plans (Shahzad et al. 2018).

2.1.4.2.3 Radiation dose in radiographic imaging

Radiographic imaging is an important source of exposure to ionizing radiation. Due to this fact, lower radiation doses are what to seek in medical imaging procedures without impairing the diagnostic imaging quality (Kalra et al. 2004, Fazel et al. 2009, McCollough et al. 2009). Radiological imaging should always be justified and optimized and follow ALARA (as low as reasonably achievable) principles (McCollough et al. 2009).

Approximately 1–10mSv of radiation from natural sources, such as radon and cosmic radiation, is received per year. Effective radiation dose in typical CT scan, depending on the exam, is 1–14mSv (McCollough et al. 2009). By using low-dose CT, radiation dose can be reduced significantly (Bulla et al. 2012). In a sinus CT scan, a person is exposed to a radiation dose of approximately 0.5mSv, and in PTG the dose is approximately 0.02mSv (STUK 2017).

As well as CT, cone beam computed tomography (CBCT) is suited for sinus imaging.

In a 2015 study, CBCT and multi slice computed tomography (MSCT) were compared to evaluate image quality and radiation dose in patients with sinonasal polyposis (De Cock et al. 2015). CBCT had an approximately 40% lower effective radiation dose compared to MSCT. Therefore, CBCT is a better imaging of choice for important sinonasal anatomical structures.

2.1.4.2.4 Radiological imaging modalities to diagnose periodontitis and periapical lesions

Alveolar bone loss in periodontitis is examined with different radiological modalities. Two-dimensional scans cause lower radiation dose compared to three-dimensional scans, but the latter are more informative (Walter et al. 2009, STUK 2017, Assiri et al. 2020, Walter et al. 2020).

In two recent review articles, compared to other modalities, CBCT is the most accurate and beneficial to identify periodontal infra-bony defects and furcation lesions (Assiri et al. 2020, Walter et al. 2020). For example, Walter et al. (2009) concluded that CBCT images provide more accurate information, which leads to a clear treatment plan compared to situation without CBCT scans, when more than one treatment opinion was indicated. Ruetters et al. (2020) found that CBCT is more accurate for imaging periodontal defects compared to digital periapical radiographs.

Salceanu et al. (2018) compared PTG scans and CBCT scans to detect periapical lesions with and without root canal fillings. They found that CBCT is more accurate to diagnose periapical lesions when root canal is already filled (17% vs 10%). Detecting periapical lesions from teeth without root canal fillings were similar in both modalities (44%) (Salceanu et al. 2018). In a 2018 study, CBCT and periapical radiographs were compared to detect endodontic periapical radiolucency and they concluded that CBCT is more accurate to detect these radiological signs compared to periapical radiographs (Lo Giudice et al. 2018). A similar result was found in a 2008 study, where CBCT, PTG and periapical radiographs were compared and CBCT was proved to be best accurate to identify periapical radiolucency (Estrela et al. 2008).

2.2 PERIAPICAL LESIONS

Apical periodontitis (periapical lesion) develops from a cascade where healthy pulp tissue faces injury or insult and progresses to inflammation. If inflammation is not resolved, pulp will become necrotic and become easily infected. Infection in turn leads to tissue destruction, which is the body's own defense system and appears in radiograph periapical bone loss (periapical lesion), radiolucency around the dental root. It takes time before apical periodontitis can be seen in X-ray scans (secondary acute and chronic apical periodontitis) (Abbott 2004). Some known risk factors for apical periodontitis are reduced marginal bone level, caries lesions, coronal fillings and crowns, and smoking (Kirkevang et al. 2007).

Lee et al. (2017) found that bacteria-positive apical periodontal teeth had two or three different species of bacteria in the root canal; 70% of which were anaerobes and 30% were aerobes. They found 34 different bacterial species and the most common were Prophyromonas endodontalis (20% of the teeth), Dialister invisus (18%), Fusobacterium nucleatum (18%), Treponema denticola (16%), Enterococcus faecalis (16%), Peptostreptococcus (12%), Olsenella uli (12%), and Veillonella (10%) (Lee et al. 2017).

There is a wide variation between populations and countries in the prevalence of apical periodontitis. From 20% to 80% of adult subjects have been reported to have apical periodontitis (Marques et al. 1998, Kabak and Abbott 2005). In a recent study of Finnish adults, apical periodontitis was more prevalent among those with root-filled teeth than those without (39% vs 10%) (Huumonen et al. 2017).

2.3 COMORBIDITIES OF PERIODONTITIS

This section discusses autoimmune diseases and chronic rhinosinusitis. Other diseases are excluded.

2.3.1 AUTOIMMUNITY AND PERIODONTITIS

Autoimmune diseases arise from an abnormal immune response of the body against substances and tissues normally present in the body (autoimmunity). Autoimmune diseases are chronic, multifactorial, heterogeneous or variable conditions that may exist in several organs or cell types (Damoiseaux and Tervaert 2002, Ercolini and Miller 2009). A large number of autoimmune diseases are recognized. Some of these have relatively high prevalence, such as rheumatoid

arthritis, type I diabetes, coeliac disease, psoriasis and multiple sclerosis, whereas others are rare (Amer Diabet Assoc 2010, Rubio-Tapia and Murray 2010, McInnes and Schett 2011, Moroni et al. 2012, Raychaudhuri et al. 2014, Kuhlmann et al. 2017). In their epidemiological study, Cooper et al. (2009) found an estimated prevalence of 29 autoimmune diseases of 7% to 9% globally (Cooper et al. 2009). Eaton et al. (2007) found the population prevalence to be over 5% of 31 autoimmune diseases in Denmark (Eaton et al. 2007).

There is a strong association between viral, bacterial and other microbial infections and autoimmunity, but association between periodontitis, as a chronic inflammatory disease, and all autoimmune diseases is unknown (Figure 2) (Ercolini and Miller 2009, Galli et al. 2012). Periodontitis has been reported to have an association with autoimmune diseases like rheumatoid arthritis and type I diabetes (Berthelot and Le Goff 2010). Smoking tobacco affects both cell-mediated and humoral immune responses, therefore it is also a risk factor for autoimmune diseases (Arnson et al. 2010). Vessey et al. (1987) were the first to study association between smoking and rheumatoid arthritis (RA) in 1987, and documented a significant increase in prevalence of RA in smokers.

Other known risk factors for autoimmunity diseases are drugs, female hormones, stress, trauma and irradiation (Galli et al. 2012, Moroni et al. 2012). Gleicher & Barad (2007) listed gender prevalence ratios for sixteen selected autoimmune diseases and showed how female sex is a risk factor for autoimmune diseases. As an example, female/male ratio was 50:1 for hypothyroidism, 9:1 for systemic lupus erythematosus, 9:1–20:1 for Sjögren's syndrome, and 9:1 for primary biliary cirrhosis (Gleicher and Barad 2007). Autoimmune diseases have been shown to also be associated with concomitant autoimmune disease and cardiovascular disease. The type of comorbidity depends on the type and mechanisms of autoimmune disease (Nagy et al. 2018, Linder et al. 2018). One known disease pair, which has decreased the chance of coexistence, is rheumatoid arthritis and multiple sclerosis (Cooper et al. 2009).

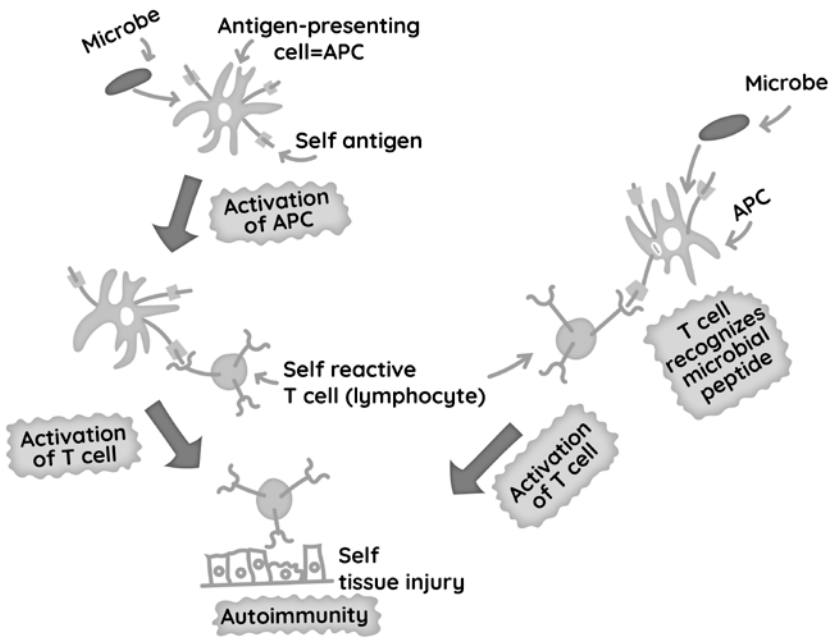

Figure 2. How periodontal bacteria may promote autoimmunity, modified from Creative Diagnostics webpage (https://www.creative-diagnostics.com/Autoimmunity.htm)

2.3.2 CHRONIC RHINOSINUSITIS AND PERIODONTITIS

Chronic rhinosinusitis is a common, multifactorial and variable disease, defined by typical symptoms (obstruction, facial pain, postnasal drip, nasal discharge, loss of sense of smell) that last at least for 12 weeks. CRS's overall prevalence has been found to be between 5–30%. CRS is reported to be associated with female gender and various different co-morbidities, such as asthma, Acetyl salicylic acid–exacerbated respiratory disease, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, bronchiectasis, primary ciliary dyskinesia, cystic fibrosis, immunodeficiency, and depression: It is unclear if CRS associates with periodontal diseases, however (Fokkens et al. 2020). However, CRS can be caused by dental apical periodontitis (periapical lesions) from the upper molars or premolars (Lechien et al. 2014). Approximately 10% of the maxillary sinusitis has dental etiology (Maillet et al. 2011, Phothikhun et al. 2012). The risk factors of CRS include smoking, occupational exposure to inhaled agents, and structural changes of sinonasal tract (Fokkens et al. 2020).

CT scan is a reliable imaging choice to diagnose CRS. Lund-Mackay staging is one of the most used CT-staging system of CRS. Staging is based on degree of opacification (normal/ partial opacification/ total opacification) for each side of the sinus: maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal sinus (Lund and Kennedy 1997, Hopkins et al. 2007)

CRS has autoinflammatory characteristics, although it is not classified as an autoimmune disease (Fokkens et al. 2020). B-cells, plasma and a local production of immunoglobulins have been demonstrated in nasal polyp tissue (Gevaert et al. 2005, Tsybikov et al. 2015, Xiao et al. 2016, Feldman et al. 2017, Lau et al. 2017, Ickrath et al. 2018, Wang et al. 2019). Antibody production is driven in part by elevated levels of the B-cell activating factor (BAFF) of polyp tissue (Kato et al. 2008). BAFF plays a role in B-cell proliferation, isotype class switching to immunoglobulins (Ig) E and IgA and development of autoimmune immunoglobulins (Fokkens et al. 2020). Tan et al. (2017) reported elevated anti-double stranded DNA IgG and IgA autoantibodies in nasal polyp tissue compared to controls, suggesting a role for autoimmunity in the more severely affected CRSwNP (CRS with nasal polyps) patients (Tan et al. 2017). Anti-BP180 (Bullous pemphigoid 180) antibodies have been detected in CRSwNP patients, suggesting autoimmune targeting of the epithelial barrier (Wang et al. 2016b).

2.4 TOBACCO PRODUCTS AND EDUCATION LEVEL

Association between lower education level and use of tobacco products has been studied and the results shows that use of tobacco products is more common among subjects with a lower education level. A 2006 study confirmed higher smoking prevalence among subjects with lower education level (Azevedo e Silva et al. 2009) which was also shown in a later report (Tomioka et al. 2020). Association between lower education level and longer duration of smoking has also been reported (Siahpush et al. 2005). Giskes et al. (2004) showed that Swedish men with lower education level were more likely tobacco smokers compared to men with higher education level (P = .27), which was later also shown for women (P = .05) (Giskes et al. 2005).

In their Swedish population study, Norberg et al. (2011) found that men with lower education level and women with higher education level use snuff. The study comprised over 92 000 subjects, including over 14 000 snuff users and over 10 000 current or previous smokers (Norberg et al. 2011).

3 AIMS AND HYPOTHESES OF THE STUDY

The aim of the current study was to investigate associations of poor periodontal health with autoimmune and autoimmune-related diseases, tobacco products and diagnostic radiologic challenges in it. The principal aim was to determine whether patients with diagnosed autoimmune disease have higher prevalence of periodontitis or poorer oral health status compared with those without autoimmune diagnoses. The second aim was to investigate the association of using tobacco products with oral health, education level and mortality. The third aim focused on reviewing the reliability of PTG, compared to CT, scans in finding alveolar bone changes in radiological signs of periodontitis. In line with this, the ability of observers with different professional backgrounds to detect radiological signs of periodontitis or anatomical sinonasal structures equally was also investigated. Hence, the specific aims of the study were:

1. to investigate if there is an association between poorer periodontal health and autoimmune and autoimmune-related diseases with the hypothesis that this would be the case. (Study I)

2. to study how the use of tobacco products (smoking/ smokeless tobacco) affects periodontal health parameters and does it associate with lower education level and risk of death; the hypothesis was that in this regard the use of tobacco products is more harmful than not using and the habit associates with lower education level and increases mortality. (Study II)

3. to study what is inter-observer agreement in detecting destructions of alveolar bone from CT and PTG scans between four professional observers with different backgrounds and if consultation is desirable before dentoalveolar operations. Also, is it possible to detect signs of alveolar destruction as reliable from PTG scans as from CT scans, with lower radiation load and lower costs in shorter time. We expected good inter-observer agreement and inter-imaging accuracy. (Study III)

4. to study inter-observer agreement in anatomical structures in sinus CT scans from chronic rhinosinusitis patients before surgical operation and whether consultation is indicated. We expected good inter-observer agreement. (Study IV)

4 SUBJECTS AND METHODS

4.1 STUDY COHORT

Studies I and II were conducted at the Department of Dental Medicine, Karolinska Institutet, Stocholm, Sweden. The study cohort included 3 273 subjects, of which 1 676 replied and were examined at baseline in 1985 (Figure 3). In that year, 1 593 333 people lived in the Stockholm area (National Statistics Centre, Örebro, Sweden). Subjects were aged 30–40 years and they were selected randomly from the registry file of the Stockholm region and invited to the study by posted letters. The subjects were born on the 20th of any month from 1945 to 1954, and were inhabitants of the Stockholm region. Of the study subjects, 50 had autoimmune diseases. In Study II, ex-users of tobacco products and patients without tobacco-product anamnesis were excluded (Figure 4). Patient characteristics in Study II are provided in Table 5.

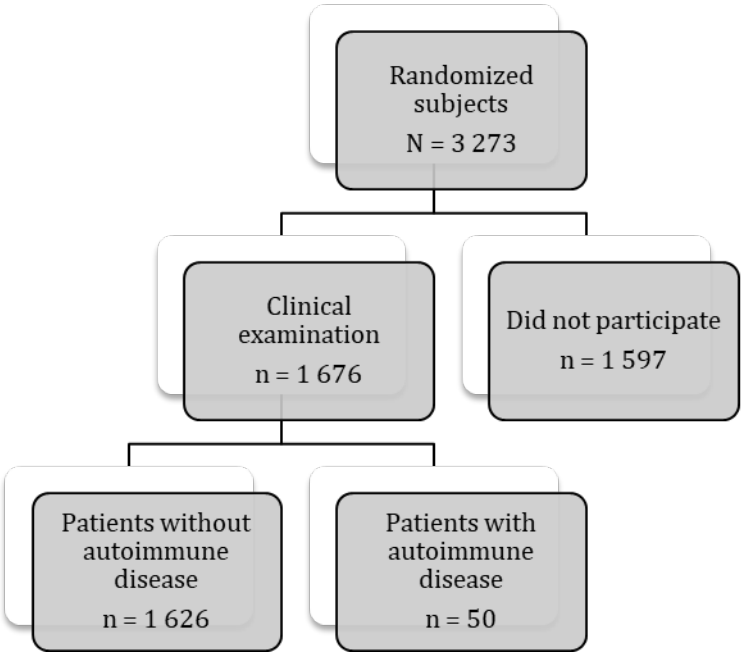

Figure 3. The selection of subjects in Study I.

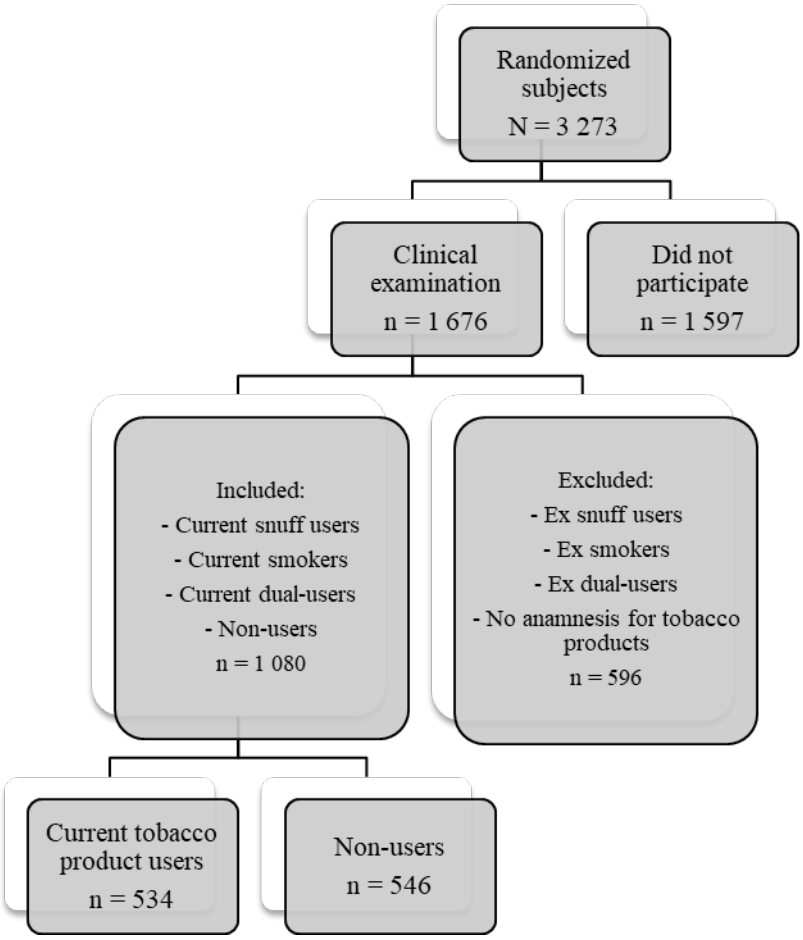

Figure 4. The selection of subjects in Study II.

Study III was conducted at the Departments of Maxillofacial Diseases and Otorhinolaryngology, Helsinki University Hospital (HUH), Helsinki, Finland. The subjects were selected randomly from the HUH database from the timeline of imaging between January 2015 and June 2016. The first 70 patients were selected to the study cohort. Patients with head and neck tumor, acute traumas, edentulous, and age under 17 were excluded. The study cohort included 59 subjects (24 males, 35 females) with a mean age of 35 years (17–75 years). The subjects underwent sinus CT scans and PTG scans within six months due to medical reasons. Reasons for CT imaging were various; 12 were scanned due to sinuses, 24 due to preoperative orthognatic surgery, 2 due to odontogenic reasons, 9 due to any preoperative surgery, 11 due to other reasons, and no reason was evident for 1.

Study IV was carried out in the Department of Otorhinolaryngology, Tampere University Hospital, Finland, from 2006 to 2009. Randomly selected study subjects had been diagnosed for chronic rhinosinusitis and had undergone sinus CT scans in the hospital during 2006–2007.

Table 5. Patient characteristics

	Current tobacco product users N = 534	**Non-users N = 546**	**Total N = 1080**	***P*-value**
Sex n (%)				.503
Male	267 (50.0)	261 (47.8)	528 (48.9)	
Female	267 (50.0)	285 (52.2)	552 (51.1)	
Total	534 (100.0)	546 (100.0)	1080 (100.0)	
Age (Mean, SD)	35.96 (2.83)	35.44 (2.86)	35.70 (2.86)	.004
Working status n (%)				.601
Employed	481 (90.2)	498 (91.2)	979 (90.6)	
Unemployed	52 (9.8)	48 (8.8)	100 (9.4)	
Total	533 (100.0)	546 (100.0)	1079 (99.9)	
Education n (%)				< .001
Compulsory School	128 (24.0)	55 (10.1)	183 (16.9)	
Higher education	406 (76.0)	491 (89.9)	897 (83.1)	
Total	534 (100.0)	546 (100.0)	1080 (100.0)	
Marital status n (%)				< .001
Single	211 (40.7)	174 (32.8)	385 (35.6)	
Married[1]	218 (42.0)	298 (56.1)	516 (47.8)	
Divorced[2]	90 (17.3)	59 (11.1)	149 (13.8)	
Total	519 (100.0)	531 (100.0)	1050 (97.2)	
Income (Mean, SD)	1776.44 (927.10)	1998.32 (1157.62)	1888.65 (1055.38)	< .001
Dental visits once a year n (%)				.008
Yes	156 (29.2)	121 (22.2)	277 (25.6)	
No	378 (70.8)	425 (77.8)	803 (0.74)	
Total	534 (100.0)	546 (100.0)	1080 (100.0)	

[1] include married and common-law married, [2] include divorced and widow.

P-values by Mann Whitney U test (Age, Income) and Fisher's exact test (Sex, Working status, Education, Marital status). *P*-values by Fisher's exact test.

Reference: Julkunen-Iivari, A. et al.; Tobacco Products, Periodontal Health and Education Level: Cohort Study from Sweden. Dent. J. 2020,8,90

4.2 CLINICAL EXAMINATIONS

In studies I and II the subjects were followed-up for 30 years for mortality and their hospital and open healthcare admissions (WHO ICD 7-9-10 codes) were recorded from the Swedish national health registers. The subjects underwent a clinical oral examination by dentist and completed a questionnaire concerning basic characteristics like education level, working and marital status, use of tobacco products, and income.

The oral examination included a calculation of number of teeth and number of missing teeth, measures for gingival index (GI), plaque index (PI), calculus index (CI), and records for periodontal pockets (Greene and Vermillion 1964, Loe 1967). GI was separated into four different scores: 0 = healthy; 1 = mild swelling and redness but not around the tooth, no bleeding on probing (BOP); 2 = swelling and redness around the tooth, BOP; 3 = severe swelling and redness, spontaneous bleeding or suppuration around the tooth (Loe 1967). PI scores were divided into four groups: 0 = absence of microbial plaque, 1 = thin film of microbial plaque along the free gingival margin, 2 = moderate accumulation with plaque in the sulcus, 3 = large amount of plaque in sulcus or pocket along the free gingiva margin (Loe 1967). CI was scored from 0 (no calculus) to 3 (abundant calculus) (Greene and Vermillion 1964). Depths of periodontal pockets were measured from all teeth and from six surfaces with a Hu-Friedy (PCPUNC 15) periodontal probe (Hu-friedy, Chicago, Ill., USA) and periodontal pockets ≥ 5mm were considered deep (Page and Eke 2007). The oral examinations were performed by six periodontists and details of the study were carefully discussed with all clinicians before the examinations.

4.3 METHODS

Studies I and II: Oral examinations were performed in 15 community dental centers in the Stockholm area by six periodontists. From the list of autoimmune diseases published by American Autoimmune Related Diseases Association (AARDA) in May 2016, we used only diseases with published evidence of autoimmunity as a main etiology. The list included over 140 autoimmune and autoimmune-related diseases. The data concerning patients' diagnoses has been collected from the Center of Epidemiology, Swedish National Board of Health and Welfare, Sweden. Diagnoses were classified according to the WHO ICD-7, -9 and -10 codes. Socioeconomic data were collected from the National Statistics Centre, Örebro, Sweden. Socioeconomic data included employed/ unemployed, compulsory school/ higher education and income. Patients completed the questionnaire

that covered smoking and snuff use habits, working status, marital status, and education level at baseline. Subjects were users of the tobacco products if they used tobacco products daily. Education level was divided into two categories; lower education level, which includes compulsory school; and higher education level, which includes all higher educations other than compulsory school.

Study III included four independent observers: a board-certified Maxillofacial radiologist, Head and neck radiologist, Ear-, nose-, throat- and rhino (ENT) practitioner, and a third-year dental student. The focus was to evaluate radiological signs of periodontitis form dental alveolar bone and perapical lesions. All four observers had the same environmental conditions while evaluating the scans and completing the evaluation forms, which were designed for the present study. Each observer had at least seven days of time interval between observing CT scans and PTG scans. Observers made a pilot study to make sure that all observers understood how to complete the form. Inter-imaging accuracy between CT and PTG were detected by the oral radiologist, where CT was a gold standard.

The form included four different evaluable signs for periodontitis in PTG scans (vertical bone loss, horizontal bone loss > 3mm, diffuse bone margin and periapical bone loss) and three evaluable signs for periodontitis in CT scans (vertical bone loss, horizontal bone loss > 3mm, periapical bone loss) from both sides (Table 6). Response options were “yes/ no/ not detectable”. The ENT practitioner also evaluated LM scores from CT scans.

Table 6. Evaluation form for inter-observer agreement and inter-imaging accuracy (Study III).

	Right side			**Left side**		
A. Lund-Mackay						
Sinus Frontalis	0	1	2	0	1	2
Sinus Ethmoid, anterior	0	1	2	0	1	2
Osteomeatal complex (OMC)	0		2	0		2
Sinus Ethmoid, posterior	0	1	2	0	1	2
Sinus Sphenoidlis	0	1	2	0	1	2
Sinus Maxillaris	0	1	2	0	1	2
Lund-Mackay scores (0-12)						
B. Periodontal findings in upper jaw: molar and premolar area	No	Yes	C	No	Yes	C
Vertical bone loss	0	1	2	0	1	2
Horizontal bone loss >3mm	0	1	2	0	1	2
Diffuse bone margin	0	1	2	0	1	2
Periapical lesion	0	1	2	0	1	2

A. Lund-Mackay: 0 = No shading/ OMC is not blocked, 1 = Partly shaded, 2 = Fully shaded

B. Periodontal findings: 0 = No signs of, 1 = Yes, 2 = Can not say reliably

Study IV included three independent observers: a fifth year ENT resident, an experienced ENT- and rhinosurgeon, and Head and neck radiologist. Observers were blinded to each other and to patient history data, and completed a 49-item form. They observed radiological anatomical sinonasal structures and CRS-related changes from both sides from sinus CT scans. All asked structures had two to five different answering choices and all choices were carefully discussed by all observers before starting evaluation. Only the ENT resident and ENT- and rhinosurgeon responded to questions "Need for septoplasty" and "Grade of surgeon's confidence based on images".

4.4 DATA ANALYZES

Statistical analysis was performed by the SPSS Base 15.0-24 Statistical Software Package (SPSS, Chicago, IL, USA). Degree of inter-observer agreement of CT scans were compared by Cohen's kappa. Kappa-value is classified into six subgroups: Poor < 0.2, Fair 0.21–0.4, Moderate 0.41–0.6, Good 0.61–0.8, and Very Good 0.81–1.0 (Viera AJ and Garrett JM 2005). Associations were assessed by the Fisher's exact test. Two-tailed *P*-values of < .050 were considered significant. Comparisons were performed by Cross-tabulation, chi-square test and binary logistic regression. Median value of PI, GI and CI were calculated.

4.5 ETHICAL ASPECTS

The present study is a human observational study and investigators have conformed to the CONSORT guidelines. No important harm or unintended effects in any group were made. Studies I and II were approved by the Ethics Committee of the Karolinska Institutet and Huddinge University Hospital in Sweden (Dnr 101/85 and revised in 2012/590-32). All study subjects provided an ethics form of consent in writing to use their data for analysis. Study III has ethics-committee approval from the Helsinki and Uusimaa Hospital Districts 31/13/03/00/15 Rhinosinusitis risk prediction (RhinoRisk). The study has also been approved by the Hospital District of Helsinki and Uusimaa (HUH research permit). Study IV was approved by the ethics committee of the Pirkanmaa Hospital District (no 96032). All studies are in accordance with the Declaration of Helsinki.

5 RESULTS

The detailed results from this series of studies (Studies I–IV) are given in the original publications. The main results are briefly summarized here.

5.1 PERIODONTAL HEALTH AND AUTOIMMUNE DISEASES (STUDY I)

Patients with autoimmune disease (n = 50) and patients without autoimmune disease (n = 1626) were compared to each other. Diagnoses for autoimmune diseases are provided in Table 7 and for periodontal findings in Table 8. The main finding was that those with diagnosed autoimmune disease had higher plaque index (PI) scores (P = .030) while calculus index (CI) and gingival index (GI) did not differ between the autoimmune and non-autoimmune groups. The presence of autoimmune disease associated with higher PI (crude OR = 2.00, 95% CI = 1.09-3.70, P = .016). When adjusted by snuff use and gender the result remained the same (adjusted OR = 2.30, 95% CI = 1.17–4.56, P = .016). Patients with autoimmune disease were more seldom in working life than subjects without autoimmune disease (P = .073). Smoking, snuff use, deepened periodontal pockets or missing teeth did not differ between the groups.

Table 7. Autoimmune diseases in the data

Autoimmune disease	ICD-10	Number of patients
Ankylosing spondylitis[1]	M45	1
Crohn's disease[2]	K50	6
Colitis ulcerosa[3]	K51	5
Diabetes mellitus Type-1[4]	E10	14
Graves´ disease[5]	E05.0	1
Guillain-Barré syndrome[6]	G61.0	2
Henoch-Schönlein purpura[7]	D69.0	1
Lichen planus[8]	L43	1
Psoriasis[9]	L40	5
Rheumatic disease[10]	M05	15
Sicca syndrome (e.g. Sjögren) [11]	M35.0	1
Systemic lupus erythematosus[12]	M32	1
Wegener's granulomatosis[13]	M31.3	1

[1] Includes: Ankylosing spondylitis (ICD-9 720),
[2] Includes: Crohn's disease of large intestine without complications (K50.1), Crohn's disease, unspecified, without complications (K50.9),
[3] Includes: Ulcerative colitis, unspecified (K51.9), Ulcerative (chronic) rectosigmoiditis (K51.3),
[4] Includes: Type 1 diabetes mellitus (E10.0), Type 1 diabetes mellitus without complications (E10.9),
[6] Includes: Guillain-Barre syndrome (G61.0),
[7] Includes: Henoch-Schönlein purpura (ICD9 287),
[8] Includes: Other Lichen planus (L43.8),
[9] Includes: Psoriasis (L40.0), Psoriasis, unspecified (L40.9),
[10] Includes: Crystal arthropathy (M11.9), Lethal midline granuloma (ICD9 446.3), Myalgia (M79.1), Other rheumatoid arthritis with rheumatoid factor of multiple site (M05.8), Other seropositive rheumatoid arthritis (M05.8), Primary osteoarthritis of other joints (M19.0), Rheumatic fever without mention of heart involvement (I00.9), Seropositive rheumatoid arthritis, unspecified (M05.9), Unilateral primary osteoarthritis of hip (M16.1), Unilateral primary osteoarthritis of knee (M17.1),
[11] Sicca Syndrome (M35.0),
[12] Includes: Systemic lupus erythematosus, unspecified (M32.9),
[13] Includes: Wegener's granulomatosis (M31.3).

Reference: Julkunen A. et al.; Autoimmune Diseases and Oral Health: 30-Year Follow-Up of a Swedish Cohort. Dent J (Basel). 2017;6(1):1. doi:10.3390/dj6010001

Table 8. Periodontal findings from the subjects of Study I.

	Patients without autoimmune disease n = 1626 (%)	**Patients with autoimmune disease** n = 50 (%)	***P*-value[a]**
Periodontal pockets ≥5mm			.849
Yes	277 (17)	9 (18)	
No	1349 (83)	41 (82)	
Missing teeth			.885
Yes	720 (44)	23 (46)	
No	906 (56)	27 (54)	
Plaque index (median 0.67)	[b]		.030
0.00–0.66	749 (46)	15 (30)	
0.67–3.00	872 (54)	35 (70)	
Gingival index (median 1.19)			.668
0.00–1.18	804 (49)	23 (46)	
1.19–3.00	822 (51)	27 (54)	
Calculus index (median 0.17)	[e]		.065
0–0.16	538 (33)	10 (20)	
0.17–3.00	1083 (67)	40 (80)	

[a] *P*-value by Fisher's exact test; [b] No data of 5 patients

Reference: Julkunen A. et al.; Autoimmune Diseases and Oral Health: 30-Year Follow-Up of a Swedish Cohort. Dent J (Basel). 2017;6(1):1. doi:10.3390/dj6010001

5.2 USE OF TOBACCO PRODUCTS AND PERIODONTAL HEALTH, EDUCATION LEVEL AND MORTALITY (STUDY II)

The results of periodontal findings are shown in Table 9. The median scores of PI, CI and GI for tobacco users were significantly higher when compared with the median of non-users (*P*-value for all < .001). Tobacco users had greater prevalence for deep periodontal pockets (5mm) (15.7%) than non-users (6.8%) (*P*< .001). Respective significant differences in the numbers of missing teeth between the groups were also observed (45.0% vs 41.2%) (*P* = .010). Non-users were more highly educated (89.9%) compared with tobacco users (76.0%) (*P*< .001). However, tobacco product users did not die earlier than non-users.

Table 9. Periodontal findings in Study II.

	Current tobacco product users n = 534	**Non-users n = 546**	***P*-value**
Plaque index Median (IQR)	 0.67 (0.67)*	 0.50 (0.50)+	< .001
Calculus index Median (IQR)	 0.33 (0.83)*	 0.17 (0.42)+	< .001
Gingival index Median (IQR)	 1.29 (0.79)*	 1.07 (0.57)+	< .001
Periodontal pockets (≥5 mm) N (%) Yes No	 84 (15.7) 450 (84.3)	 37 (6.8) 509 (93.2)	< .001
Missing teeth N (%)° Yes No	 262 (45.0) 272 (55.0)	 225 (41.2) 321 (58.8)	.010

P-values by Mann-Whitney U test (plaque index, calculus index, gingival index) and Fisher's exact test (periodontal pockets, missing teeth)

* No data from 2 patients

+ No data from 1 patients

° Reason for tooth loss is unknown

Reference: Julkunen-Iivari, A. et al.; Tobacco Products, Periodontal Health and Education Level: Cohort Study from Sweden. Dent. J. 2020,8,90

5.3 INTER-OBSERVER AGREEMENT IN RADIOLOGICAL SIGNS OF PERIODONTITIS (STUDY III)

The inter-observer agreement was mostly moderate between the oral radiologist and the head and neck radiologist in PTG scans. Agreement in the CT scans was mostly fair. The greatest disagreements were in recording the vertical bone loss in PTG (kappa 0.163) and CT scans (kappa 0.158).

The inter-observer agreement was mostly poor or fair between the oral radiologist and the dental student in PTG scans. Agreement in the CT scans was mostly fair. The highest disagreement in PTG scans was in recording the periapical lesions (kappa 0.017) and in CT scans vertical bone loss (kappa 0.126), yet these were not statistically significant.

The inter-observer agreement was mostly poor between the oral radiologist and the ear-, nose-, throat- and rhino specialist in PTG and CT scans. The smallest kappa values (reflecting greatest disagreement), were on recording vertical bone loss in both scans (in PTG [kappa 0.039] and CT [kappa -0.054] scans), yet these were not statistically significant. The results are given in Table 10.

Table 10. Inter-observer agreement. The oral radiologist compared with the three other observers (Study III)

	1. Kappa	1. *P*-value	2. Kappa	2. *P*-value	3. Kappa	3. *P*-value
PTG Vertical	0.163	<.001	0.095	.020	0.039	1.000
PTG Horizontal	0.416	<.001	0.377	<.001	0.455	.001
PTG Diffuse	0.406	<.001	0.324	.018	0.205	.023
PTG Periapical	0.431	<.001	0.017	.706	0.115	.064
CT Vertical	0.158	.010	0.126	.042	-0.054	1.000
CT Horizontal	0.246	<.001	0.269	.001	0.132	.011
CT Periapical	0.209	.003	0.271	.072	0.112	.175

1. The oral radiologist vs the head and neck radiologist
2. The oral radiologist vs the dental student
3. The oral radiologist vs the ear-, nose-, throat- and rhino specialist

PTG = panoramic radiography, CT = computed tomography, Vertical = vertical bone loss, Horizontal = horizontal bone loss > 3mm, Diffuse = diffuse bone margin, Periapical = periapical radiolucency, *P*-values by Fisher's exact test.

Agreement	kappa
poor	< 0.2
fair	0.21–0.4
moderate	0.41–0.6
good	0.61–0.8
very good	0.81–1.0

5.4 INTER-IMAGING ACCURACY BETWEEN PANORAMIC RADIOGRAPHIC AND COMPUTED TOMOGRAPHY SCANS (STUDY III)

When evaluating inter-imaging accuracy between sinus CT and PTG scans, based on the records by the oral radiologist, correlation in vertical bone loss was good (kappa 0.603), for horizontal bone loss (> 3mm) very good (kappa 0.908) and for periapical radiolucency moderate (kappa 0.565).

5.5 INTER-OBSERVER AGREEMENT IN COMPUTED TOMOGRAPHY SCANS OF CHRONIC RHINOSINUSITIS PATIENTS (STUDY IV)

In general, inter-observer agreement of the structures was moderate-to-good between the three observers by Cohen's kappa coefficient (Table 11). When evaluating the agreement between the head and neck radiologist and the ENT

resident, in the majority of structures the inter-observer agreement was moderate (kappa 0.4–0.6). In assessing the size of anterior and posterior ethmoid sinus and frontal recess showed best agreement. Detecting the anterior ethmoidal artery and assessing the quality of nasal mucosa showed the biggest disagreements.

Inter-observer agreement between the head and neck radiologist, the ENT specialist, and the rhinosurgeon was fair for the majority of structures (kappa 0.2–0.4). Signs of previous sinus surgery and LM score of the ostiomeatal unit showed the greatest agreement. Septum turbinate and orbital lamina of ethmoidal bone showed the greatest disagreements.

Inter-observer agreement between the ENT specialist, the rhinosurgeon and the ENT resident was overall fair (kappa 0.2–0.4). The greatest agreements were at detecting previous sinus surgery performed and in assessing the LM sinus score of the frontal sinus. The greatest disagreements were in septum turbinate and location of the anterior ethmoidal.

Table 11. The structures and the level of inter-observer agreement in the alphabetical order

Good* **0.61–0.8**	Frontal Recess, Lund-Mackay: Frontal sinus, Sphenoid sinus. Previous sinus surgery performed
Moderate 0.41–0.6	Lund-Mackay: Anterior ethmoid sinus, Maxillary sinus, Ostiomeatal unit, Posterior ethmoid sinus. OMC region, Pneumatized superior attachment of uncinate process, Sinus mucosal abnormalities: of Anterior ethmoid sinus, of Frontal sinus, of Maxillary sinus, of Posterior ethmoid sinus, of Shenoid sinus. Sphenoethmoidal recess.
Fair 0.21–0.4	Atrophy-normal-hypertrophy of Inferior turbinate, Concha bullosa media, Grade of surgeon´s confidence based on images, Infraorbital cell, Hypoplasia/ normal/ hyperplasia of Anterior ethmoid sinus, Hypoplasia/ normal/ hyperplasia of Posterior ethmoida sinus, Mucosa of pneumatized Middle turbinate, Ostiomeatal complex (OMC) region: Acessory maxillary Sinus ostium, Hiatus, Infundibulum, Maxillary antrum, Superior attachment of uncinate precess, Prominent ethmoid bulla. Pneumatized Superior turbinate, Septum deviation.
Poor <0.2	Anterior ethmoidal artery, Atrophy-normal-hypertrophy of Middle turbinate, Concha bullosa superior, Contact to middle turbinate of orbital lamina ethmoidal bone, Hypoplasia/ normal/ hyperplasia of Frontal sinus, Hypoplasia/ normal/ hyperplasia of Maxillary sinus, Hypoplasia/ normal/ hyperplasia of Sphemoidal sinus, Keros classification, Mucosa of nasal cavity (extent of edema), Mucosa of nasal cavity (normal-polypous), Optic nerve, Paradoxical Middle turbinate, Paradoxical Superior turbinate, Septal deviation obstructing middle meatus, Septum Crest, Septum Spur.

The level of agreement is determined by the lowest kappa values detected in the inter-observer comparisons of the structure per each side.

*No “very good” agreements were detected.

6 DISCUSSION

The purpose of this thesis investigation was to examine periodontitis and some of its systemic, like autoimmune diseases and chronic rhinosinusitis, and local associations, like horizontal and vertical bone loss and periapical radiolucency with CT and PTG scans and its diagnostic radiologic challenges, and whether the use of tobacco products is associated with mortality.

The main findings from this series of studies are that subjects with autoimmune and autoimmune-related disease had higher PI compared to non-autoimmune subjects. Subjects who used tobacco products had poorer oral health and lower education level compared to non-users, although tobacco-products did not associate with mortality. Inter-observer agreement has variation when observing radiological signs of periodontitis and periapical lucency from sinus CT and PTG scans. PTG was as reliable an imaging method as CT to diagnose horizontal bone loss but not vertical bone loss or periapical radiolucency. There was variation in inter-observer agreement in sinus CT scans when observing surgically important sinonasal structures.

6.1 LESSONS LEARNED FROM CO-MORBIDITY

The aim of this work was to investigate the association between periodontal health and autoimmune and autoimmune-related diseases with the hypothesis that there is an association between these conditions. Our hypothesis was partly confirmed by the result showing that PI, a marker for poor oral health, was significantly higher among the patients with autoimmune diseases compared to healthy individuals. Unexpectedly, however, CI, GI, number of missing teeth, deepened periodontal pocket, smoking or snuff use was not higher among autoimmune patients.

Most of the autoimmune diseases recorded in the study cohort were rheumatic diseases or type I diabetes. It is well know that these diseases associate with periodontal diseases, so this finding was not new (Genco et al. 2005, Berthelot and Le Goff 2010). Patients with rheumatic diseases may have problems with manual dexterity and this might be one factor explaining why the patients with autoimmune diseases as a group had higher PI scores compared with healthy ones. Association between plaque, as an inducer of inflammation, and autoimmune diseases is probably a two-direction path.

6.2 LESSONS LEARNED FROM RISK FACTORS

The purpose was to investigate how the use of different tobacco products (current smoking/ smokeless tobacco and dual-using) affects periodontal health parameters with the hypothesis that use of tobacco products is more harmful than not using them. Our results showed that the current use of tobacco products does associate with poorer periodontal health, which is in line with previous studies (Heikkinen et al. 2008, Genco and Borgnakke 2013, Boulaamaim et al. 2020). Previous studies have shown that smoking tobacco has undisputed impact on periodontal health by lowering the status, unlike use of snuff has controversial results (Bergstrom 2004, Bergstrom et al. 2006, Heikkinen et al. 2008, Hugoson and Rolandsson 2011, Genco and Borgnakke 2013, Katuri et al. 2016, Boulaamaim et al. 2020). Upregulation of pro-inflammatory cytokines and inflammatory mediators may be caused by nicotine and other compounds from snuff and cigarette affecting the tooth supporting tissues thus leading to periodontal disease (Martinez-Canut et al. 1995, An et al. 2014).

The aim was also to see if using tobacco products associates with lower education level and our investigations showed that they do associate. Again, association between smoking tobacco and lower education level has been undisputed, while association with snuff use and education level has been unclear (Giskes et al. 2005, Azevedo e Silva et al. 2009, Norberg et al. 2011, Tomioka et al. 2020). Using snuff might be trendier than smoking tobacco, which is why it may be a more popular way to use nicotine among educated people. Lower educated people may not have the knowledge of side effects of smoking as well as highly educated people. Highly educated people may also want to take better care of their health compared to people with lower education level.

Another focus of this investigation was whether tobacco products associated with mortality. This time the hypothesis was refuted, due to the results showing that tobacco-product users did not seem to die earlier than non-users. From previous studies, tobacco products are known risk factors for mortality, which is contrary to the findings. Timberlake et al. (2017) showed that current use of snuff increases the risk for mortality of coronary heart disease, whilst Inoue-Choi et al. (2019) reported that daily use of tobacco products is a risk factor for mortality.

Study subjects were aged 30–40 years at baseline and after 30 years follow-up they were only 60–70 years old. This might be the reason why no association was found between smoking and mortality in this study. In their 50-year follow-up study, Doll et al. (2004) observed that 1900–1930 born men, who smoked cigarettes continuously, died on average about 10 years younger than lifelong non-smokers. Cessation of smoking at age 60, 50, 40, or 30 increased, respectively, approximately 3, 6, 9, or 10 years expectation of life (Doll et al. 2004).

6.3 LESSONS LEARNED FROM RADIOLOGICAL DIAGNOSTICS

The aim of the study was to investigate inter-observer agreement in recording signs of alveolar bone loss and periapical radiolucency in CT and PTG scans and if consultation is desirable before dental operations. We expected good inter-observer agreement, thus our hypothesis was refuted. The study demonstrated significant variance in the evaluation of radiological periodontal and periapical findings between the observers, which is in line with previous studies (Tewary et al. 2011, Shahzad et al. 2018). The explanation for the results of our study may be that only oral radiologists and dental students are trained to observe radiological signs of pathology of dentoaleolar structures. Oral radiologists are the most experienced in this field.

Inter-observer agreement was also investigated in relation to anatomical structures in sinus CT scans from chronic rhinosinusitis patients before surgical procedure. Good inter-observer agreement was expected. However, here the hypothesis was mostly refuted. The study showed large variation in the evaluation of sinus CT scans between the three observers. Generally, the observers had good agreement for structures like "Previous sinus surgery performed", "Frontal recesses" and "Lund-Mackay score of posterior ethmoid sinus". In contrast, there were numerous structures where there were fair to poor inter-observer agreement. An especially alarming finding was that a few operatively critical structures had poor inter-observer reproducibility, like "Location of anterior ethmoidal artery", "Optic nerve", "Insertion on the uncinated process" and "Keros class". While performing advanced surgery of the sinonasal track, these vital structures and their contact and location compared to the operation areas need to be clear. (Stammberger 1986, Zinreich et al. 1987)

In comparison to the present findings, corresponding results on the variability of inter-observer agreement from other anatomic sites than investigated here need to be discussed. In the study by Cheung et al. (2019), variability was found in inter-observer agreement in pelvic x-ray scans. Two reviewers, both experienced physicians in the emergency department, classified the pelvic radiographs using the Young-Burgess classification system. Three evaluable points were analyzed using Cohen's kappa statistics: (1) mechanism of injury, (2) stable versus unstable pelvic fracture, and (3) complete Young-Burgess classifications. Inter-observer agreement regarding assessing the mechanism of injury was good (kappa 0.72), in the stable vs unstable pelvic fracture the agreement was moderate (kappa 0.6) and in the complete Young-Burgess classification the agreement was also moderate (kappa 0.55). Inter-method agreement in x-ray diagnoses vs those of the CT scans were moderate regarding the mechanism of injury (kappa 0.42),

also moderate regarding the stable vs unstable state (kappa 0.59) while it was fair regarding the Young-Burgess classification (kappa 0.38) (Cheung et al.).

Our aim was also to find whether it is possible to detect periodontal findings with lower radiation load and lower costs in shorter time. We expected good inter-imaging accuracy between CT and PTG scans. Our hypothesis was only partly confirmed by the results. The results showed that in diagnosing local horizontal alveolar bone loss PTG is as reliable as CT, but not in diagnosing vertical bone loss or periapical radiolucency. Previous studies show almost unanimously that three-dimensional imaging is more accurante than two-dimensional and leads to clearer treatment plan (Walter et al. 2009, Ruetters et al. 2020).

To sum up, the studies showed that diagnosing from radiographic images is highly subjective. This is problematic in the view of making the right diagnosis and treatment plan. Consultation is thus highly recommended, especially before surgical operations where life-threatening anatomical structures, like arteries, can be harmed. A proper treatment plan, which every patient should have, affects general health and quality of life, and can be even lifesaving. This is why we should pay attention to inter-observer agreements, but especially disagreements.

6.4 STRENGTHS OF THE STUDIES

In studies I and II: To the best of our knowledge this study was the first investigation to evaluate periodontal-health parameters and all recorded autoimmune diseases in the same study population. Another strength of the study is that periodontal pocket depths were measured from all teeth and from six surfaces, not only from index teeth. Further strength was the long follow-up time of 30 years with corresponding nationwide death records and registers data that included information of the diseases of the deceased subjects had had.

In studies III and IV: To the best of our knowledge this study was the first to evaluate inter-observer agreement and inter-imaging accuracy from sinus CT and PTG scans. One strength of the studies is that instead of two observers, there were three and four different viewers with different expertise and experience. Images were evaluated under the same conditions in Study III; lightning and screen were the same kind in two radiologic departments in HUH.

6.5 LIMITATIONS OF THE STUDIES

A limitation of studies I and II was the lack of data on alcohol consumption, tooth brushing habits, or the amount of tobacco products used. In the year 1985, when the cohort investigation was started, it was thought inappropriate to ask

questions about use of alcohol in Sweden. Also, the number of subjects with autoimmune disease was small. We did not use socioeconomic status in study I, only if a subject was currently working or not, which is also a limitation. Use of tobacco products was asked from subjects in writing, not analyzed from breathing air or blood, which is a limitation. We did not adjust tobacco products with gender, which is a limitation too.

Studies III and IV were limited due to a lack of information from clinical periodontal examination or patient's symptoms. In Study III, 24 of the patients were scanned for ortognatic surgical planning and most of them were young and healthy, which is why periodontal findings were low among these patients. In Study III, only molars and premolars from the upper jaw were included to the study instead of all teeth, which is also a limitation.

7 CONCLUSIONS

1. Patients with diagnosed autoimmune disease may have a higher amount of dental plaque, a marker for poor periodontal health, compared with patients without autoimmune disease. Patients with autoimmune disease may not have higher prevalence of periodontitis than non-autoimmune patients.

2. Patients, who are users of tobacco products (snuff or/ and smoking tobacco), may have a higher prevalence for deep periodontal pockets and missing teeth, and higher PI, CI and GI, markers for poor periodontal health, compared with non-users. Use of tobacco products seems to also associate with lower education level. Use on tobacco products may not associate with risk of death.

3. While evaluating radiological signs of the alveolar bone loss and periapical radiolucency, inter-observer agreements may have variations when recording the findings in sinus CT scans and PTG scans. Therefore consultation may be indicated before dentoalveolar treatment plan.

4. PTG may be as reliable an imaging modality as CT for diagnosing horizontal bone loss, but not for diagnosing vertical bone loss or periapical radiolucency.

5. There may be significant inter-observer disagreement between professional observers in surgically important structures. Therefore consultation may be indicated when evaluating sinus CT scans before surgical operation of CRS patients.

8 PRACTICAL IMPLICATION

Patients with diagnosed autoimmune disease should receive careful dental health education and help with ergonomics of dental cleaning due to potential rising risk for higher plaque index. Healthcare professionals should more often advise and motivate patients to stop using tobacco products according the clinical guideline (5As) (Martinez et al. 2017). If a patient uses tobacco products, clinicians should give more attention to that patient's periodontal health by inspecting and treating so periodontal inflammation will not progress into chronic periodontitis. Since the study shows that patients with lower education level are suffering from poorer periodontal health, health education from dental professionals as well as other healthcare professionals is highly important.

If a patient has already been examined in sinus CT scan there may not be relevance to take a PTG scan as well if the origin of the infection is in the upper jaw. Radiologist consultation may be recommended by a clinical dentist if radiological signs of dental or alveolar pathology is unclear or before treatment plan. Clinicians may have multi-professional meetings and consultations before surgical operation of a CRS patient to be sure if important structures like nerves or arteries are in the operation area. Clinicians should not assume that every professional observer agrees on anatomical or radiological signs of pathological structures in radiographic scans.

9 RECOMMENDATION FOR FUTURE STUDIES

More studies on periodontal health and chronic systemic diseases, including the autoimmune diseases investigated, are needed. We need more evidence if periodontitis, as chronic inflammatory disease, can induce autoimmune diseases. A large population study with long follow-up time is needed to answer these questions.

Longitudinal studies are needed to clarify the association between periodontal disease and the use of different tobacco products. These should include standardized measurements of periodontal disease, a long enough follow-up time, and a proper adjustment of known confounders, like use of alcohol and oral health habits.

Although these longitudinal studies are needed, research design is hard in these kinds of studies. For example it is hard to commit study subjects to the study for a long period of time.

More studies are also called for on the inter-observer agreement in different oral radiographs and sinus CT scans and how the observers' opinions affect treatment plans. Nonetheless, we might have artificial intelligence and high technology to diagnose all radiographic scans in the future. Finally, whether it would be possible to detect periodontal findings with lower radiation load and with lower costs in a shorter time also calls for further investigation.

ACKNOWLEDGEMENTS

This study was conducted at Helsinki University Hospital, at Department of Oral and Maxillofacial Diseases and Transplantation laboratory, Haartman Institute, University of Helsinki, and at Tampere University Hospital. I thank Dean Risto Renkonen for providing the facilities at my disposal. The contributions of many people have made this doctoral thesis possible.

The study was supported by Karolinska Institutet and by grants from University of Helsinki, Väinö and Laina Kivi foundation, Ida Montin foundation, The Finnish ORL-HNS Foundation, Dentists of the Helsinki Region Association, Instrumentarium Foundation, Tampere Tuberculosis Foundation, The Finnish Dental Society Apollonia, Finnish Female Dentist Association, Otto A. Malmi fund, Päivikki and Sakari Sohlberg's Foundation and Minerva Foundation Selma and Maja-Lisa Selander's fund for research in odontology.

I am deeply grateful to Professor Jukka Meurman, my supervisor, for generous support and guidance in field of science. It has been an honor to me to belong in your research group and spend nice time in the lab, research group dinners and international congresses. You have been there for me all the time. Thank you for inspirational spirit and encouragement.

My other supervisor, Docent Sanna Toppila-Salmi deserves great praise for supporting and guiding me in life and science. Your eagerness in science and work has been highly inspirational and with the energy that you have given me, I kept working through this project. Thank you for your trust in me. We have enjoyed research group meetings and just two of us talking about life.

My other supervisor, Anna Maria (Mari) Heikkinen, who has been warm, motherly supportive and strict at the same time deserves also many thanks from me. Thank you for believing in me. Your enthusiasm for science and work has guided me through this process and you are an inspiration to me. We have spent so many wonderful times together and you have always been my support in life and science.

To all my supervisors, thank you for pushing me and also supporting me thru hard times. It's been a great honor for me to have you as my supervisors and I can not imagine better ones.

Professors Birgitta and Per-Östen Söder. This thesis respects the memory of Professor Per-Östen, one of the kindest men I have ever met. Thank you Birgitta for your welcoming support and guidance. Thank you for having me in your beautiful home in Stockholm and in your fabulous summerhouse in Malviken.

It has been an honor for me to work with you and use your invaluable datasets for my studies.

Professor Sisko Huumonen and Docent Merja Laine, the official reviewers of this thesis, are gratefully acknowledged for valuable comments and criticism of the manuscript.

Professor Timo Sorsa and Docent Maija Hytönen, the thesis follow-up group, thank you for your interest in my work and your support.

Thank you to all my co-authors for your valuable input; Emma Terna, Jura Numminen, Antti Markkola, Prasun Dastidar, Matti Karjalainen, Heini Huhtala, Markus Rautiainen, Satu Apajalahti, Riste Saat, Ismo T. Räisänen and Hellevi Ruokonen. Figure 2 illustration by Petteri Vilkki.

To my parents and siblings; thank you for all love, support and wisdom you have given me. To my friends, co-workers and other PhD students; thank you for your encouragement and peer support.

Finally I owe my deepest gratitude to my family, Timo and Pihla, for your endless love and support. Thank you for giving me the time and space to concentrate on my thesis, but, most importantly, you have given me the counterbalance to work and science. You are the love and joy of my life.

22.11.2020 Tampere

REFERENCES

Abbott, P. V. 2004. Classification, diagnosis and clinical manifestations of apical periodontitis. Endodontic Topics 8: 36-54.

Aichelmann-Reidy, M. E., Wrigley, D. L. & Gunsolley, J. C. 2010. HIV infection and bone loss due to periodontal disease. Journal of periodontology 81: 877-884.

Airila-Mansson, S., Soder, B. & Klinge, B. 2005. Bone height changes in individuals with periodontal disease: a 17-year prospective longitudinal study. Journal of clinical periodontology 32: 822-827.

Al Kasab, S., Nakagawa, D., Zanaty, M., Bathla, G., Policeni, B., Soni, N., Allan, L., Hudson, J., Limaye, K., Ortega-Gutierrez, S., Samaniego, E. A. & Hasan, D. 2019. In vitro accuracy and inter-observer reliability of CT angiography in detecting intracranial aneurysm enlargement. Journal of Neurointerventional Surgery 11: 1015-1018.

Almerich-Silla, J. M., Alminana-Pastor, P. J., Boronat-Catala, M., Bellot-Arcis, C. & Montiel-Company, J. M. 2017. Socioeconomic factors and severity of periodontal disease in adults (35-44 years). A cross sectional study. Journal of clinical and experimental dentistry 9: e988-e994.

Amer Diabet Assoc 2010. Diagnosis and Classification of Diabetes Mellitus. Diabetes care 33: S62-S69.

An, N., Andrukhov, O., Tang, Y., Falkensammer, F., Bantleon, H., Ouyang, X. & Rausch-Fan, X. 2014. Effect of Nicotine and Porphyromonas gingivalis Lipopolysaccharide on Endothelial Cells In Vitro. Plos One 9: e96942.

Araujo, R. d. O., Villoria, G. E. M., Luiz, R. R., Esteves, J. C., Thome Leao, A. T. & Feres-Filho, E. J. Association between periodontitis and Alzheimer's disease and its impact on the self-perceived oral health status: a case-control study. Clinical oral investigations .

Arcavi, L. & Benowitz, N. 2004. Cigarette smoking and infection. Archives of Internal Medicine 164: 2206-2216.

Armitage, G. C. 1999. Development of a classification system for periodontal diseases and conditions. Annals of periodontology 4: 1-6.

Armitage, G. 2004. The complete periodontal examination. Periodontology 2000 34: 22-33.

Arnson, Y., Shoenfeld, Y. & Amital, H. 2010. Effects of tobacco smoke on immunity, inflammation and autoimmunity. Journal of Autoimmunity 34: J258-J265.

Assiri, H., Dawasaz, A. A., Alahmari, A. & Asiri, Z. 2020. Cone beam computed tomography (CBCT) in periodontal diseases: a Systematic review based on the efficacy model. Bmc Oral Health 20: 191.

Axelsson, P., Nystrom, B. & Lindhe, J. 2004. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults - Results after 30 years of maintenance. Journal of clinical periodontology 31: 749-757.

Azevedo e Silva, G., Valente, J. G., de Almeida, L. M., de Moura, E. C. & Malta, D. C. 2009. Tobacco smoking and level of education in Brazil, 2006. Revista de saude publica 43: 48-56.

Barbour, S., Nakashima, K., Zhang, J., Tangada, S., Hahn, C., Schenkein, H. & Tew, J. 1997. Tobacco and smoking: Environmental factors that modify the host response (immune system) and have an impact on periodontal health. Critical Reviews in Oral Biology & Medicine 8: 437-460.

Barr, C., Lopez, M. & Ruadobles, A. 1992. Periodontal Changes by Hiv Serostatus in a Cohort of Homosexual and Bisexual Men. Journal of clinical periodontology 19: 794-801.

Baum, A., Garofalo, J. & Yali, A. 1999. Socioeconomic status and chronic stress - Does stress account for SES effects on health? Socioeconomic Status and Health in Industrial Nations: Social, Psychological, and Biological Pathways 896: 131-144.

Benninger, M. 2003. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngology-Head and Neck Surgery 129: S1-S32.

Bergstrom, J. 2004. Influence of tobacco smoking on periodontal bone height. Long-term observations and a hypothesis. Journal of clinical periodontology 31: 260-266.

Bergstrom, J., Keilani, H., Lundholm, C. & Radestad, U. 2006. Smokeless tobacco (snuff) use and periodontal bone loss. Journal of clinical periodontology 33: 549-554.

Berthelot, J. & Le Goff, B. 2010. Rheumatoid arthritis and periodontal disease. Joint Bone Spine 77: 537-541.

Borrell, L. N. & Crawford, N. D. 2012. Socioeconomic position indicators and periodontitis: examining the evidence. Periodontology 2000 58: 69-83.

Boulaamaim, T., Tenenbaum, H., Davideau, J. & Huck, O. 2020. Selective Influence of Smoking on Periodontal Treatment Outcomes after 3 Years of Follow-up. Oral Health & Preventive Dentistry 18: 823-831.

Bulla, S., Blanke, P., Hassepass, F., Krauss, T., Winterer, J. T., Breunig, C., Langer, M. & Pache, G. 2012. Reducing the radiation dose for low-dose CT of the paranasal sinuses using iterative reconstruction: Feasibility and image quality. European Journal of Radiology 81: 2246-2250.

Chen, L., Wu, Y., Yan, J., Sun, W., Sun, Y. & Ojcius, D. 2005. Association between coinfection of Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans and Treponema denticola and periodontal tissue destruction in chronic periodontitis. Chinese medical journal 118: 915-921.

Cheung, J., Wong, C. K. K., Yan, M. L. C., Wong, O. F., Cheung, M., Luis, C. T. & Tsuis, K. L. Young-Burgess classification: Inter-observer and inter-method agreement between pelvic radiograph and computed tomography in emergency polytrauma management. Hong Kong Journal of Emergency Medicine : UNSP 1024907919857008.

Cooper, G. S., Bynum, M. L. K. & Somers, E. C. 2009. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. Journal of Autoimmunity 33: 197-207.

Corbet, E. F., Ho, D. K. L. & Lai, S. M. L. 2009. Radiographs in periodontal disease diagnosis and management. Australian Dental Journal 54: S27-S43.

Croft, J., Riddell, A., Koh, D., Downey, K., Blackledge, M., Usher, M., Boyd, K., Kaiser, M. & Messiou, C. 2020. Inter-observer agreement of baseline whole body MRI in multiple myeloma. Cancer Imaging 20: 48.

Damoiseaux, J. G. & Tervaert, J. W. 2002. The definition of autoimmune disease: are Koch's postulates applicable? The Netherlands journal of medicine 60: 266-268.

De Cock, J., Zanca, F., Canning, J., Pauwels, R. & Hermans, R. 2015. A comparative study for image quality and radiation dose of a cone beam computed tomography scanner and a multislice computed tomography scanner for paranasal sinus imaging. European radiology 25: 1891-1900.

Doll, R., Peto, R., Boreham, J. & Sutherland, I. 2004. Mortality in relation to smoking: 50 years' observations on male British doctors. Bmj-British Medical Journal 328: 1519-1528.

Eaton, W. W., Rose, N. R., Kalaydjian, A., Pedersen, M. G. & Mortensen, P. B. 2007. Epidemiology of autoimmune diseases in Denmark. Journal of Autoimmunity 29: 1-9.

Eke, P. I., Dye, B. A., Wei, L., Slade, G. D., Thornton-Evans, G. O., Borgnakke, W. S., Taylor, G. W., Page, R. C., Beck, J. D. & Genco, R. J. 2015. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. Journal of periodontology 86: 611-622.

Ercolini, A. & Miller, S. 2009. The role of infections in autoimmune disease. Clinical and experimental immunology 155: 1-15.

Esfahanian, V., Shamami, M. S. & Shamami, M. S. 2012. Relationship between osteoporosis and periodontal disease: review of the literature. Journal of dentistry (Tehran, Iran) 9: 256-264.

Estrela, C., Bueno, M. R., Leles, C. R., Azevedo, B. & Azevedo, J. R. 2008. Accuracy of cone beam computed tomography and panoramic and periapical radiography for detection of apical periodontitis. Journal of endodontics 34: 273-279.

Fazel, R., Krumholz, H. M., Wang, Y., Ross, J. S., Chen, J., Ting, H. H., Shah, N. D., Nasir, K., Einstein, A. J. & Nallamothu, B. K. 2009. Exposure to Low-Dose Ionizing Radiation from Medical Imaging Procedures. New England Journal of Medicine 361: 849-857.

Feldman, S., Kasjanski, R., Poposki, J., Hernandez, D., Chen, J. N., Norton, J. E., Suh, L., Carter, R. G., Stevens, W. W., Peters, A. T., Kern, R. C., Conley, D. B., Tan, B. K., Shintani-Smith, S., Welch, K. C., Grammer, L. C., Harris, K. E., Kato, A., Schleimer, R. P. & Hulse, K. E. 2017. Chronic airway inflammation provides a unique environment for B cell activation and antibody production. Clinical and Experimental Allergy 47: 457-466.

Fokkens, W. J., Lund, V. J., Hopkins, C., Hellings, P. W., Kern, R., Reitsma, S., Toppila-Salmi, S., Bernal-Sprekelsen, M., Mullol, J., Alobid, I., Terezinha Anselmo-Lima, W., Bachert, C., Baroody, F., von Buchwald, C., Cervin, A., Cohen, N., Constantinidis, J., De Gabory, L., Desrosiers, M., Diamant, Z., Douglas, R. G., Gevaert, P. H., Hafner, A., Harvey, R. J., Joos, G. F., Kalogjera, L., Knill, A., Kocks, J. H., Landis, B. N., Limpens, J., Lebeer, S., Lourenco, O., Meco, C., Matricardi, P. M., O'Mahony, L., Philpott, C. M., Ryan, D., Schlosser, R., Senior, B., Smith, T. L., Teeling, T., Tomazic, P. V., Wang, D. Y., Wang, D., Zhang, L., Agius, A. M., Ahlstrom-Emanuelsson, C., Alabri, R., Albu, S., Alhabash, S., Aleksic, A., Aloulah, M., Al-Qudah, M., Alsaleh, S., Baban, M. A., Baudoin, T., Balvers, T., Battaglia, P., Bedoya, J. D., Beule, A., Bofares, K. M., Braverman, I., Brozek-Madry, E., Richard, B., Callejas, C., Carrie,

S., Caulley, L., Chussi, D., de Corso, E., Coste, A., El Hadi, U., Elfarouk, A., Eloy, P. H., Farrokhi, S., Felisati, G., Ferrari, M. D., Fishchuk, R., Grayson, W., Goncalves, P. M., Grdinic, B., Grgic, V., Hamizan, A. W., Heinichen, J. V., Husain, S., Ping, T. I., Ivaska, J., Jakimovska, F., Jovancevic, L., Kakande, E., Kamel, R., Karpischenko, S., Kariyawasam, H. H., Kawauchi, H., Kjeldsen, A., Klimek, L., Krzeski, A., Kopacheva Barsova, G., Kim, S. W., Lal, D., Letort, J. J., Lopatin, A., Mahdjoubi, A., Mesbahi, A., Netkovski, J., Nyenbue Tshipukane, D., Obando-Valverde, A., Okano, M., Onerci, M., Ong, Y. K., Orlandi, R., Otori, N., Ouennoughy, K., Ozkan, M., Peric, A., Plzak, J., Prokopakis, E., Prepageran, N., Psaltis, A., Pugin, B., Raftopulos, M., Rombaux, P., Riechelmann, H., Sahtout, S., Sarafoleanu, C. C., Searyoh, K., Rhee, C. S., Shi, J., Shkoukani, M., Shukuryan, A. K., Sicak, M., Smyth, D., Snidvongs, K., Soklic Kosak, T., Stjarne, P., Sutikno, B., Steinsvag, S., Tantilipikorn, P., Thanaviratananich, S., Tran, T., Urbancic, J., Valiulius, A., Vasquez de Aparicio, C., Vicheva, D., Virkkula, P. M., Vicente, G., Voegels, R., Wagenmann, M. M., Wardani, R. S., Welge-Lussen, A., Witterick, I., Wright, E., Zabolotniy, D., Zsolt, B. & Zwetsloot, C. P. 2020. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 58: 1-464.

Galli, L., Chiappini, E. & de Martino, M. 2012. Infections and Autoimmunity. Pediatric Infectious Disease Journal 31: 1295-1297.

Gautam, D. K., Jindal, V., Gupta, S. C., Tuli, A., Kotwal, B. & Thakur, R. 2011. Effect of cigarette smoking on the periodontal health status: A comparative, cross sectional study. Journal of Indian Society of Periodontology 15: 383-387.

Genco, R., Grossi, S., Ho, A., Nishimura, F. & Murayama, Y. 2005. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. Journal of periodontology 76: 2075-2084.

Genco, R. J. & Borgnakke, W. S. 2013. Risk factors for periodontal disease. Periodontology 2000 62: 59-94.

Gevaert, P., Holtappels, G., Johansson, S. G., Cuvelier, C., Cauwenberge, P. & Bachert, C. 2005. Organization of secondary lymphoid tissue and local IgE formation to Staphylococcus aureus enterotoxins in nasal polyp tissue. Allergy 60: 71-79.

Giskes, K., Kunst, A., Benach, J., Borrell, C., Costa, G., Dahl, E., Dalstra, J., Federico, B., Helmert, U., Judge, K., Lahelma, E., Moussa, K., Ostergren, P., Platt, S., Prattala, R., Rasmussen, N. & Mackenbach, J. 2005. Trends in smoking behaviour between 1985 and 2000 in nine European countries by education. Journal of epidemiology and community health 59: 395-401.

Gleicher, N. & Barad, D. H. 2007. Gender as risk factor for autoimmune diseases. Journal of Autoimmunity 28: 1-6.

Graves, D., Jiang, Y. & Genco, C. 2000. Periodontal disease: bacterial virulence factors, host response and impact on systemic health. Current opinion in infectious diseases 13: 227-232.

Greene, J. & Vermillion, J. 1964. Simplified Oral Hygiene Index. Journal of the American Dental Association 68: 7-13.

Groth, A. M., May, S. A., Weaver, M. P. & Weller, R. 2009. Intra- and interobserver agreement in the interpretation of navicular bones on radiographs and computed tomography scans. Equine veterinary journal 41 (2): 124-129.

Hajishengallis, G. 2010. Too old to fight? Aging and its toll on innate immunity. Molecular oral microbiology 25: 25-37.

Heikkinen, A. M., Pajukanta, R., Pitkaniemi, J., Broms, U., Sorsa, T., Koskenvuo, M. & Meurman, J. H. 2008. The Effect of Smoking on Periodontal Health of 15-to 16-Year-Old Adolescents. Journal of periodontology 79: 2042-2047.

Hellen-Halme, K., Lith, A. & Shi, X. 2020. Reliability of marginal bone level measurements on digital panoramic and digital intraoral radiographs. Oral Radiology 36: 135-140.

Highfield, J. 2009. Diagnosis and classification of periodontal disease. Australian Dental Journal 54: S11-S26.

Holt, S. & Ebersole, J. 2005. Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia: the 'red complex', a prototype polybacterial pathogenic consortium in periodontitis. Periodontology 2000 38: 72-122.

Hopkins, C., Browne, J. P., Slack, R., Lund, V. & Brown, P. 2007. The Lund-Mackay staging system for chronic rhinosinusitis: How is it used and what does it predict? Otolaryngology-Head and Neck Surgery 137: 555-561.

Hugoson, A. & Laurell, L. 2000. A prospective longitudinal study on periodontal bone height changes in a Swedish population. Journal of clinical periodontology 27: 665-674.

Hugoson, A. & Rolandsson, M. 2011. Periodontal disease in relation to smoking and the use of Swedish snus: epidemiological studies covering 20 years (1983-2003). Journal of clinical periodontology 38: 809-816.

Hutchinson, D., Shepstone, L., Moots, R., Lear, J. & Lynch, M. 2001. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. Annals of the Rheumatic Diseases 60: 223-227.

Huumonen, S., Suominen, A. L. & Vehkalahti, M. M. 2017. Prevalence of apical periodontitis in root filled teeth: findings from a nationwide survey in Finland. International endodontic journal 50: 229-236.

Ickrath, P., Kleinsasser, N., Ding, X., Ginzkey, C., Beyersdorf, N., Hagen, R., Kerkau, T. & Hackenberg, S. 2018. Accumulation of CD69(+) tissue-resident memory T cells in the nasal polyps of patients with chronic rhinosinusitis. International journal of molecular medicine 42: 1116-1124.

Inoue-Choi, M., Shiels, M. S., McNeel, T. S., Graubard, B., I., Hatsukami, D. & Freedman, N. D. 2019. Contemporary Associations of Exclusive Cigarette, Cigar, Pipe, and Smokeless Tobacco Use With Overall and Cause-Specific Mortality in the United States. Jnci Cancer Spectrum 3: UNSP pkz036.

Jiang, Y., Zhou, X., Cheng, L. & Li, M. 2020. The Impact of Smoking on Subgingival Microflora: From Periodontal Health to Disease. Frontiers in Microbiology 11: 66.

Kabak, Y. & Abbott, P. 2005. Prevalence of apical periodontitis and the quality of endodontic treatment in an adult Belarusian population. International endodontic journal 38: 238-245.

Kallberg, H., Ding, B., Padyukov, L., Bengtsson, C., Ronnelid, J., Klareskog, L., Alfredsson, L. & EIRA Study Grp 2011. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Annals of the Rheumatic Diseases 70: 508-511.

Kalra, M., Maher, M., Toth, T., Hamberg, L., Blake, M., Shephard, J. & Saini, S. 2004. Strategies for CT radiation dose optimization. Radiology 230: 619-628.

Kassebaum, N. J., Bernabe, E., Dahiya, M., Bhandari, B., Murray, C. J. L. & Marcenes, W. 2014. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Metaregression. Journal of dental research 93: 1045-1053.

Kato, A., Peters, A., Suh, L., Carter, R., Harris, K. E., Chandra, R., Conley, D., Grammer, L. C., Kern, R. & Schleimer, R. P. 2008. Evidence of a role for B cell-activating factor of the TNF family in the pathogenesis of chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology 121: 1385-92, 1392.e1-2.

Katuri, K. K., Alluri, J. K., Chintagunta, C., Tadiboina, N., Borugadda, R., Loya, M., Marella, Y. & Bollepalli, A. C. 2016. Assessment of Periodontal Health Status in Smokers and Smokeless Tobacco Users: A Cross-Sectional Study. Journal of Clinical and Diagnostic Research 10: ZC143-ZC146.

Kaufman, E. & Lamster, I. 2000. Analysis of saliva for periodontal diagnosis - A review. Journal of clinical periodontology 27: 453-465.

Kiriyama, H., Kaneko, H., Itoh, H., Yoshida, Y., Nakanishi, K., Mizuno, Y., Daimon, M., Morita, H., Yamamichi, N. & Komuro, I. 2020. Effect of cigarette smoking on carotid artery atherosclerosis: a community-based cohort study. Heart and vessels 35: 22-29.

Kirkevang, L. -., Vaeth, M., Horsted-Bindslev, P., Bahrami, G. & Wenzel, A. 2007. Risk factors for developing apical periodontitis in a general population. International endodontic journal 40: 290-299.

Kivity, S., Agmon-Levin, N., Blank, M. & Shoenfeld, Y. 2009. Infections and autoimmunity - friends or foes? Trends in immunology 30: 409-414.

Kuhlmann, T., Ludwin, S., Prat, A., Antel, J., Brueck, W. & Lassmann, H. 2017. An updated histological classification system for multiple sclerosis lesions. Acta Neuropathologica 133: 13-24.

Lam, C. A., McGettigan, M. J., Thompson, Z. J., Khazai, L., Chung, C. H., Centeno, B. A., McIver, B. & Valderrabano, P. 2019. Ultrasound characterization for thyroid nodules with indeterminate cytology: inter-observer agreement and impact of combining pattern-based and scoring-based classifications in risk stratification. Endocrine 66: 278-287.

Lamont, R. J. & Hajishengallis, G. 2015. Polymicrobial synergy and dysbiosis in inflammatory disease. Trends in molecular medicine 21: 172-183.

Lau, A., Lester, S., Moraitis, S., Ou, J., Psaltis, A. J., McColl, S., Rischmueller, M., Wormald, P. J. & Vreugde, S. 2017. Tertiary lymphoid organs in recalcitrant chronic rhinosinusitis. The Journal of allergy and clinical immunology 139: 1371-1373.e6.

Lechien, J. R., Filleul, O., Costa de Araujo, P., Hsieh, J. W., Chantrain, G. & Saussez, S. 2014. Chronic maxillary rhinosinusitis of dental origin: a systematic review of 674 patient cases. International journal of otolaryngology 2014: 465173.

Lee, L. W., Lee, Y. L., Hsiao, S. H. & Lin, H. P. 2017. Bacteria in the apical root canals of teeth with apical periodontitis. Journal of the Formosan Medical Association = Taiwan yi zhi 116: 448-456.

Lefrancois, P., Chapdelaine, H., Cote, B. & Desrosiers, M. 2016. A role for auto-immunity in chronic rhinosinusitis? Lessons learned from sub-epidermal bullous disorders of the skin. Allergy Asthma and Clinical Immunology 12: 38.

Lie, M. A., Van Der Weijden, G. A., Timmerman, M. F., Loos, B. G., Van Steenbergen, T. J. M. & Van Der Velden, U. 2001. Occurrence of Prevotella intermedia and

Prevotella nigrescens in relation to gingivitis and gingival health. Journal of clinical periodontology 28: 189-193.

Ligthart, S., Steenaard, R. V., Peters, M. J., van Meurs, J. B. J., Sijbrands, E. J. G., Uitterlinden, A. G., Bonder, M. J., Hofman, A., Franco, O. H., Dehghan, A. & BIOS Consortium 2016. Tobacco smoking is associated with DNA methylation of diabetes susceptibility genes. Diabetologia 59: 998-1006.

Linder, D., Piaserico, S. & Alaibac, M. 2018. Comorbidities in Autoimmune Skin Diseases. Jama Dermatology 154: 264-265.

Lo Giudice, R., Nicita, F., Puleio, F., Alibrandi, A., Cervino, G., Lizio, A. S. & Pantaleo, G. 2018. Accuracy of Periapical Radiography and CBCT in Endodontic Evaluation. International Journal of Dentistry 2018: 2514243.

Loe, H. 1967. The Gingival Index, the Plaque Index and the Retention Index Systems. Journal of periodontology 38 (6): Suppl:610-6.

Lund, V. & Kennedy, D. 1997. Staging for rhinosinusitis. Otolaryngology-Head and Neck Surgery 117: S35-S40.

Maillet, M., Bowles, W. R., McClanahan, S. L., John, M. T. & Ahmad, M. 2011. Cone-beam Computed Tomography Evaluation of Maxillary Sinusitis. Journal of endodontics 37: 753-757.

Marques, M. D., Moreira, B. & Eriksen, H. M. 1998. Prevalence of apical periodontitis and results of endodontic treatment in an adult, Portuguese population. International endodontic journal 31: 161-165.

Marsh, P. D., Head, D. A. & Devine, D. A. 2015. Dental plaque as a biofilm and a microbial community-Implications for treatment. Journal of Oral Biosciences 57: 185-191.

Martinez, C., Castellano, Y., Andres, A., Fu, M., Anton, L., Ballbe, M., Fernandez, P., Cabrera, S., Riccobene, A., Gavilan, E., Feliu, A., Baena, A., Margalef, M. & Fernandez, E. 2017. Factors associated with implementation of the 5A's smoking cessation model. Tobacco Induced Diseases 15: 41.

Martinez-Canut, P., Lorca, A. & Magan, R. 1995. Smoking and Periodontal-Disease Severity. Journal of clinical periodontology 22: 743-749.

Matuliene, G., Pjetursson, B. E., Salvi, G. E., Schmidlin, K., Braegger, U., Zwahlen, M. & Lang, N. P. 2008. Influence of residual pockets on progression of periodontitis and tooth loss: Results after 11 years of maintenance. Journal of clinical periodontology 35: 685-695.

McCollough, C. H., Primak, A. N., Braun, N., Kofler, J., Yu, L. & Christner, J. 2009. Strategies for Reducing Radiation Dose in CT. Radiologic clinics of North America 47: 27-40.

McInnes, I. B. & Schett, G. 2011. Mechanisms of Disease The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine 365: 2205-2219.

Mercado, F., Marshall, R., Klestov, A. & Bartold, P. 2001. Relationship between rheumatoid arthritis and periodontitis. Journal of periodontology 72: 779-787.

Miller, C., King, C., Langub, C., Kryscio, R. & Thomas, M. 2006. Salivary biomarkers of existing periodontal disease - A cross-sectional study. Journal of the American Dental Association 137: 322-329.

Moroni, L., Bianchi, I. & Lleo, A. 2012. Geoepidemiology, gender and autoimmune disease. Autoimmunity Reviews 11: A386-A392.

Mullally, B., Breen, B. & Linden, G. 1999. Smoking and patterns of bone loss in early-onset periodontitis. Journal of periodontology 70: 394-401.

Nagy, G., Nemeth, N. & Buzas, E. I. 2018. Mechanisms of vascular comorbidity in autoimmune diseases. Current opinion in rheumatology 30: 197-206.

Natvig Norderhaug I., Dybing E. & Gilljam H. et al. 2005, Health Effects and Dependency Associated with Snuff Consumption. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH). Report from Norwegian Knowledge Center for the Health Services (NOKC) No. 06-2005.

Nibali, L., Farias, B. C., Vajgel, A., Tu, Y. K. & Donos, N. 2013. Tooth Loss in Aggressive Periodontitis A Systematic Review. Journal of dental research 92: 868-875.

Norberg, M., Malmberg, G., Ng, N. & Brostrom, G. 2011. Who is using snus? - Time trends, socioeconomic and geographic characteristics of snus users in the ageing Swedish population. Bmc Public Health 11: 929.

Page, R. C. & Eke, P. I. 2007. Case definitions for use in population - Based surveillance of periodontitis. Journal of periodontology 78: 1387-1399.

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman, K. S., Kumar, P. S., Loos, B. G., Machtei, E., Meng, H., Mombelli, A., Needleman, I., Offenbacher, S., Seymour, G. J., Teles, R. & Tonetti, M. S. 2018. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Journal of clinical periodontology 45: S162-S170.

Payne, J., Reinhardt, R., Nummikoski, P. & Patil, K. 1999. Longitudinal alveolar bone loss in postmenopausal osteoporotic/osteopenic women. Osteoporosis International 10: 34-40.

Perricone, C., Versini, M., Ben-Ami, D., Gertel, S., Watad, A., Segel, M. J., Ceccarelli, F., Conti, F., Cantarini, L., Bogdanos, D. P., Antonelli, A., Amital, H., Valesini, G. & Shoenfeld, Y. 2016. Smoke and autoimmunity: The fire behind the disease. Autoimmunity Reviews 15: 354-374.

Persson, R., Tzannetou, S., Feloutzis, A., Bragger, U., Persson, G. & Lang, N. 2003. Comparison between panoramic and intra-oral radiographs for the assessment of alveolar bone levels in a periodontal maintenance population. Journal of clinical periodontology 30: 833-839.

Phothikhun, S., Suphanantachat, S., Chuenchompoonut, V. & Nisapakultorn, K. 2012. Cone-Beam Computed Tomographic Evidence of the Association Between Periodontal Bone Loss and Mucosal Thickening of the Maxillary Sinus. Journal of periodontology 83: 557-564.

Pihlstrom, B., Michalowicz, B. & Johnson, N. 2005. Periodontal diseases. Lancet 366: 1809-1820.

Raychaudhuri, S. K., Maverakis, E. & Raychaudhuri, S. P. 2014. Diagnosis and classification of psoriasis. Autoimmunity Reviews 13: 490-495.

Rocas, I., Siqueira, J., Santos, K., Coelho, A. & de Janeiro, R. 2001. "Red complex" (Bacteroides forsynthus, Porphyromonas gingivalis, and Treponema denticola) in endodontic infections: A molecular approach. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics 91 (4): 468-471.

Rong, X., Xiang, L., Li, Y., Yang, H., Chen, W., Li, L., Liang, D. & Zhou, X. 2020. Chronic Periodontitis and Alzheimer Disease: A Putative Link of Serum Proteins Identification by 2D-DIGE Proteomics. Frontiers in Aging Neuroscience 12: 248.

Rubio-Tapia, A. & Murray, J. A. 2010. Classification and management of refractory coeliac disease. Gut 59: 547-557.

Ruetters, M., Hagenfeld, D., ElSayed, N., Zimmermann, N., Gehrig, H. & Kim, T. 2020. Ex vivo comparison of CBCT and digital periapical radiographs for the quantitative assessment of periodontal defects. Clinical oral investigations 24: 377-384.

Sadrameli, M., Bathini, P. & Alberi, L. 2020. Linking mechanisms of periodontitis to Alzheimer's disease. Current opinion in neurology 33: 230-238.

Salceanu, M., Melian, A., Topoliceanu, C., Hamburda, T. & Ghiorghe, C. 2018. Study regarding the Possibilities to Detect the Incipient Periapical Lesions by Radiography and Cbct. Romanian Journal of Oral Rehabilitation 10: 45-49.

Sankaranarayanan, R., Keranen, A. L., Saxlin, T., Myllykangas, R., Knuuttila, M., Ylostalo, P. & Suominen, A. L. 2019. Association between alcohol use and periodontal pockets in Finnish adult population. Acta Odontologica Scandinavica 77: 371-379.

Sanz, M., Marco del Castillo, A., Jepsen, S., Gonzalez-Juanatey, J. R., D'Aiuto, F., Bouchard, P., Chapple, I., Dietrich, T., Gotsman, I., Graziani, F., Herrera, D., Loos, B., Madianos, P., Michel, J., Perel, P., Pieske, B., Shapira, L., Shechter, M., Tonetti, M., Vlachopoulos, C. & Wimmer, G. 2020. Periodontitis and cardiovascular diseases: Consensus report. Journal of clinical periodontology 47: 268-288.

Shahzad, A., Nauman, Q. & Rubab, U. E. 2018. In Panoramic Radiographs Variability in Inter Observer Assessment of Mental Foramen Radiographically and its Appearance. Indo American Journal of Pharmaceutical Sciences 5: 11466-11470.

Siahpush, M., Heller, G. & Singh, G. 2005. Lower levels of occupation, income and education are strongly associated with a longer smoking duration: Multivariate results from the 2001 Australian National Drug Strategy Survey. Public health 119: 1105-1110.

Silva, N., Abusleme, L., Bravo, D., Dutzan, N., Garcia-Sesnich, J., Vernal, R., Hernandez, M. & Gamonal, J. 2015. Host response mechanisms in periodontal diseases. Journal of Applied Oral Science 23: 329-355.

Soder, B., Jin, L. & Wickholm, S. 2002. Granulocyte elastase, matrix metalloproteinase-8 and prostaglandin E-2 in gingival crevicular fluid in matched clinical sites in smokers and non-smokers with persistent periodontitis. Journal of clinical periodontology 29: 384-391.

Sonnenschein, S. K. & Meyle, J. 2015. Local inflammatory reactions in patients with diabetes and periodontitis. Periodontology 2000 69: 221-254.

Sorsa, T., Alassiri, S., Grigoriadis, A., Raisanen, I. T., Parnanen, P., Nwhator, S. O., Gieselmann, D. & Sakellari, D. 2020. Active MMP-8 (aMMP-8) as a Grading and Staging Biomarker in the Periodontitis Classification. Diagnostics 10: 61.

Stammberger, H. 1986. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations.

Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 94: 143-147.

STUK 2017. https://www.stuk.fi/web/en/topics/use-of-radiation-in-health-care/radiographic-examinations/radiation-doses-of-radiographic-examinations. Cited 09/15.

Tan, B. K., Klingler, A. I., Poposki, J. A., Stevens, W. W., Peters, A. T., Suh, L. A., Norton, J., Carter, R. G., Hulse, K. E., Harris, K. E., Grammer, L. C., Schleimer, R. P., Welch, K. C., Smith, S. S., Conley, D. B., Kern, R. C. & Kato, A. 2017. Heterogeneous inflammatory patterns in chronic rhinosinusitis without nasal polyps in Chicago, Illinois. The Journal of allergy and clinical immunology 139: 699-703.e7.

Tewary, S., Luzzo, J. & Hartwell, G. 2011. Endodontic Radiography: Who Is Reading the Digital Radiograph? Journal of endodontics 37: 919-921.

Timberlake, D. S., Nikitin, D., Johnson, N. J. & Altekruse, S. F. 2017. A longitudinal study of smokeless tobacco use and mortality in the United States. International Journal of Cancer 141: 264-270.

Tomioka, K., Kurumatani, N. & Saeki, K. 2020. The Association Between Education and Smoking Prevalence, Independent of Occupation: A Nationally Representative Survey in Japan. Journal of Epidemiology 30: 136-142.

Torres, S. R., Silva Pedrazas, C. H., Veloso Correia, M. P., Leitao de Azevedo, M. N., Zamprogno, T., Silva Junior, A., Goncalves, L. S. & de Souza Papi, J. A. 2016. Drugs or disease: evaluating salivary function in RA patients. Brazilian Oral Research 30.

Tsybikov, N. N., Egorova, E. V., Kuznik, B. I., Fefelova, E. V. & Magen, E. 2015. Anticytokine autoantibodies in chronic rhinosinusitis. Allergy and Asthma Proceedings 36: 473-480.

Vessey, M. P., Villard-Mackintosh, L. & Yeates, D. 1987. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. 457-464.

Viera AJ & Garrett JM 2005. Understanding interobserver agreement: the kappa statistic. Family medicine 37: 360-363.

Walter, C., Kaner, D., Berndt, D. C., Weiger, R. & Zitzmann, N. U. 2009. Three-dimensional imaging as a pre-operative tool in decision making for furcation surgery. Journal of clinical periodontology 36: 250-257.

Walter, C., Schmidt, J. C., Rinne, C. A., Mendes, S., Dula, K. & Sculean, A. 2020. Cone beam computed tomography (CBCT) for diagnosis and treatment planning in periodontology: systematic review update. Clinical oral investigations 24: 2943-2958.

Wang, J., Lv, J., Wang, W. & Jiang, X. 2016a. Alcohol consumption and risk of periodontitis: a meta-analysis. Journal of clinical periodontology 43: 572-583.

Wang, M., Zhang, N., Zheng, M., Li, Y., Meng, L., Ruan, Y., Han, J., Zhao, N., Wang, X., Zhang, L. & Bachert, C. 2019. Cross-talk between T(H)2 and T(H)17 pathways in patients with chronic rhinosinusitis with nasal polyps. Journal of Allergy and Clinical Immunology 144: 1254-1264.

Wang, X., Zhang, N., Bo, M., Holtappels, G., Zheng, M., Lou, H., Wang, H., Zhang, L. & Bachert, C. 2016b. Diversity of TH cytokine profiles in patients with chronic rhinosinusitis: A multicenter study in Europe, Asia, and Oceania. The Journal of allergy and clinical immunology 138: 1344-1353.

Warnakulasuriya, S., Dietrich, T., Bornstein, M. M., Casals Peidro, E., Preshaw, P. M., Walter, C., Wennstrom, J. L. & Bergstrom, J. 2010. Oral health risks of tobacco use and effects of cessation. International dental journal 60: 7-30.

Whisnant, J., Homer, D., Ingall, T., Baker, H., Ofallon, W. & Wiebers, D. 1990. Duration of Cigarette-Smoking is the Strongest Predictor of Severe Extracranial Carotid-Artery Atherosclerosis. Stroke 21: 707-714.

Will, J., Galuska, D., Ford, E., Mokdad, A. & Calle, E. 2001. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. International journal of epidemiology 30: 540-546.

World Health Organization 2020. https://www.who.int/news-room/fact-sheets/detail/oral-health. Cited 03/25.

Xiao, L., Jia, L., Bai, L., He, L., Yang, B., Wu, C. & Li, H. 2016. Phenotypic and functional characteristics of IL-21-expressing CD8+T cells in human nasal polyps. Scientific Reports 6: 30362.

Yanbaeva, D. G., Dentener, M. A., Creutzberg, E. C., Wesseling, G. & Wouters, E. F. M. 2007. Systemic effects of smoking. Chest 131: 1557-1566.

Yilmaz Sastim, C., Gursoy, M., Kononen, E., Kasurinen, A., Norvio, S., Gursoy, U. K. & Dogan, B. 2020. Salivary and serum markers of angiogenesis in periodontitis in relation to smoking. Clinical oral investigations. https://doi.org/10.1007/s00784-020-03411-4.

Zarco, M. F., Vess, T. J. & Ginsburg, G. S. 2012. The oral microbiome in health and disease and the potential impact on personalized dental medicine. Oral diseases 18: 109-120.

Zinreich, S. J., Kennedy, D. W., Rosenbaum, A. E., Gayler, B. W., Kumar, A. J. & Stammberger, H. 1987. Paranasal sinuses: CT imaging requirements for endoscopic surgery. Radiology 163: 769-775.