From THE DEPARTMENT OF DENTAL MEDICINE
Karolinska Institutet, Stockholm, Sweden

PERIODONTITIS AND INVASIVE ORAL TREATMENT IN RELATION TO MYOCARDIAL INFARCTION - EPIDEMIOLOGICAL STUDIES

Eva Nordendahl

Karolinska Institutet

Stockholm 2019

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Cover illustration by Lena Nordendahl
Printed by Arkitektkopia AB 2019

ISBN 978-91-7831-568-0

To my beloved family

PERIODONTITIS AND INVASIVE ORAL TREATMENT IN RELATION TO MYOCARDIAL INFARCTION - EPIDEMIOLOGICAL STUDIES
THESIS FOR DOCTORAL DEGREE (Ph.D.)

Eva Nordendahl

The thesis will be defended in public at the Department of Dental Medicine, lecture hall 4V, Alfred Nobels Allé 8, Karolinska Institutet, Huddinge, Friday the 13th of December 2019, at 9:00 am

Principal Supervisor:
Professor Anders Gustafsson
Karolinska Institutet
Department of Dental Medicine
Division of Periodontology

Co-supervisors:
Professor Anna Norhammar
Karolinska Institutet
Department of Medicine
Division of Cardiology

Associate Professor Barbro Kjellström
Karolinska Institutet
Department of Medicine
Division of Cardiology

Associate Professor Michael Fored
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

Opponent:
Professor Ola Norderyd
Malmö University
Faculty of Odontology
Department of Periodontology

Examination Board:
Associate Professor Anders Holmlund
Uppsala University
Department of Medical Sciences
Division of Cardiovascular Epidemiology

Professor Maria Feychting
Karolinska Institutet
Institute of Environmental Medicine
Division of Epidemiology

Senior Professor Karin Schenck-Gustafsson
Karolinska Institutet
Department of Medicine
Division of Cardiology

LIST OF SCIENTIFIC PAPERS

I. Rydén L, Buhlin K, **Ekstrand E**, De Faire U, Gustafsson A, Holmer J, Kjellström B, Lindahl B, Norhammar A, Nygren Å, Näsman P, Rathnayake N, Svenungsson E, Klinge B
Periodontitis Increases the Risk of a First Myocardial Infarction A Report From the PAROKRANK Study
Circulation, 2016;133:576-583

II. **Nordendahl E**, Gustafsson A, Norhammar A, Näsman P, Rydén L, Kjellström B
Severe Periodontitis Is Associated with Myocardial Infarction in Females
Journal of Dental Research, 2018;97:1114-1121

III. **Nordendahl E**, Fored M, Kjellström B, Ekbom A, Norhammar A, Gustafsson A
Association Between Periodontitis and Myocardial Infarction
- A Registry-Based Case-Control Study
Submitted to Journal of Clinical Periodontology 2019

IV. **Nordendahl E**, Kjellström B, Fored M, Ekbom A, Svensson T, Norhammar A, Gustafsson A
Invasive Dental Treatment and Risk for a First Myocardial Infarction
Journal of Dental Research, 2018;97:1100-1105

CONTENTS

LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
CI	Confidence intervals
DNA	Deoxyribonucleic acid
DHR	Dental Health Register (Sweden)
HbA1c	Hemoglobin A1c
HR	Hazard ratio
hsCRP	High sensitive C-reactive protein
ICD	International Classification of Disease
IPR	National Inpatient Register (Sweden)
LDL	Low-density lipoprotein
LISA	Longitudinal integration database for health insurance and labour market studies (Sweden)
NBHW	National Board of Health and Welfare (Sweden)
NSTEMI	Non-ST-segmented elevation myocardial infarction
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAROKRANK	Periodontitis and Its Relation to Coronary Artery Disease
PAVE	Periodontitis and Vascular Events
PCI	Percutaneous coronary intervention
PIN	Personal identity number
RR	Relative risk
SCB	Statistics Sweden
SNP	Single nucleotide polymorphism
SPDR	Swedish Predcribed Drug Register
STEMI	ST-elevation myocardial infarction
TPR	Total Population Register (Sweden)

ABSTRACT

Background: Cardiovascular disease and periodontitis are major global health problems that are a large burden for the individual and society. During the last 30 years, it has been discussed whether there is an association between the two diseases. One explanation of a possible association between these conditions is systemic low-grade inflammation derived from periodontitis or acute inflammation from invasive dental procedures and which initiates or accelerates the development of atherosclerosis. It has not yet been established whether the relation is causal or only an expression of shared risk factors.

Aims: To investigate the relation between oral health and cardiovascular disease by exploring the association between:

1. Periodontitis and myocardial infarction.
2. Periodontitis and myocardial infarction by gender.
3. Invasive dental treatment and incidence of myocardial infarction.

Association between periodontitis and a first myocardial infarction in the PAROKRANK study

The PAROKRANK study, a prospective case-control study, recruited 805 cases and 805 controls from 17 Swedish hospitals. Cases were patients <75 years with a first myocardial infarction, which were examined including a dental examination and panorama radiograph 6 to 10 weeks after the index infarction. Disease and health-preserving risk variables were queried at the time of the examination. Similar investigations were performed in controls matched for age, gender, and geographic area. Periodontitis was defined by bone loss: healthy (≥80% remaining bone), mild-to-moderate (79–66%), or severe (<66%). Moderate-to-severe periodontitis was more common in cases (43 vs. 33%, p<0.001). Moderate-to-severe periodontitis significantly increased the risk of a first myocardial infarction after adjusting for diabetes, smoking habits, education level, and marital status (OR 1.28; 95% CI: 1.03–1.60). In 785 cases (19% women) and 792 controls (19% women), severe periodontitis increased the risk of a first myocardial infarction in women (adjusted OR 3.72; 95% CI: 1.24–11.16), especially below age 65 years (adjusted OR 5.26; 95% CI: 1.03–26.76).

Association between periodontitis and a first myocardial infarction in a nation-wide setting

Merging data from The National Board of Health and Welfare with data from Statistics Sweden identified cases (n=51,884) with a first myocardial infarction (ICD 10 code I.21) and controls (n=246,978) during 2011-2013. Controls were matched 5:1 by age, gender and geographic area and free from prior myocardial infarction. Periodontal treatment derived from The Dental Health Register three years before the index date was used as a surrogate marker for periodontitis: *(i)* No record of dental treatment, *(ii)* No record of periodontal treatment, *(iii)* One or more non-advanced periodontal treatments, or *(iv)* One or more advanced periodontal treatments. No association between advanced periodontal treatment and incident myocardial infarction was found after adjustments (OR 1.02; 95% CI: 1.00–1.05), or in subjects with a high yearly frequency of advanced periodontal treatment, including periodontal surgery (OR 1.14; 95% CI: 1.00–1.29).

Association between invasive dental treatment and a first myocardial infarction

In the nation-wide case-control study population, the association between invasive dental treatment (defined by procedure and codes for sub-gingival curettage, dento-alveolar surgery, tooth extractions, implant surgery, apical surgery or periodontal surgery) and a first myocardial infarction (ICD 10 code I.21) within 4 weeks was investigated. Invasive dental treatment before a first myocardial infarction was not associated with an increased risk of a myocardial infarction (adjusted OR 0.98; 95% CI: 0.91–1.06).

Conclusions: In nationwide contemporary populations periodontitis slightly increased the risk for experiencing a first myocardial infarction with even stronger risks in women, particular in those 65 years or younger. However, when using periodontal treatment as a surrogate marker for periodontitis there was no evidence that an association to a first myocardial infarction was of any significance in the general Swedish population. Invasive dental treatment, including dental surgery and tooth extractions, was not associated with an increased risk of a first myocardial infarction.

SAMMANFATTNING

Bakgrund: Hjärt-kärlsjukdom och parodontit är stora globala folksjukdomar som orsakar mycket lidande och som leder till stora hälsoproblem. Under de senaste 30 åren har ett eventuellt samband mellan dessa två tillstånd diskuterats. Som en förklaringsmodell har inflammation föreslagits, genom att låggradig systemisk inflammation orsakad av parodontit eller akut inflammation från invasiva tandingrepp, kan påverkar progressionen av ateroskleros.

Det råder dock fortfarande delade meningar om det föreligger ett direkt orsakssamband mellan dessa två tillstånd eller om det bara beror på gemensamma riskfaktorer.

Målsättning: Att undersöka om oral hälsa utgör en riskfaktor för utvecklingen av hjärt-kärlsjukdom, framförallt sambandet mellan parodontit, invasiva tandingrepp och hjärtinfarkt.

1. Studera sambandet mellan parodontit och hjärtinfarkt
2. Studera sambandet mellan parodontit och hjärtinfarkt ur ett könsperspektiv
3. Studera sambandet mellan invasiva tandingrepp och risken för en hjärtinfarkt

Sambandet mellan parodontit och hjärtinfarkt, PAROKRANK studien

Sambandet mellan parodontit och hjärtinfarkt undersöktes i en prospektiv fall-kontroll studie inkluderande 805 patienter (fall) 75 år eller yngre med en första händelse av hjärtinfarkt vid någon av 17 deltagande sjukhus runt om i Sverige. Kontroller var personer som matchades på ålder, kön och bostadsort samt var fria från tidigare hjärtinfarkt. Samtliga deltagare genomgick medicinsk- och tandundersökning inkluderande röntgen. Parodontit klassificerades i tre grupper utifrån alveolär benhöjd: Frisk (≥80% kvarvarande ben), mild/moderat (79-66%) eller grav (<66%). Mild/moderat eller grav parodontit var mer förekommande hos fallen (43 mot 33 %, p<0.001). Moderat till grav parodontit var signifikant associerat med hjärtinfarkt, efter hänsyn tagen till andra viktiga faktorer; diabetes, rökning, utbildning och civilstånd, OR 1.28; 95% CI: 1.03-1.60. Hos 785 fall (19% kvinnor), och 792 kontroller (19% kvinnor), var grav parodontit signifikant associerad till hjärtinfarkt, (justerat OR 3.72; 95% CI: 1.24-11.16), framför allt i åldersgruppen 65 år eller yngre (justerat OR 5.26; 95% CI: 1.03-26.76).

Sambandet mellan parodontit och hjärtinfarkt i en nationell registerbaserad fall-kontroll studie

Data från Socialstyrelsen samt från Statistiska Centralbyrån inhämtades mellan 2011-2013 och resulterade i 51 884 fall med en förstagångs hjärtinfarktdiagnos (ICD 10 kod I.21) och 246 978 kontroller som var matchade 5:1 för ålder, kön och geografisk bostadsort. Exklusionskriterium för kontroller var tidigare hjärtinfarkt. För exponeringen parodontit användes parodontal behandling som ett surrogat mått för parodontit. Information om tandvårdsåtgärder hämtades från Tandhälsoregistret (3 år innan infarkttillfället). Information gällande parodontala behandlingar klassificerades i fyra olika grupper: *i)* Ingen registrerad tandvård, *ii)* Ingen registrerad parodontal vård, *iii)* En eller fler utförda lätta parodontala behandlingar eller *iv)* En eller fler utförda avancerade parodontala behandlingar. Resultaten visade inget samband mellan avancerad parodontal behandling och hjärtinfarkt, efter att hänsyn tagits till relevanta faktorer; diabetes, inkomst och utbildningsgrad (OR 1.02; 95% CI: 1.00-1.05), inte heller för individer som utförde 3 eller fler avancerade parodontal behandlingar, i kombination med parodontal kirurgi (OR 1.14; 95% CI: 1.00–1.29).

I samma studiepopulation undersöktes sambandet mellan invasiva tandingrepp och hjärtinfarkt. Inget samband mellan invasiva tandåtgärder och risken för en förstagångs hjärtinfarkt kunde påvisas efter justering av relevanta faktorer; tidigare hjärt-kärlsjukdom, hjärt-kärl läkemedel, diabetes, inkomst och utbildningsgrad (OR 0.98; 95% CI: 0.91-1.06).

Sammanfattning: I en modern population, är parodontit vanligare hos patienter som har överlevt en förstagångs hjärtinfarkt i jämförelse med friska kontroller. Grav parodontit verkar vara en starkare riskfaktor för hjärtinfarkt hos kvinnor i jämförelse med män, framförallt hos kvinnor 65 år eller yngre. Resultat från ett nationellt material visar dock ingen förhöjd risk för hjärtinfarkt hos individer med parodontit, när man använder parodontal behandling som en markör för parodontit. Invasiva tandingrepp, inkluderande operationer och extraktioner, är inte förenade med en förhöjd risk för hjärtinfarkt i en svensk befolkning.

INTRODUCTION

During the last century, the effects of oral infections on systemic health have been a much discussed topic.[1] Dr. Willoughby D. Miller suggested that oral infections could cause different diseases. This started "the focal infection theory", which was accepted by general medicine in the 1920s.[2] The main principle of the theory was that oral microorganisms and the metabolic products produced by the ensuing local infections entered the bloodstream and caused systemic disorders. This resulted in extreme dental treatments, such as therapeutic edentulation, where otherwise healthy teeth were extracted to prevent the occurrence of systemic diseases.[3] Over time, clinicians began to question this radical form of treatment, especially as patients who underwent total tooth extraction reaped no apparent health benefits compared with those who had not had such invasive treatment, rather the opposite occurred. By the 1940s, researchers had discredited the focal infection theory, and the discussion slowly faded thereafter.[4]

Figure 1. Dr. Willoughby D. Miller

In the late 1980s, an association between oral infections and cardiovascular disease gained renewed attention and the theory re-emerged.[5,6] Numerous publications in this field have since suggested an inflammatory link between the two conditions. Inflammation is the human body's natural defense and an essential process that protects us from our environment. Aulus Cornelius Celsus (c. 25 BC – c. AD 50) was one of the first to describe the four cardinal signs of inflammation: redness (*rubor*), warmth (*calor*), swelling (*tumor*), and pain (*dolor*).[7] This defense helps the body resist bacterial invasion in damaged tissue and initiate a healing process. If the infection could not be resolved, it would, with high probability, become a chronic pathological condition with persistent inflammation and tissue destruction.

Although a potential causal relationship has been suggested between oral infection and cardiovascular disease with inflammation as the link, and many studies have reported positive associations, there are still knowledge gaps in the field.

PERIODONTAL DISEASE

Periodontal disease is an inflammatory condition and a major global public health problem that affects the majority of most populations after the age of 35−40 years.[8,9] The disease includes both a reversible and an irreversible condition. Gingivitis, the reversible form, involves inflammation of the gingival tissue and the irreversible, periodontitis, affects the supporting tissue of the teeth.[10] Figure 2 illustrates the periodontium and the development of periodontitis.

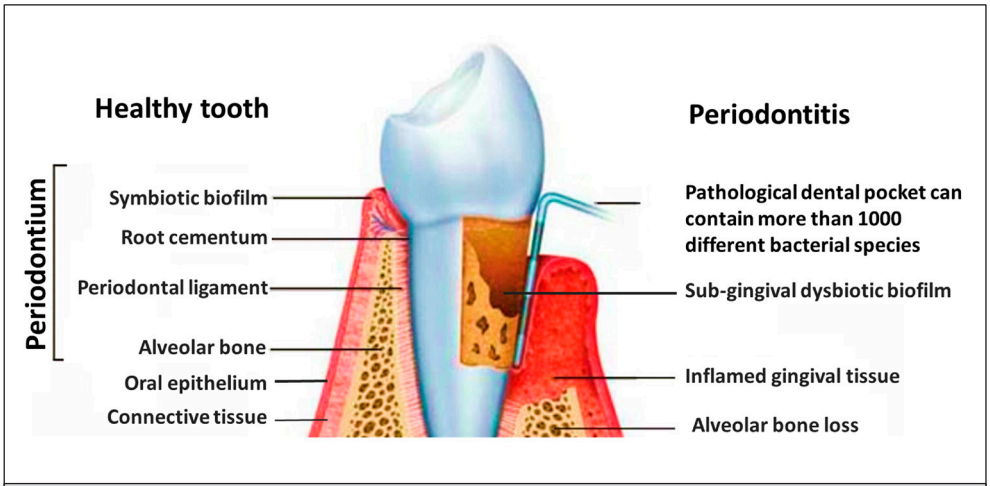

Figure 2. Schematic illustration of the periodontium and the development of periodontitis.

GINGIVITIS

Gingivitis is a reversible inflammation of the gingival tissue, usually initiated by bacteria from dental plaque; but nonplaque-induced gingivitis, such as allergies and viral infections are also known.[9] A clinical examination will identify gingivitis, which comprises redness, swelling, and bleeding of the gingival tissue. Optimizing oral hygiene can reverse the condition.[11] Gingivitis affects 50−90% of the adult population worldwide.[12] Data on 50-year-olds in Sweden show that gingivitis decreased from 38% in 1973 to 15% in 2013 (Figure 3).[13]

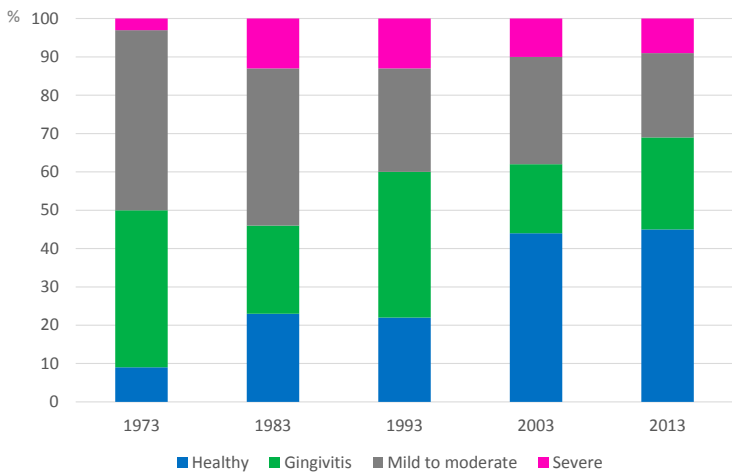

Figure 3. Distribution of all individuals 20–70 years according to periodontal health and periodontal disease experience in Jönköping County, Sweden 1973–2013. Reprinted with permission from Norderyd O et al., Swedish Dental Journal, 2015;39:69-86.[13]

PERIODONTITIS

Periodontitis is characterized by loss of attachment and alveolar bone and the formation of periodontal pockets.[9,10] Periodontitis is diagnosed by clinical and/or radiographic examinations. The most important parameters for the diagnosis are pocket depth ≥4 mm, bleeding on probing of the dental pocket, clinical and radiographic signs of attachment loss, amount of dental plaque, furcation-involved teeth, and tooth mobility.[11] Different classifications of periodontitis have been suggested over the years (Table 1). The current classification is based on the 2017 World Workshop on the Classification of Periodontal and Peri- implant Diseases and Conditions.[14]

Table 1. International consensus criteria for the classification of periodontitis.

Classification according to		Case definition			
Armitage 1999[15] "Development of a Classification System for Periodontal Diseases and Conditions"	**Extent**	Localized	≤ 30% of the sites affected		
		Generalized	> 30% of the sites affected		
	Severity	Slight	1 – 2 mm CAL		
		Moderate	3 – 4 mm CAL		
		Severe	≥ 5 mm CAL		
Page and Eke 2007[16] "Case Definitions for Use in Population Based Surveillance of Periodontitis"		No/mild periodontitis	Not fulfilling criteria for moderate or severe disease		
		Moderate periodontitis	≥ 2 interproximal sites with CAL ≥ 4 mm (not on the same tooth) or ≥ 2 interproximal sites with PPD ≥ 4 mm (not on the same tooth)		
		Severe periodontitis	≥ 2 interproximal sites with CAL ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal sites with PPD ≥ 5 mm (not on the same tooth)		
		Disease Severity and Complexity of Management			
Papapanou et al. 2018[14] "Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and PeriImplant Diseases and Conditions"		**Stage I:** Initial periodontitis	**Stage II:** Moderate periodontitis	**Stage III:** Severe periodontitis with potential for additional tooth loss	**Stage IV:** Advanced periodontitis with extensive tooth loss and potential for loss of dentition
Evidence or risk of rapid progression, anticipated treatment response, and effects on systemic health	**Grade A Grade B Grade C**	Stage (Table 2) Grade (Table 3)			

CAL = clinical attachment level, PPD = periodontal pocket depth

The new classification system adds a multi-dimensional perspective and includes both current status (stage; Table 2) and the risk of disease progression (grade; Tables 3).[14]

Table 2. Periodontitis stage according to the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions.[14]

		Periodontitis stage			
		I	**II**	**III**	**IV**
Severity	**Interdental CAL at site of greatest loss**	1 to 2 mm	3 to 4 mm	≥ 5 mm	≥ 5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤ 4 teeth	Tooth loss due to periodontitis of ≥ 5 teeth
Complexity	**Local**	Maximum probing depth ≤ 4 mm. Mostly horizontal bone loss	Maximum probing depth ≤ 5 mm. Mostly horizontal bone loss	In addition to stage II complexity : Probing depth ≥ 6 mm. Vertical bone loss ≥ 3 mm. Furcation involvement Class II or III. Moderate ridge defect.	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction. Secondary occlusal trauma (tooth mobility degree ≥ 2). Severe ridge defect, Bite collapse, drifting, flaring. Less than 20 remaining teeth (10 opposing pairs).
Extent and distribution	**Add to stage as descriptor**	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

CAL = clinical attachment level

Table 3. Periodontitis grade according to the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions.[14]

			Periodontitis grade		
			A **Slow rate of progression**	**B** **Moderate rate of progression**	**C** **Rapid rate of progression**
Primary criteria	**Direct evidence of progression**	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	< 2 mm over 5 years	≥ 2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	< 0.25	0.25 to 1.0	> 1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g., molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	**Risk factors**	Smoking	Non-smoking	Smoker < 10 cigarettes/day	Smoker ≥ 10 cigarettes/day
		Diabetes	Normoglycemic/ no diagnosis of diabetes	HbA1c < 7.0% in patients with diabetes	HbA1c ≥ 7.0% in patients with diabetes
Risk of systemic impact of periodontitis	**Inflammatory burden**	hsCRP	< 1 mg/L	1 to 3 mg/L	> 3 mg/L
Biomarkers	**Indicators of CAL/bone loss**	Saliva, gingival crevicular fluid, serum			

CAL = Clinical attachment level, HbA1c = Hemoglobin A1c, hsCRP = High sensitivity CRP

One of several reasons for changing the classification of periodontitis was the difficulty of estimating the extent of periodontal destruction in epidemiological studies. The new classification system provides a more detailed understanding of the periodontal destruction and is more suitable for epidemiological research. In this thesis, prevalence data on periodontitis are based on the 1999 International Consensus Report on Periodontitis[15] and case definitions: the Centers for Disease Control and Prevention and the American Academy of Periodontology[16] and the Community Periodontal Index of Treatment Needs.[17]

The prevalence of periodontitis has been estimated at 30−50% but varies considerably between populations.[9] The advanced form, severe periodontitis with a high inflammatory host-response, is less prevalent and has been estimated at 9−11%.[18,19] In Sweden, prevalence has decreased from 13% in 1983 to 9% in 2013 (Figure 3).[13]

The pathogenesis of periodontitis

Periodontitis is a microbially induced, tissue degrading, non-resolving inflammation. It primarily affects the collagen fibers that attach the tooth to the alveolar bone and secondly the bone itself. A pathogenic biofilm is a required precondition for development, but it is insufficient to cause disease.[20] Periodontitis results from an imbalance between a pathogenic biofilm and the inflammatory response of the host, where the inflammatory immune response has a central role (Figure 4).[21]

Periodontitis is influenced by multiple risk factors: some, such as behavioral factors (e.g., smoking) are modifiable; others (e.g., diabetes) are intrinsic; and some are genetic.[9,22,23] Site-specific factors, such as anatomical differences, may also favor disease development.

Interactions between the local inflammatory response and bacterial plaque can induce changes in the biofilm that favor bacterial species, which in susceptible individuals accumulate and make the biofilm more pathogenic.[20,21] This heightens the host response, which may lead to gingival inflammation, gingivitis. The biofilm becomes incipient dysbiotic, and in non-susceptible individuals, the disease develops no further than gingival inflammation.

However, if the individual is susceptible to periodontitis, the incipient dysbiotic biofilm activates a disproportional host response, increasing the release of proinflammatory cytokines, reactive oxygen species, and tissue-degrading proteases. Periodontal tissue degradation and chronic inflammation then result. This chronic inflammatory state is characterized by efforts to heal, (angiogenesis and fibrosis), all the while inflammation is actively sustaining dysbiosis in the pathogenic biofilm. If the biofilm is not disrupted or removed, frank dysbiosis will perpetuate chronic (non-resolving), destructive inflammation. To resolve this progressing periodontitis, the biofilm must be eliminated though intervention, so that health-promoting microbial species can be re-established and initiate a reduction in inflammation.[21]

CARDIOVASCULAR DISEASE

Cardiovascular disease, a common term for heart and vascular disorders related to atherosclerosis, is a major global health problem.[24] Globally, cardiovascular disease is the leading cause of death; it is decreasing in the Western world but on the rise in developing countries.[25]

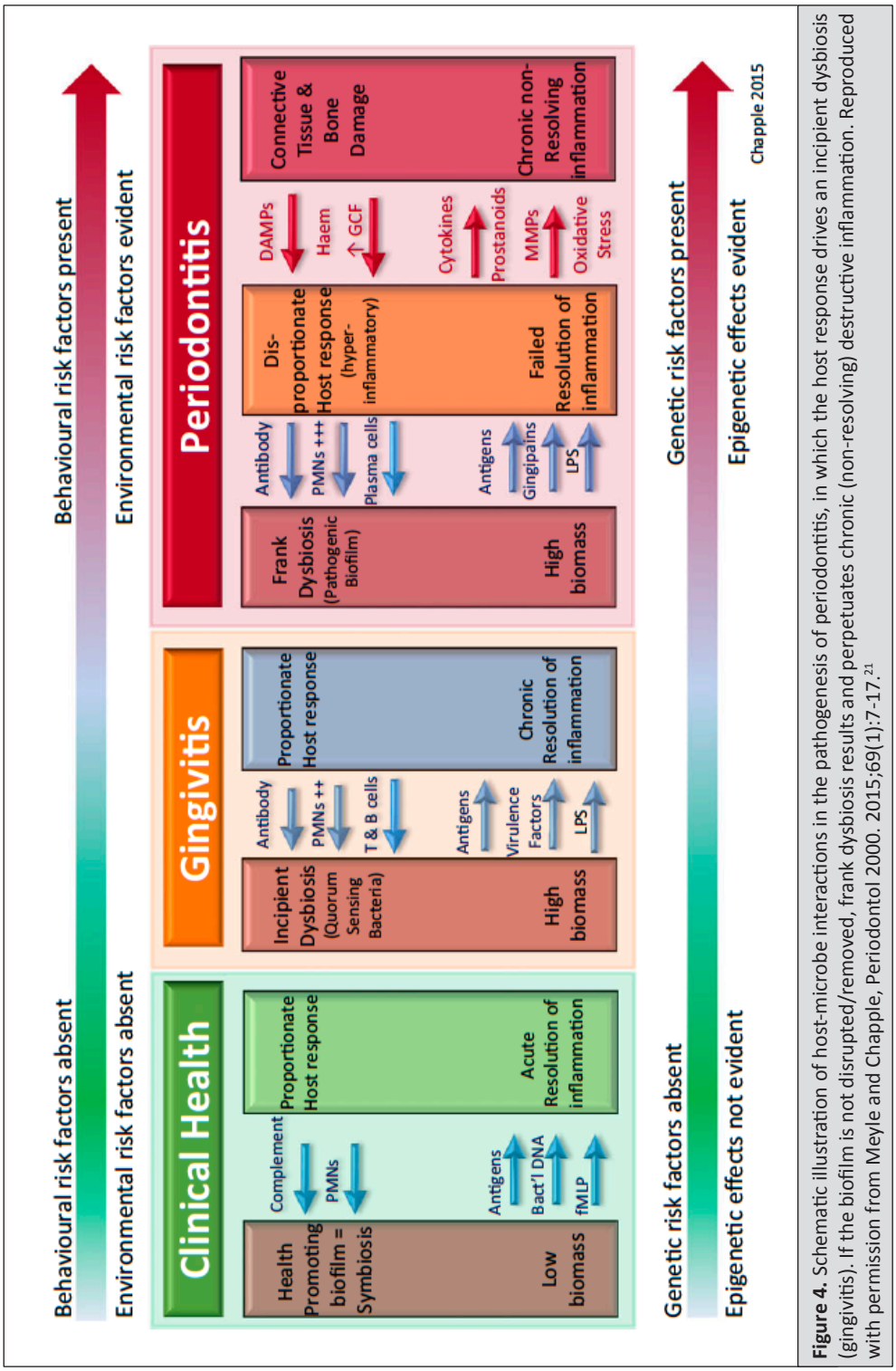

Figure 4. Schematic illustration of host-microbe interactions in the pathogenesis of periodontitis, in which the host response drives an incipient dysbiosis (gingivitis). If the biofilm is not disrupted/removed, frank dysbiosis results and perpetuates chronic (non-resolving) destructive inflammation. Reproduced with permission from Meyle and Chapple, Periodontol 2000. 2015;69(1):7-17.[21]

In 2015, an estimated 423 million people worldwide suffered from cardiovascular disease; 18 million died from the disease, with 7.3 million deaths due to myocardial infarction.[24] In Europe, 2.2 million women and 1.8 million men died from cardiovascular disease, accounting for 49% and 40% of all deaths in women and men.[26] Men, however, are more often affected earlier in life compared to women. Myocardial infarction is responsible for the majority of deaths due to cardiovascular disease.[24] In 2017, approximately 26,000 individuals suffered from a myocardial infarction in Sweden; 15% were fatal within the first 28 days, and 4% were below the age of 50 years.[27] Figure 5 illustrates the trends in myocardial infarction incidence and mortality in Sweden during 2002−2017, dichotomized for women and men. As the INTERHEART study describes, risk factors for myocardial infarction are similar around the world.[28] Based on 29,972 cases and controls from 52 countries, it was shown that nine modifiable factors could explain 90% of all myocardial infarction in men and women. Six were risk factors (smoking, hypertension, elevated apolipoprotein B, abdominal obesity, psychosocial stress, and diabetes) and three were protective factors (physical activity, moderate consumption of alcohol, and high proportions of vegetables and fruit intake).

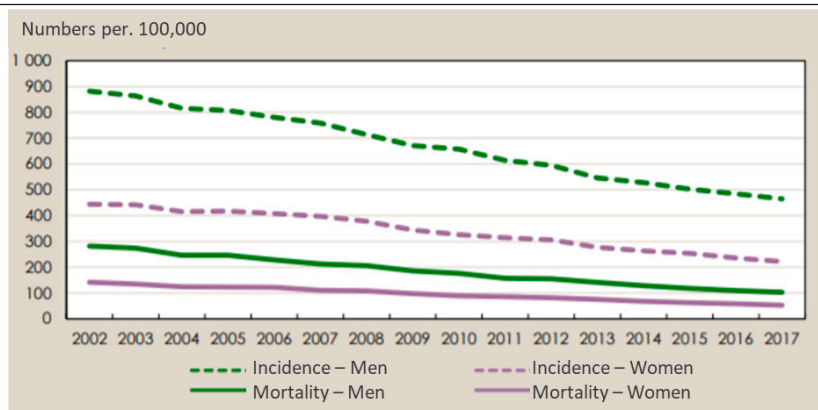

Figure 5. Incidence and number of deaths due to myocardial infarction in Sweden 2002-2017, dichotomized for women and men. Adapted with permission from The Swedish National Board of Health and Welfare.[27]

The pathogenesis of atherosclerosis

Atherosclerosis begins early in life but progresses slowly, thus clinical symptoms are rare before 40 years of age. Though it has been well established that inflammation plays a central role in the pathophysiology of the disease, the underlying biological mechanisms of its development are still not fully clarified.[29,30]

During early development of atherosclerotic plaque, various factors activate the endothelial cells of the vessel wall; one of these factors is low-density lipoprotein (LDL).[31] LDL particles attach to glucosaminoglycans in the intima region of the vessel wall and become oxidized. Oxidized LDL activates the endothelium, whereby molecules are secreted and adhesion molecules expressed. As a result, monocytes and T-lymphocytes, which normally resist attachment to arterial endothelial cells, are attracted and attach to the vessel wall.[29] Once the monocytes have entered the artery wall, they differentiate into tissue macrophages and begin to express scavenger receptors, which attach to the oxidized LDL. Macrophages transform into lipid foam

cells by absorbing modified lipoproteins, leading to fatty-streak formation in the vessel intima and further development of the plaque. In the center of the atherosclerotic plaque, a core region is formed by an increase of foam cells and extracellular lipids. The atherosclerotic plaque is surrounded by smooth muscles, including collagen and elastin, forming a fibrous cap, which covers the plaque. Some foam and smooth muscle cells in the plaque die through apoptosis and release lipids that accumulate in the central region of the plaque, which together with cellular debris form a lipid-rich core, called the necrotic core.[30] The atherosclerotic plaque causes the inner surface of the arteries to be irregular and the lumen, narrow, which restricts the flow of blood and eventually causes tissue ischemia and other clinical manifestations.[29-34] In time, areas of the plaque can rupture, and a blood clot forms. If this occurs in the coronary artery, the result can be a myocardial infarction. Figure 6 is a schematic picture of the pathogenesis of atherosclerosis, showing the stages from plaque formation to plaque rupture.

Myocardial infarction

The most common mechanism of a myocardial infarction is atherosclerotic plaque rupture in the coronary artery, resulting in thrombosis and occlusion of the coronary artery. Blood supply is reduced with ensuing ischemia in the myocardium and possibly necrosis.[35] A confirmed

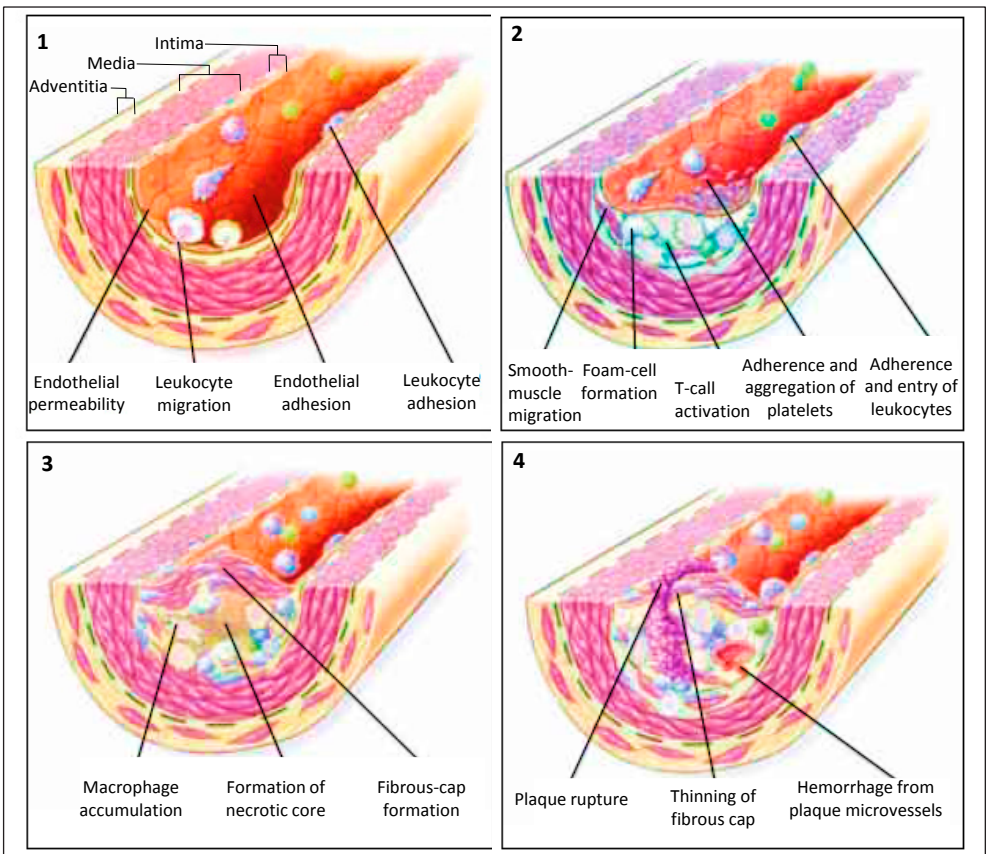

Figure 6. The pathogenesis of atherosclerosis: (1) Endothelial dysfunction, (2) Fatty-streak formation, (3) Formation of an advanced lesion, and (4) Unstable fibrous plaque. Reproduced with permission from Ross, R. N Engl J Med 1999;340(2):115-26, Copyright Massachusetts Medical Society.[30]

myocardial infarction includes one of the following criteria: characteristic electrocardiogram changes, elevated cardiac troponin values or an autopsy-confirmed myocardial infarction, according to joint recommendations from the European Society of Cardiology and the American College of Cardiology in 2000 and 2018, with slight adjustments during the years.[35,36]

An acute myocardial infarction has one of two clinical presentations: an ST-segment elevation myocardial infarction (STEMI) or a non-ST-segment elevation myocardial infarction (NSTEMI). STEMI is caused by more severe ischemia due to acute occlusion of a major coronary artery and will require rapid reperfusion.[35]

Today, there are five types of myocardial infarction, based on pathological, clinical, and prognostic factors. Treatment strategies for the different types varies. Type 1 is the most common form. A type-1 myocardial infarction is designated as an atherothrombotic coronary artery disease, which is usually caused by atherosclerotic plaque disruption (Figure 7). Typical symptoms include central chest pain or discomfort. Symptoms of a myocardial infarction may, however, differ between men and women. Atypical symptoms occasionally predominate and are suggested to be more common in women. These include shortness of breath; pain in the upper back, jaw, or neck; flu-like symptoms; fatigue or weakness; feelings of anxiety; or loss of appetite.[37] Myocardial infarction that is precipitated by an ischemic myocardial injury, due to a discrepancy between oxygen supply and demand, is classified as a type-2 myocardial infarction (Figure 7). When detected at autopsy, cardiac death before biomarker sampling is classified as a type-3 myocardial infarction. Type-4 myocardial infarctions develop in situations related to percutaneous coronary intervention (PCI) or stent complications. Type-5 myocardial infarctions are associated with coronary artery bypass grafting.[35] Acute treatment for myocardial infarction is PCI with stent implantation or if unavailable, thrombolysis.

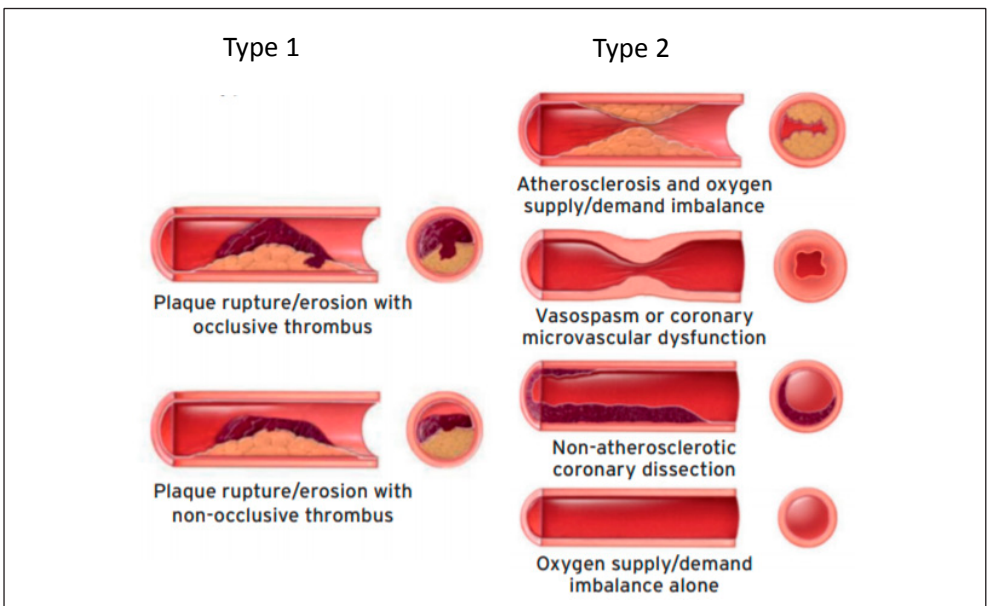

Figure 7. Development of type-1 and type-2 myocardial infarction. Adapted with permission from Thygesen et al., Eur Heart J. 2019;40:237-69.[35]

ASSOCIATION BETWEEN PERIODONTAL AND CARDIOVASCULAR DISEASE

In 1989, Mattila et al. drew new interest to the area when they demonstrated a clear association between myocardial infarction and dental infections.[5] Since then, numerous of epidemiological studies − cross-sectional,[38-46] case-control[5,47-63] and cohort studies[6,64-68] – have reported positive associations between periodontitis and cardiovascular disease. Due to the varying definitions of periodontitis used, results have been difficult to compare. For instance, periodontitis could be reported as clinical findings from a partial-mouth or a full mouth examination, and be measured differently (i.e. attachment loss, pocket depth, tooth loss, or radiographically measured bone loss). Other methodological considerations are varying sizes of study population, different classifications systems of periodontitis, historical controls, only retrospective data, self-reported exposures or outcomes, and inaccurate clinical examination techniques.

Table 4 presents a selection of positive and negative publications based on relatively large study populations. Some of these, however, lack matched controls, some lack information on confounders, and some only include men. Study results diverge; some studies found positive associations between periodontitis and cardiovascular disease that varied from 1.1 to an extreme 14.1 while others found no association. Two meta-analyses,[69,70] based on several of the studies in Table 4,[39,42,43,51,60,64,71-74] found an association between periodontitis and cardiovascular disease where the pooled odds ratio (OR) for cross-sectional and case-control studies varied from 2.22 to 2.35 and relative risk (RR) for cohort studies from 1.14 to 1.34.

In 2012, the American Heart Association concluded that epidemiological studies have demonstrated a correlation between periodontitis and cardiovascular disease, but evidence of a causal relation is lacking.[83] In this context, it is important to remember that a positive association, due to biological mechanisms or simply by shared confounding risk factors, differs from causality (Figure 8). Moreover, despite positive associations, the evidence that periodontal interventions prevent cardiovascular disease has been inconclusive.[84]

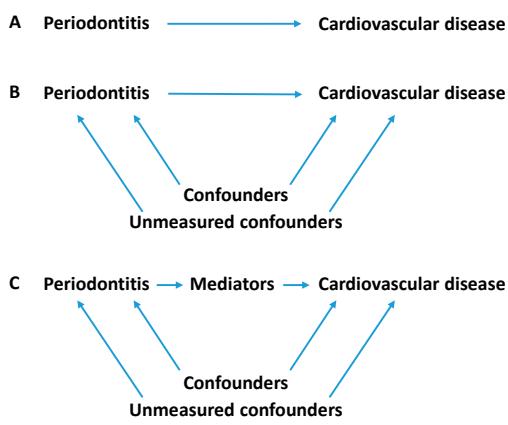

Figure 8. Schematic illustration of a potential causal pathway between periodontitis and cardiovascular disease. (A) A true causal relationship between periodontitis and cardiovascular disease. (B) An association between periodontitis and cardiovascular disease due to an extraneous factor. (C) An association between periodontitis and cardiovascular disease due to a modifying and an extraneous factor. Nordendahl 2019 (unpublished)

Table 4. Overview of observational epidemiological studies on the association between periodontitis and cardiovascular disease.

Authors	Country	Study designs	Study population n (M/W)	Years enrolled	Exposure	Outcome	Adjustments	Measure of association
Beukers et al., 2017[75]	Netherlands	Cross-sectional	60,174 (27,591/32,378) Missing data on gender n = 205	1998–2013	Periodontitis based on diagnostic and treatment codes	CVD	Age, gender, socioeconomic status, smoking, hypertension and hypercholesterolemia	OR for periodontitis in CVD events: 1.59 (1.39–1.81); OR for periodontitis in CVD events in men: 1.61 (1.36–1.91); OR for periodontitis in MI events: 1.60 (1.33–1.92)
Yu et al., 2015[68]	USA	Cohort	39,863 Women	1992-1995	Prevalent periodontitis or incident periodontitis	Major CVD (non-fatal MI, stroke or death from CVD. Total CVD (major CVD, bypass surgery, or percutaneous coronary angioplasty.	Age, race, education, smoking, diabetes, BMI, hypertension, hypercholesterolemia, family history of MI, physical activities and hsCRP	HR for the major CVD events in women with prevalent periodontitis: 1.17 (0.99–1.37); in incident periodontitis: 1.31 (1.01–1.71); HR for total CVD events in women with prevalent periodontitis 1.12 (1.05–1.36); in women with incident periodontitis 1.2 (0.97–1.49); HR for MI events in women with prevalent periodontitis 1.35 (1.05–1.73); for MI events in women with incident periodontitis 1.65 (1.11–2.45)
Jung et al., 2014[76]	South Korea	Cross-sectional	5,359 (2,217/3,142)	2008-2010	Periodontitis (clinical)	Carotid intima–media thickness	Age, gender, smoking, BMI, education, year of survey, diabetes, hypertension, dyslipidemia, high-density lipoprotein, log-transformed triglyceride, total cholesterol, glucose and systolic blood pressure.	OR for moderate periodontitis: 1.17 (0.98–1.38); OR for severe periodontitis: 1.18 (0.97–1.43)
Kodovazenitis et al., 2014[77]	Greece	Case-control	306 (218/88) 204 MI (156/48) 102 Controls (62/40	2007-2009	Periodontitis (clinical)	MI	Age, gender, smoking, hypertension and total cholesterol	OR for missing teeth: 1.08 (1.06–1.13); OR for attachment loss of ≥ 3 mm in two or more nonadjacent teeth: 1.47 (0.45–4.53)
Willershausen et al., 2014[78]	Germany	Case-control	497 (380/117) 248 MI (201/47) 249 Controls 179/70)	2007-2011	Periodontitis (clinical)	MI	Age, gender and smoking	OR for periodontitis: 0.88 (0.53–1.47)

BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio, hsCRP = higher serum C-reactive protein, MI = myocardial infarction, NR = not reported, OR = odds ratio, RR = relative risk

Table 4. (Continued) Overview of observational epidemiological studies on the association between periodontitis and cardiovascular disease.

Authors	Country	Study designs	Study population n (M/W)	Years enrolled	Exposure	Outcome	Adjustments	Measure of association
Yu et al., 2014[46]	China	Cross-sectional	847 (434/413)	2005	Periodontitis (clinical)	Carotid intima–media thickness ≥1.2 mm	Age, gender, smoking family income, education, BMI, waist:hip ratio, diabetes blood lipid level and hypertension	OR for mean attachment loss: 1.08 (0.91–1.28)
Dorn et al., 2010[79]	USA	Cohort	884 (668/216)	1996-2004	Periodontitis (clinical)	Overall CVD (fatal, nonfatal, revascularization)	Age, gender, education, BMI, physical activity, diabetes, hyperlipidemia, diet, statin intake and hypertension	HR for mean attachment level in never-smokers: 1.43 (1.06–1.91); in ever-smokers: 0.99 (0.86–1.15)
Holmlund et al., 2010[80]	Sweden	Cohort	7,674 (3,300/4,374)	1976-2002	Tooth loss; periodontitis (clinical)	CHD and CVD mortality	Age, gender and smoking	CVD mortality: HR for <10 teeth vs >25 teeth: 4.41 (2.47–7.85); HR for severe periodontitis vs no disease: 1.62 (0.59–4.46) CHD mortality: HR for <10 teeth vs >25 teeth: 7.33 (4.11–13.07); HR for severe periodontitis vs no disease: 0.78 (0.27–2.21)
Heitmann and Gamborg 2008[81]	Denmark	Cohort	2,932 (1,474/1,458)	1987-88 and 1993-94	Tooth loss	Fatal/nonfatal CVD and CHD	Age, education, smoking, diabetes, alcohol consumption, BMI and systolic blood pressure	HR (5th vs 1st quintile) for CVD: 1.50 (1.02–2.19); HR for CHD: 1.31 (0.74–2.31)
Senba et al., 2008[82]	Japan	Cross-sectional	29,904 (6,816/23,088)	2004	Self-reported periodontitis or tooth loss	CHD	Age, gender, smoking, BMI diabetes, hypertension and race	OR in men for periodontitis 1.51 (0.90–2.52); for tooth loss of ≥5 teeth: 1.54 (0.90–2.62); OR in women for periodontitis: 1.48 (0.95–2.32); for tooth loss of ≥5 teeth: 1.68 (1.08–2.61)
Starkhammar Johannson et al., 2008[47]	Sweden	Case-control	323 (294/58) 161 CHD (132/29) 162 Controls (133/29)	2000-2003	Periodontitis (clinical/ radiographic)	CHD	Age and smoking	OR 5.74 (2.07–15.90)
Dietrich et al., 2008[67]	USA	Cohort	1,203 Men	1966-2004	Periodontitis (clinical/ radiographic)	CHD	Age, socioeconomic status, smoking, diabetes, BMI, alcohol consumption, marital status, high-density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic and diastolic blood pressure	HR for age <60 y clinical: 1.94 (1.23–3.05); radiographic: 2.12 (1.26–3.60) HR for ages >60 y clinical: 0.73 (0.45–1.19); radiographic: 1.81 (NR)

BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio, hsCRP = higher serum C-reactive protein, MI = myocardial infarction, NR = not reported, OR = odds ratio, RR = relative risk

Table 4. (Continued) Overview of observational epidemiological studies on the association between periodontitis and cardiovascular disease.

Authors	Country	Study designs	Study population n (M/W)	Years enrolled	Exposure	Outcome	Adjustments	Measure of association
Andriankaja et al, 2007[58]	USA	Case-control	1,461 (828/633) 574 MI (443/131) 887 Controls (385/502)	1997-2001	Periodontitis (clinical)	MI	Age, gender, smoking, cholesterol, diabetes, BMI, physical activity, lifetime total pack-years of cigarette smoking	OR for mean attachment loss: 1.46 (1.26–1.69)
Andriankaja et al., 2006[63]	USA	Case-control	1,337 (765/572) 537 MI (414/123) 800 Controls (351/449)	1997-2001	Periodontitis (clinical)	MI	Age, gender, hypertension, diabetes, cholesterol and smoking	OR for 3rd tertile of sites with attachment loss ≥3 mm and pocket depth ≥4 mm: 2.24 (1.60–3.13)
Holmlund et al., 2006[42]	Sweden	Cross-sectional	4,254 (1,866/2,388)	1976-2000	Periodontal bone loss	Self-reported, hospital-treated MI	Age, gender, smoking	OR for bone loss in ages 40–60 only: 2.69 (1.12–6.46); OR for n remaining teeth: 0.80 (0.64–0.96)
Spahr et al., 2006[51]	Germany	Case-control	789 (174/614) 263 CHD (87/176) 525 Controls (87/438)	2000-2002	Periodontitis (clinical)	CHD	Age, gender, smoking, alcohol consumption, diabetes, hypertension, hypolipoproteinemia, education, physical activity, BMI and statin intake	OR for incremental increase in clinical periodontal score by 1 unit: 1.67 (1.08–2.58)
Cueto et al., 2005[60]	Spain	Case-control	149 (89/60) 72 MI (50/22) 77 Controls (39/39)	2002	Periodontitis (clinical; partial recording)	MI	Age, gender, smoking, hypertension, diabetes, hypercholesterolemia and physical activity	OR for moderate or severe periodontitis: 3.31 (1.42–7.71)
Buhlin et al., 2002[39]	Sweden	Cross-sectional	1,577 (NR)	1998	Self-reported oral status	Self-reported CVD	Unadjusted	Total CVD events: OR for bleeding gums: 1.60 (1.19–2.15); OR for loose teeth: 0.96 (0.62–1.48); OR for deep pockets: 1.08 (0.78–51); MI events: OR for bleeding gums: 0.55 (0.22–1.36); OR for loose teeth: 0.98 (0.32–3.04); OR for deep pockets: 1.32 (0.51–3.38)

BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio, hsCRP = higher serum C-reactive protein, MI = myocardial infarction, NR = not reported, OR = odds ratio, RR = relative risk

Table 4. (Continued) Overview of observational epidemiological studies on the association between periodontitis and cardiovascular disease.

Authors	Country	Study designs	Study population n (M/W)	Years enrolled	Exposure	Outcome	Adjustments	Measure of association
Persson et al., 2003[73]	Sweden	Case-control	160 (138/22) 80 MI (68/12) 80 Controls (70/10)	(NR)	Periodontitis (radio graphical)	MI	Smoking	OR for periodontitis: 14.1 (5.8–34.4); OR for non-smoker for periodontitis: 7.0 (2.0–24.3)
Tuominen et al, 2003[74]	Finland	Cohort	6,527 (3,091/3,436)	1978-1980	Periodontitis (clinical); tooth loss	CVD mortality	Age, education, hypertension, hypercholesterolemia, smoking and diabetes	RR for tooth loss in men: 0.9 (0.5–1.6); in women: 0.3 (0.1–1.0); RR for periodontitis in men: 1.0 (0.6–1.6); in women: 1.5 (0.6–3.8)
Howell et al., 2001[72]	USA	Cohort	22,071 Men	1982-1995	Self-reported Periodontitis	MI CVD mortality	Age, aspirin, β-carotene treatment, smoking, alcohol consumption, hypertension, BMI, diabetes, physical activity, family history of MI and history of angina	RR for MI: 1.01 (0.82–1.24); RR for CVD mortality: 1.00 (0.79–1.26)
Arbes et al., 1999[43]	USA	Cross-sectional	5,564 (2,757/2,807)	1988-1994	Periodontitis (clinical)	Self-reported MI	Age, race, gender, socioeconomic status , smoking, diabetes, hyperlipidemia, hypertension and BMI	OR for highest vs lowest extent of attachment loss: 3.77 (1.46–9.74)
Beck et al., 1996[6]	USA	Cohort	1,147 Men	1968-1992	Periodontitis (clinical/radiographic)	Incident CHD	Age, hyperlipidemia, hypertension and BMI	Incidence OR for those with bone loss: 1.5 (1.04–2.14); Incidence OR for those with pockets >3 mm at all their teeth: 3.1 (1.30–7.30)
Joshipura et al., 1996[71]	USA	Cohort	44,119 Men	1986-1992	Self-reported oral health status	Incident CHD	Age, smoking, BMI, alcohol consumption, physical activity, family history of CVD and current access to dentist	RR in those with periodontitis: 1.04 (0.86–1.25); RR among those reporting periodontitis and ≤10 teeth: 1.67 (1.03–2.71)
DeStefano et al, 1993[64]	USA	Cohort	9,760 Men	1971-1986	Periodontitis (clinical)	Incident fatal and nonfatal CHD	Age, race, gender, socioeconomic status, smoking, diabetes, hyperlipidemia, hypertension, BMI, alcohol consumption and physical activity	RR for gingivitis: 1.05 (0.88–1.26); RR for periodontitis: 1.25 (1.06–1.48); RR for edentulous: 1.23 (1.05–1.44)

BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazard ratio, hsCRP = higher serum C-reactive protein, MI = myocardial infarction, NR = not reported, OR = odds ratio, RR = relative risk

POSSIBLE EXPLANATIONS FOR AN ASSOCIATION BETWEEN PERIODONTITIS AND CARDIOVASCULAR DISEASE

Some well-established risk factors for cardiovascular disease are also risk factors for the development of periodontitis and are described below.

Smoking

The harmful effects and prognostic implications of smoking on periodontitis and cardiovascular disease are well documented, and smoking is likely the strongest risk factor for both diseases.[23,28,85-88]

The biological effects of smoking on the oral environment are not fully understood. However, it is established that smoking affects inflammatory and immunological responses and the healing potential of periodontal connective tissue.[89]

A 10-year prospective study reported a lower level of periodontal health in smokers compared to non-smokers.[85] Studies have consistently shown both higher prevalence and greater severity of periodontitis in smokers compared to non-smokers.[86,90,91] A recent meta-analysis has further highlighted the increased risk of periodontitis in smokers − an 85% higher risk.[92] The INTERHEART study concluded that smoking is the one, most important factor in the development of myocardial infarction globally.[28] They reported a resilient and graded relation between number of smoked cigarettes and risk of myocardial infarction. Reducing or quitting smoking could lower the risk of a myocardial infarction by as much as, or more than, three-quarters.[93] In men, smoking was associated with a 43% risk of myocardial infarction compared with 15% in women; however, smoking has also been documented to be more harmful in women than men aged 65 years and under.[28,94]

Diabetes mellitus

Diabetes mellitus (diabetes) is a well-established risk factor for both periodontitis and cardiovascular disease. The incidence of diabetes is higher in patients with periodontitis and patients with diabetes appear to have more severe periodontitis.[95-98]

Diabetes is a metabolic disorder caused by reduced insulin secretion and/or reduced insulin sensitivity, resulting in hyperglycemia. The disease is associated with macro- and microvascular complications, which compromises wound healing. In the oral cavity, high glucose levels potentially impact the microbiota, reduce defenses, and make wound healing difficult, increasing the risk of deeper pockets and more severe periodontitis.[99,100] Additionally, periodontal inflammation increases levels of systemic proinflammatory biomarkers, which aggravates insulin resistance.[95,96]

Due to impaired vascular circulation and accelerated macro- and microangiopathy, diabetes is an important risk factor for cardiovascular disease.[101,102] Diabetes has been associated with a 2−4-fold higher risk of myocardial infarction,[28,103,104] and a worse outcome of myocardial infarction, especially in women younger than 65 years.[105-107]

Socioeconomic status

It has been suggested that low education and low socioeconomic status are related to the development of periodontitis.[108-111] However, whether the socioeconomic status itself

increases the risk or if it is only a risk indicator is uncertain. A systematic review on socioeconomic status, including income, occupation, education, unemployment, social class, living conditions, and race, reported that if the results were adjusted for smoking, the increased risk of periodontitis disappeared.[112] This indicates that this risk factor is more of an risk indicator. In contrast, a Swedish cross-sectional study reported an association between low socioeconomic standards and oral health. The economic situation was worse in patients with severe periodontitis and a third of the patients had avoided dental care in the last year.[111] Socioeconomic factors influence the risk of developing cardiovascular disease.[113] Data from the Women's Health Study shows that the RR of incident cardiovascular disease events decreased with increasing education and income.[114] One possible explanation is that individuals with low socioeconomic status have lifestyles that include lower use of health care, chronic stress, and environmental and behavioral issues. In addition, the prognosis after myocardial infarction is worse for those with lower socioeconomic status.[115]

Gender

The prevalence of periodontitis has been reported to be more common in men compared to women.[23,116] Gingival inflammation and bleeding, as well as higher levels of plaque and calculus, have been more frequently reported in men. However, attitude and lack of good oral health behavior have been suggested to be the likely explanation for this difference.[23] A meta-analysis of gender differences for periodontitis found that men seem to be at a higher risk of developing the disease. However, men seem to have the same risk as women for severe destruction of the periodontium.[117]

Women suffer from their first myocardial infarction approximately 10 years later in life than men with increasing incidence after menopause.[88,94] Several pathophysiological explanations have been proposed, and the protection of estrogen is regarded as a major component.[118] Other factors after menopause are adverse lipid profile and hypertension.[94,119] Despite this, some women experience a myocardial infarction before menopause; the mechanisms for this are not completely understood.[106]

SUGGESTED MECHANISMS OF THE POTENTIAL CAUSAL RELATIONSHIP BETWEEN PERIODONTITIS AND CARDIOVASCULAR DISEASE

Several pathophysiological mechanisms between periodontitis and cardiovascular disease have been suggested.[120] The two pathways that dominate the discussion are described below: (1) An indirect link whereby the actions of periodontal bacteria induce local inflammation, which leaks proinflammatory mediators into the systemic circulation and gives rise to systemic inflammation, and (2) A direct link whereby periodontal bacteria and bacterial products spread throughout the body via the bloodstream.

The indirect link suggests that individuals with periodontitis have a hyper-inflammatory response, characterized by increased plasma levels of proinflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-alpha.[121] These cytokines promote the atherosclerotic process in the vessel wall, whereby the inflammatory response encourages the aggregation and adhesion of platelets, activates leukocytes, and attracts cholesterol.[29,32] The

periodontal inflammatory lesion also causes release of lipopolysaccharides. This activates the endothelial function to express more adhesion molecules, which then attract monocytes and results in the formation of foam cells (Figure 9).[120,122-125]

The suggestion of a direct link is based on the theory that periodontal pathogens actually reach systemic circulation and enter the endothelium of the vessel wall. Once in the endothelium, it is suggested that the pathogens heighten defense reactions via an inflammatory response, which attracts even more immune cells and induces the migration of foam and smooth muscle cells; the atherosclerotic plaque core continues to grow while the surrounding fibrous cap thins.[120,126] Deoxyribonucleic acid (DNA) from oral pathogens has been found in atherosclerotic plaque.[127-129] However, studies have yet to demonstrate that bacteria induce plaque formation.

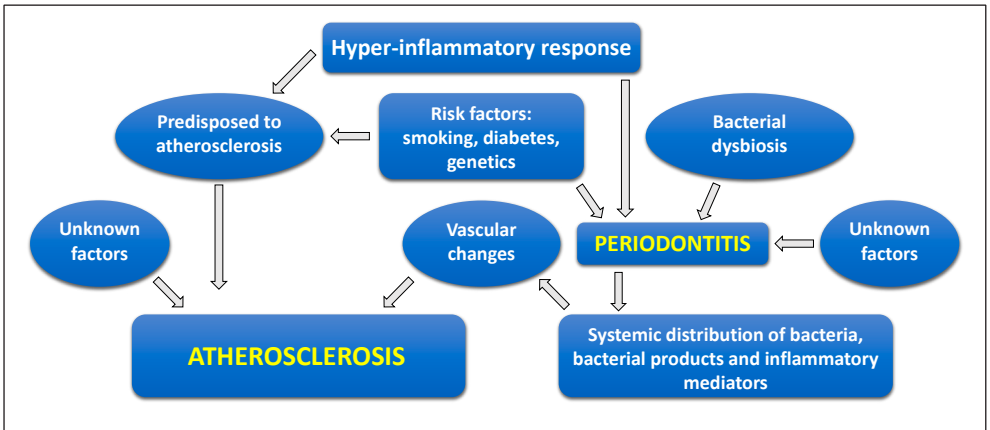

Figure 9. Flow chart illustrating potential associations between periodontitis and cardiovascular disease. An individual with a hyper-inflammatory response, in combination with bacterial dysbiosis and the presence of risk factors, is more prone to develop periodontitis. Periodontitis leads to a systemic spread of bacteria, which may cause vascular changes, and increase the risk of developing atherosclerosis. Nordendahl 2019 (Unpublished)

PERIODONTAL INTERVENTION AND CARDIOVASCULAR DISEASE

How periodontal treatment affects the development of cardiovascular events or their complications is still unclear. Intervention studies have used surrogate markers for, periodontitis such as inflammatory markers and markers of subclinical cardiovascular disease.[38,44,130-132] Studies have shown that periodontal treatment decreases levels of inflammatory markers such as interleukin-6, fibrinogen, total cholesterol and high sensitivity C-reactive protein (hsCRP)[133-135] and improve endothelial function. Until now, only one multicenter pilot study has investigated the effects of periodontal intervention on secondary prevention of cardiac events, the Periodontitis and Vascular Events (PAVE) study.[136,137] Patients with periodontitis and a history of cardiovascular disease (angiographically proven coronary artery disease or recent myocardial infarction or surgical or PCI revascularization) were randomized to community dental care or a special program including oral hygiene instructions and nonsurgical periodontal intervention. At the 25-month follow-up, there was no significant difference

between the groups in occurrence of adverse cardiovascular events or in the results of the periodontal intervention after one year. One suggestion as to why there was no difference between the groups was that the group attending community dental care received additional periodontal therapy outside the study. A Systematic Cochrane review from 2017 concluded that the evidence was inadequate to support the theory that periodontal intervention can prevent the recurrence of cardiovascular disease in patients with periodontitis.[84]

ORAL INVASIVE TREATMENT AND CARDIOVASCULAR DISEASE

The microflora in the oral cavity consists of more than one thousand bacterial species.[138] Bacteremia originating in the oral cavity may occur when bacteria penetrate the ulcerated epithelia of pathological periodontal pockets or from bacterial invasion in damaged tissue after dental extraction. Invasive oral treatment has been suggested to lead to an acute inflammatory response.[139] Furthermore, it has been described that bacteremia occur after dental extractions, although short-lived.[140,141] Whether such bacteremia after dental procedures may have an impact on the development of cardiovascular disease is not clear. However, there are indications that after general surgery, bacterial infections and acute inflammation are associated with a short-term increased risk of developing vascular events.[142] The knowledge about immune inflammatory and stress response in relation to invasive dental procedures is sparse. In a prospective intervention study inflammatory markers (interleukin-6 and hsCRP) increased 24 hours after intensive periodontal therapy.[131] After one week, all inflammatory markers were normalized, indicating that the inflammatory response might be transient. Another study presented an increased risk of vascular events during the first four weeks after an invasive dental procedure, however when only analyzing events of myocardial infarctions, there was no increased association.[139]

SUMMARY AND GAPS IN KNOWLEDGE

The association between periodontitis and myocardial infarction is still not fully understood. The amount of research into this association is vast, but of varying quality, mainly due to methodological considerations. Furthermore, impact of gender, is less explored.

In Sweden, where medical health and dental care hold high standards and where nationwide registry data on cardiovascular disease and dental care are available, opportunities for studying such research questions are unique compared with many other countries. Access to these national registries also allows the study of how invasive dental treatment affects vascular events in large populations.

AIMS

The general aim of this thesis was to increase our knowledge of the relation between oral health and cardiovascular disease, in particular the association between periodontitis, invasive oral treatment and a first myocardial infarction. Specific aims were to test the hypotheses that:

I. Periodontitis is associated with a first myocardial infarction in a prospective case-control study (*Study I*) and in a nationwide registry cohort (*Study III*), in contemporary settings.

II. The association between periodontitis and a first myocardial infarction differs between men and women (*Study II*).

III. Invasive dental treatment is associated with the incidence of a first myocardial infarction (*Study IV*).

MATERIALS AND METHODS

STUDY DESIGN

Table 5. Descriptions of the four studies in this thesis.

	Study I	Study II	Study III	Study IV
Study design	Multicenter case-control with prospective data PAROKRANK	Multicenter case-control with prospective data PAROKRANK	Registry-based case-control	Registry-based case-control
Data source	The PAROKRANK database	The PAROKRANK database	**NBHW:** The IPR, The DHR, The SPDDR, and The Cause of Death register **SCB:** The TPR and LISA	**NBHW:** The IPR, The DHR, The SPDR, and The Cause of Death register **SCB**: The TPR and LISA
Study population	**Cases**: Patients ≤75 years with a first MI admitted to 1 of 17 participating hospitals (n = 805) **Controls:** The TPR matched for age, gender and geographic area, no previous MI (n = 805)	**Cases:** Patients ≤75 with a first MI admitted to 1 of 17 participating hospitals (n = 785) No X-rays were excluded **Controls:** The TPR matched for age, gender and geographic area, no previous MI (n = 792) No X-rays were excluded	**Cases**: Individuals in Sweden with a first MI (n = 51,880) **Controls**: Individuals in Sweden matched 5:1, for age, gender and geographic area, no previous MI (n = 246,978)	**Cases**: Individuals in Sweden with a first MI (n = 51,880) **Controls**: Individuals in Sweden matched 5:1, for age, gender and geographic area and no previous MI (n = 246,978)
Enrollment	2010–2014	2010–2014	2011–2013	2011–2013
Exposure	Periodontitis (Radiographic)	Periodontitis (Radiographic)	Periodontitis (DHR periodontal treatment codes)	Invasive dental treatments (DHR dental treatment codes)
Outcome	A first MI	A first MI	A first MI	A first MI
Adjustments	Matched variables (age, gender, geographic area of residence), diabetes, smoking, education, and marital status	Age, diabetes, smoking, education, and marital status	Matched variables (age, gender, geographic area of residence), diabetes, previous CVD, CVD drug treatment, education, and income.	Matched variables (age, gender, geographic area of residence), diabetes, education, and income.
Statistical tests	Student's t-test, McNemar's test, Wilcoxon signed rank test, conditional logistic regression	Student's t-test, chi-squared test, logistic regression	Student's t-test, chi-squared test, conditional logistic regression	Student's t-test, chi-squared test, conditional logistic regression

CVD = cardiovascular disease, DHR = Dental Health Registry, IPR = National Inpatient Register, LISA = Longitudinal integration database for health insurance and labour market studies, MI = myocardial infarction, NBHW = National Board of Health and Welfare, PAROKRANK = Periodontitis and Its Relation to Coronary Artery Disease study, SCB = Statistics Sweden, SPDR = Swedish Prescribed Drug Register, TPR = Total Population Register

DATA SOURCES

The present thesis investigated two study populations.

S*tudies I* and *II* based their analyses on the Periodontitis and Its Relation to Coronary Artery Disease (PAROKRANK) study cohort data, which was prospectively collected during 2010–2014. The study population comprised patients (*cases*) which were included during hospitalization of a first myocardial infarction, who were admitted to 1 of 17 participating Swedish hospitals (Figure 10), were younger than 75 years of age, and had no heart valve replacement. The controls were chosen from the National Population Registry; were matched by age, gender and geographic area of living (postal code) and free of myocardial infarction and heart valve replacement. Study nurses at the coordinating center (Cardiology Unit, Department of Medicine at Karolinska Institutet) contacted the controls, who were then examined at their local center. The myocardial infarction diagnosis was according to international criteria for acute STEMI or acute NSTEMI.[143,144]

Figure 10. Map of the participating hospitals in Studies I & II: Akademiska sjukhuset, Uppsala; Centralsjukhuset, Karlstad; Centralsjukhuset, Kristianstad; Danderyds sjukhus, Stockholm; Centralsjukhuset, Växjö; Falu lasarett, Falun; Karolinska Universitetssjukhuset, Huddinge; Karolinska Universitetssjukhuset, Solna; Kärnsjukhuset, Skövde; Mölndals sjukhus; Norrlands Universitetssjukhus, Umeå; Sahlgrenska Universitetssjukhuset, Göteborg; Skellefteå lasarett; Södersjukhuset AB, Stockholm; Skånes Universitetssjukhus, Lund; Universitetssjukhuset, Örebro; and Västmanlands sjukhus, Västerås. (Site investigators listed in the original article[61]).

S*tudies III* and *VI* retrieved their data from Swedish national registers, the National Board of Health and Welfare (NBHW), and Statistics Sweden (SCB; Figure 12). The Swedish personal identity number (PIN) makes it possible to link data on an individual in Sweden between the various nationwide registers. The PIN was introduced in 1947 and is assigned to all individuals who have resided in Sweden on a permanent basis at any time.[145] *Studies III* and *IV* used a myocardial infarction diagnosis based on the International Classification of Diseases (ICD-10 code I.21), as recorded in the Swedish National Patient Register (IPR).[146]

Study procedures (Studies I & II)
Study participants fasted and refrained from smoking for 12 hours before their visit at the cardiology department. The physical examination included measurements of heart rate, blood pressure after 5 minutes of rest in a sitting position, height, body weight, and waist circumference. The national quality registry SWEDEHEART[147] was used to collect medical information from the patients at the time of their initial hospitalization (Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions) and at the secondary prevention follow-up (Secondary Prevention after Heart Intensive Care Admission) 6 to 10 weeks after the myocardial infarction. Corresponding information was collected for the control population.

Laboratory measurements
All patients with no known diabetes were administered the oral glucose tolerance test (OGTT; 75 g glucose in 200 mL water). Venous P-glucose was sampled 2 hours after glucose intake while the patient was fasting (point-of care HemoCue 201; HemoCue AB, Ängelholm, Sweden).

Venous blood samples: A local laboratory analyzed complete blood count, phospholipids (total and high-density lipoprotein cholesterol and triglycerides), P-creatinine, P-fibrinogen, P-glucose, and glycohemoglobin A1c (HbA1c).

High-sensitive C-reactive protein: A central laboratory (redhot diagnostics AB, Södertälje, Sweden) carried out the quantitative determination of hsCRP with a functional sensitivity of 0.1 mg/L using an enzyme-linked immunosorbent assay method (MP Biomedicals, New York, NY USA).

Questionnaire: All cases and controls completed a questionnaire requesting information on medical and family history, risk and health preserving factors, and the Montgomery Åsberg Depression Rating Scale.[148]

Dental examination (Studies I & II)
A dentist or a dental hygienist at a local hospital dental clinic examined all study participants according to a standardized procedure. Included in the examination were 28 teeth; third molars were excluded from the examination. Complete or partial dentures and complete implant bridges were classified as removable dentures. A periodontal pocket was considered pathological when the probing pocket depth exceeded 4 mm and was noted as a continuous variable. Gingival inflammation, bleeding on probing, was expressed as the proportion of bleeding sites among all sites in the dentition. Digital or analog panorama radiographs were made of all participants, whether dentate or edentulous.

All panoramic X-rays were sent to the Department of Dental Medicine, Karolinska Institutet Huddinge, for central analysis with ImageJ (Image Tool 3.0, Department of Dental Diagnostics Science, University of Texas Health Science Center, San Antonio, TX): Three trained dentists at the core center made all measurements using a high-resolution computer monitor in a darkened room. The dentists were blinded to the group status (case or control) of the radiograph. Measurements from the marginal bone crest to the tooth apex and from the cementoenamel junction to the tooth apex were made at the site with the most pronounced bone loss for each

tooth with visible cementoenamel junctions and apices (Figure 11); dental implants and third molars were excluded. Total bone height was used to calculate the proportion of remaining bone height for each tooth and determine the arithmetic mean of all examined teeth for each participant.

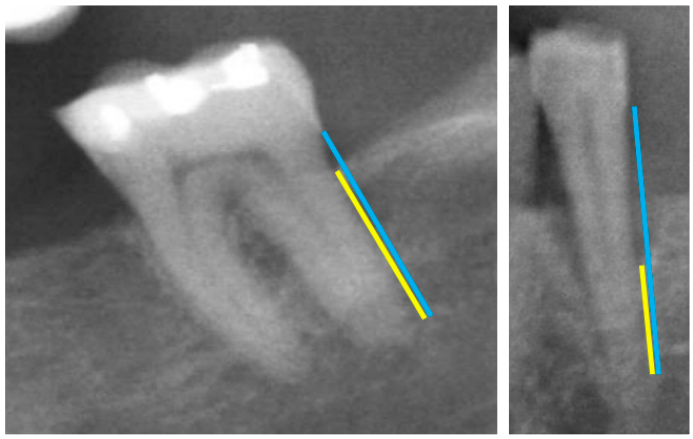

Figure 11. Radiographic measurements from the marginal bone to the tooth apex (yellow line – bone height) and from the cementoenamel junction to the tooth apex (blue line – total root length) for calculating the proportion of remaining bone. Reproduced with permission from Rydén et al, Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study, Circulation. 2016;133:576-83.[61] (Study I)

Based on mean remaining bone height, cases and controls were placed in one of three groups: healthy (≥ 80% remaining bone), mild to moderate periodontitis (79–66%), and severe periodontitis (< 66%). The three dentists were calibrated using 42 randomly selected panoramic X-rays. All three were in full agreement concerning mean remaining bone height on 121 (96%) of the radiographs. The correlation between dentists 1 and 2 was 0.95; between 1 and 3, 0.90; and between 2 and 3, 0.90.

The National Inpatient Register (Studies III & IV)

The NBHW established the IPR in 1964 to manage the collection of nationwide data on somatic inpatient care. [149] In 1987, the IPR achieved complete coverage with collection of data on more than 99% of all somatic and psychiatric hospital discharges. The register classifies diagnoses according to the Swedish International Classification of Disease (ICD, based on the World Health Organization ICD) system.[146,149] The positive predictive value of diagnoses in this register is around 85–95%.

Studies III and *IV* obtained data on first time-registered diagnoses of myocardial infarction for cases and on other health events for all study participants from the IPR. To preserve patient anonymity, the NBHW replaced all PINs with coded serial numbers before releasing the data.

The Dental Health Register (Studies III & IV)

The Dental Health Register (DHR) began collecting data on the dental health of the population in 2008 and administers data on the dental health of all residents aged 19 years and older.

The Swedish Insurance Agency is involved in government reimbursements of dental care providers and administrates data collection.[150] The NBHW, which is the register holder of the DHR, collects information on dental health from the Swedish Insurance Agency. All dental health care providers connected to the dental reimbursement system, approximately 99%, are obligated to report all performed dental treatments electronically.[151]

The DHR contains information on number of remaining teeth, number of intact teeth, diagnoses, and dental treatments. A dental diagnosis is only recorded in the register when it is combined with a performed dental intervention. The Dental and Pharmaceutical Benefits Agency of Sweden sets up the classifications for the diagnoses and dental procedures and determines the level of reimbursement for these procedures.[152]

Through linkage of the PIN to the DHR, *Studies III* and *IV* were able to retrieve information on dental interventions and treatments for all study participants.

Periodontal treatment (Study III)
Periodontal treatment was classified as either non-advanced or advanced. Non-advanced treatment included supra-gingival curettage or non-specific periodontal treatment with a periodontal diagnosis. Advanced treatment included sub-gingival curettage and/or periodontal surgery with a periodontal diagnosis. Four categories of treatment were created based on the treatment and diagnosis codes in the DHR (Appendix 1):

(i) No record of dental treatment.
(ii) No record of periodontal treatment.
(iii) One or more records of non-advanced periodontal treatment.
(iv) One or more records of advanced periodontal treatment.

Invasive dental treatment (Study IV)
Invasive dental treatment was defined as one or more of the following dental procedures registered in the DHR (Appendix 2):

(i) Sub-gingival curettage
(ii) Dento-alveolar surgery and/or tooth extractions
(iii) Implant surgery
(iv) Periodontal surgery
(v) Apical surgery

The Swedish Prescribed Drug Register (Studies III & IV)
The Swedish Prescribed Drug Register (SPDR) was established in July 2005 and is maintained by the NBHW.[153] This register contains data on all dispensed prescription drugs for residents throughout Sweden. Two research groups have validated the SPDR through cross-referencing with patient medical records.[153,154]

S*tudies III* and *IV* obtained information from the SPDR on all dispensed prescription drugs for the study participants.

The Cause of Death Register (Studies III & IV)

The NBHW manages the Cause of Death Register, which has had national coverage since 1952. The Cause of Death Register archives information on the date of death and primary causes of death for all residents in Sweden and deaths of Swedish citizens that occurred abroad.[155]
Studies III and *IV* retrieved information from the Cause of Death Register on the time of death of deceased study participants.

The Total Population Register (Studies III & IV)

The Total Population Register (TPR) is a merger of several national registers; the SCB has maintained it since 1961.[156] The primary mandate of the TPR is to gather information on individuals residing in Sweden, such as birth, marriage, death, change of name, highest educational level, and family relation. This register is a fundamental instrument in epidemiological research in Sweden. Due to indexing with the Swedish PIN, the TPR can be linked with other national registers and is invaluable for identifying controls in studies.

Studies III and *IV* identified potential controls from information provided by the TPR. The control group was formed using risk set sampling, a random selection procedure which included sampling with replacement. The controls were matched at a ratio of 5:1, for age, gender, and geographic area of residence.

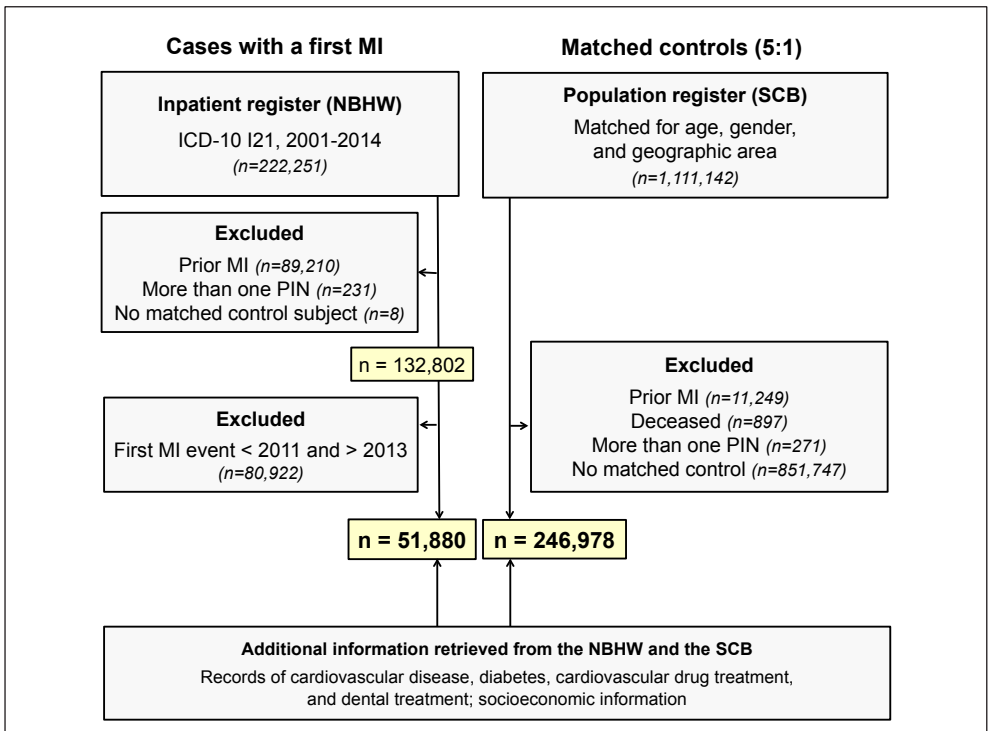

Figure 12. Flowchart of case-and-control selection from registers maintained by The National Board of Health and Welfare (NBHW) and Statistics Sweden (SCB, Studies III & IV). MI = myocardial infarct; PIN = the Swedish personal identity number; ICD-10 121 = International Classification of Disease, Swedish version, code for MI; 2001–2014 = database search of years 2001 - 2014.

The Longitudinal integration database for health insurance and labour market studies – LISA (Studies III & IV)

The Longitudinal integration database for health insurance and labour market studies (LISA) is a database that consolidates information from several national registers. It registers longitudinal data related to the life situation, health, work, and and labour market of residents in Sweden.[157]

Studies III and *IV* procured information from the LISA on cases and controls concerning education level, income, and socioeconomic status.

STATISTICAL METHODS

Studies I and *II* used a power calculation to determine the group size necessary for detecting an increased risk of myocardial infarction with a power of 80% (OR = 1.4). The calculation, based on the first 120 cases and 120 controls, found that 800 cases and 800 matched controls would be needed to detect a difference in myocardial infarction risk with a 95% level of confidence.
Study I used the Student's t-test, a common test for analyzing normally distributed means, to compare the differences between continuous variables. The McNemar test and Wilcoxon signed-rank test were used to compare differences between categorical values. To estimate the effect of the risk on the outcome in a matched study population, a conditional logistic regression modeling was used. Regression analyses investigated whether periodontitis was associated with an increased incidence for a first myocardial infarction after controlling for potential confounders: matched variables (age, gender, and geographic area of living [postal code]), diabetes, smoking, education, and marital status.

In *Study II*, the chi-squared test analyzed differences in categorical variables between cases and controls. The Student's t-test was used to compare differences between continuous variables. *Study II* was a post hoc analysis of data from *Study I*, stratified by gender. Logistic regression modelling analyzed the association between severe periodontitis and a first myocardial infarction. The regression analyses were adjusted for diabetes, previous cardiovascular disease, cardiovascular drug treatment, education, and income.

Studies III and *IV* used the chi-squared test to analyze the differences in categorical variables between cases and controls. The Student's t-test was used to compare differences between continuous variables. In *Study III*, conditional logistic regression modeling analyzed the association between periodontitis, using periodontal treatment as a surrogate marker, and a first myocardial infarction after adjusting for relevant confounders: diabetes, education, and income. In *Study IV*, conditional logistic regression modeling investigated the association between invasive dental treatment and a first myocardial infarction. The regression analyses were adjusted for matched variables (age, gender, and geographic area of residence), diabetes, previous cardiovascular disease, cardiovascular drug treatment, education, and income.

The relative risk estimates are presented as ORs with 95% confidence intervals (CIs); in all four studies, a two-sided p-value of $< 5\%$ was considered significant. *Studies I–IV* used SAS system statistical software (The SAS system for Windows version 9.4, SAS Institute Inc., Cary, NC, USA) for all analyses.

ETHICAL CONSIDERATIONS

The four studies in this research project followed the ethical principals for medical research laid out in the Declaration of Helsinki and were conducted in accordance with current legislation in Sweden. The Regional Ethics Committee in Stockholm approved all studies: *Studies I* and *II* (Daybook no.: 2008/152-31/2) and *Studies III* and *IV* (Daybook no.: 2015/279-31/1). The Swedish Radiation Safety Authority also approved *Studies I* and *II* (Daybook no.: 2/08).

Before enrollment in *Studies I* and *II*, participants gave their written, informed consent to participate in the study. Participants could withdraw from the studies at any time. The risks for the patients and controls in *Studies I* and *II* were small. All investigators and study coordinators were experienced, and the added risks for the individuals participating in the study were considered small. The examinations are well established in clinical practice. Blood sampling and dental examinations can cause minor discomfort. The additional radiation from the X-rays in the study was small, and the Radiation Protection Committee approved the examination. The advantages of the study to the patient included a thorough medical and dental examination that compensates for the relatively small risks. In those cases where a dental or medical condition needed treatment or follow-up, the participants were advised how to proceed.

Data in *Studies III* and *IV* were from Swedish national registers where no informed consent was required from the participants (according to The Patient Data Act 2008:355). Appendices 1 and 2 describe the codes used by the IPR, the SPDR, and the DHR. The NBHW replaced the PIN of each individual with a coded serial number before releasing any information in order to preserve anonymity.

RESULTS

STUDY I

In total, 922 cases were included but 117 withdrew their consent before the study visit. Remaining were 805 cases and 805 matched controls who underwent the study procedures. The ratio of men:women was 81:19; mean age was 62±8 years (Table 6).

Table 6. Clinical characteristics in Study I.

Data are presented as mean ± SD or number (%).Information on pharmacological treatment and smoking habits in patients were registered at the time for hospital admission.

	Cases	Controls	*p*
Characteristics	**n=805**	**n=805**	
Age (years)	62±8	62±8	NS
Men	654 (81)	654 (81)	NS
Family history of CVD	302 (38)	183 (23)	*<.001*
Medical history			
Hypertension	286 (36)	268 (34)	NS
Peripheral artery disease	20 (3)	10 (1)	NS
Stroke	22 (3)	18 (2)	NS
Diabetes	79 (10)	65 (8)	NS
Rheumatic disease	164 (21)	136 (17)	NS
Pulmonary disease	106 (14)	85 (11)	NS
Kidney disease	33 (4)	32 (4)	NS
Cancer	66 (8)	58 (7)	NS
Depression	76 (9)	71 (9)	NS
Pharmacological treatment			
Renin-angiotensin inhibitors	194 (24)	213 (27)	NS
Aspirin	90 (11)	82 (10)	NS
Beta-blockers	116 (15)	106 (13)	NS
Statins	119 (15)	134 (17)	NS
Anti-inflammatory agents (NSAID)	15 (2)	32 (4)	*0.018*
Corticosteroids	26 (3)	30 (4)	NS
Number of Teeth	24±6	25±5	*<0.001*
Smoking habits			
Current	206 (26)	96 (12)	
Previous	286 (36)	361 (45)	*<0.001*
Never	297 (38)	348 (43)	
Waist circumference (cm)	99±11	98±12	NS
Body Mass Index (kg/m2)	27±4	27±4	NS
Blood pressure (mm Hg)			
Systolic	129±17	137±17	*<0.001*
Diastolic	77±10	84±10	*<0.001*

CVD = cardiovascular disease

Clinical characteristics

No significant between-group differences were observed in variables, such as history of hypertension, stroke, rheumatic disease, pulmonary disease, or cancer (Table 6). A family history of cardiovascular disease was more common among cases (Table 6). Cases were more frequently smokers upon admission to hospital, but by the time of the study visit, this difference between groups had disappeared (Table 6). There was no difference in proportions with established diabetes among the groups (cases 10 vs. controls 8%; $p<0.250$; Table 6). After including individuals with newly detected diabetes, 153 (19%) cases and 107 (13%) controls, in the established diabetes group diabetes became more common among cases than controls (9 vs. 5%; $p<0.003$).

Treatment with cardiovascular drugs did not differ between groups at hospital admission (Table 6). By the time of the follow-up, more cases than controls were being treated with cardiovascular drugs, resulting in lower blood pressure and lipids among cases compared to controls.

Socioeconomic factors

Education level and occupation differed non-significantly between groups. Annual household income was significantly lower among cases compared to controls (13 vs 11%; $p<0.048$) and cases were significantly more often divorced (15 vs. 10%; $p<0.046$).

Clinical dental characteristics

Cases had fewer remaining teeth (24±6 vs. 25±5; $p<0.001$; Table 6) and more mild to moderate or severe periodontitis (43 vs. 33%; $p<0.001$) compared to controls (Figure 13).

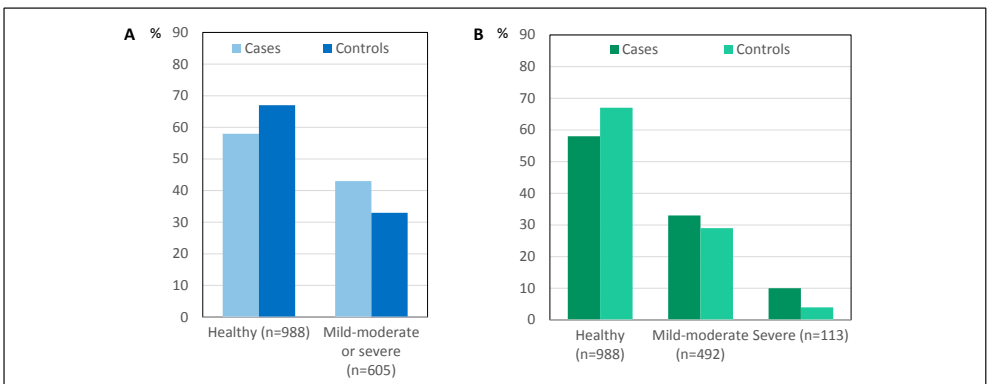

Figure 13. Frequency (%) of periodontal status among the case and control groups. **(A)** Healthy, mild-moderate, and severe. **(B)** Healthy, and mild-moderate or severe. (Study I)

Periodontitis increased the risk of a first myocardial infarction (crude OR 1.46; 95% CI: 1.19−1.80). After adjusting for relative confounders − diabetes, smoking habits, years of education, and marital status − the positive association between periodontitis and myocardial infarction remained (OR 1.28; 95% CI: 1.03−1.60; Figure 14).

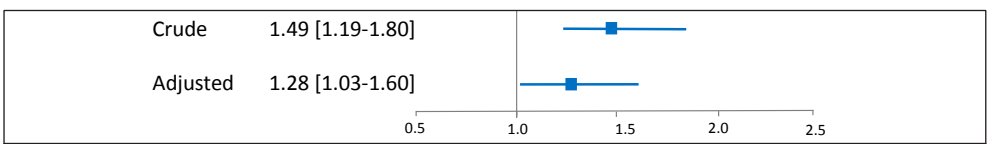

Figure 14. Associated risks (Odds ratios with 95% CIs) between periodontitis and a first myocardial infarction. Adjusted for diabetes, smoking, marital status and education. Cases [458/339] vs. controls [530/266]. (Study I)

STUDY II

Study II stratified the analyses by gender and age. The case-control comparisons for women were 147:147 and for men, 638:645. Mean ages were 64±7 years for women and 62±8 for men (Table 7).

Table 7. Clinical characteristics in Study II of women and men separated by group. Data are presented as mean±SD or number (%). Information on pharmacological treatment and smoking habits in patients were registered at the time for hospital admission.

	Women			Men		
Characteristics	**Case**	**Controls**		**Cases**	**Controls**	
	n= 147	**n=147**	***P***	**n=638**	**n= 645**	***P***
Age (years)	64±7	64±7	NS	62±8	62±8	NS
Family history of CVD	61 (42)	42 (29)	NS	231 (36)	137 (21)	*<.001*
Medical history						
Hypertension	62 (42)	44 (30)	*0.029*	218 (34)	220 (34)	NS
Diabetes mellitus	34 (23)	12 (8)	*<.001*	116 (18)	92 (14)	*0.048*
Pulmonary disease	30 (21)	16 (11)	*0.020*	71 (11)	64 (10)	*NS*
Rheumatic disease	52 (36)	51 (35)	NS	108 (17)	83 (13)	NS
Pharmacological treatment						
Renin-angiotensin inhibitors	14 (10)	12 (8)	NS	89 (14)	86 (13)	NS
Aspirin	23 (16)	10 (7)	*0.015*	65 (10)	69 (11)	NS
Beta-blockers	32 (22)	16 (11)	*0.011*	82 (13)	88 (14)	NS
Statins	31 (21)	21 (14)	NS	85 (13)	110 (17)	NS
Number of teeth	23±5	24±5	NS	24±5	24±5	NS
Smoking habits						
Current/Previous	93 (65)	83 (56)	NS	381 (61)	365 (57)	NS
Never	51 (35)	64 (43)		245 (39)	280 (43)	

CVD = cardiovascular disease

Case-control comparison among women

Women cases had a higher frequency of hypertension, pulmonary disease, and diabetes and were more often being treated with aspirin and beta-blockers compared to controls (Table 7). Severe periodontitis was also more frequent among cases than controls (14 vs. 4%; p=0.005; Figure 15).

Among women, the association between severe periodontitis and a first myocardial infarction was significant (adjusted OR 3.72; 95% CI: 1.24−11.16; Figure 16).

Case-control comparison among women by age group ≤65 and >65 years

In the 65-year and under age group of women, severe periodontitis (16 vs. 3%; p=0.007; Figure 15) and diabetes were significantly more common in cases than controls and statins were more frequently prescribed at admission to hospital for the first myocardial infarction, (Table 8). Among women below 65 years, the association between severe periodontitis and a first myocardial infarction was significant (OR 6.75; 95% CI: 1.46−31.31), and remained after adjustment (OR 5.26; 95% CI: 1.03−26.76; Figure 16).

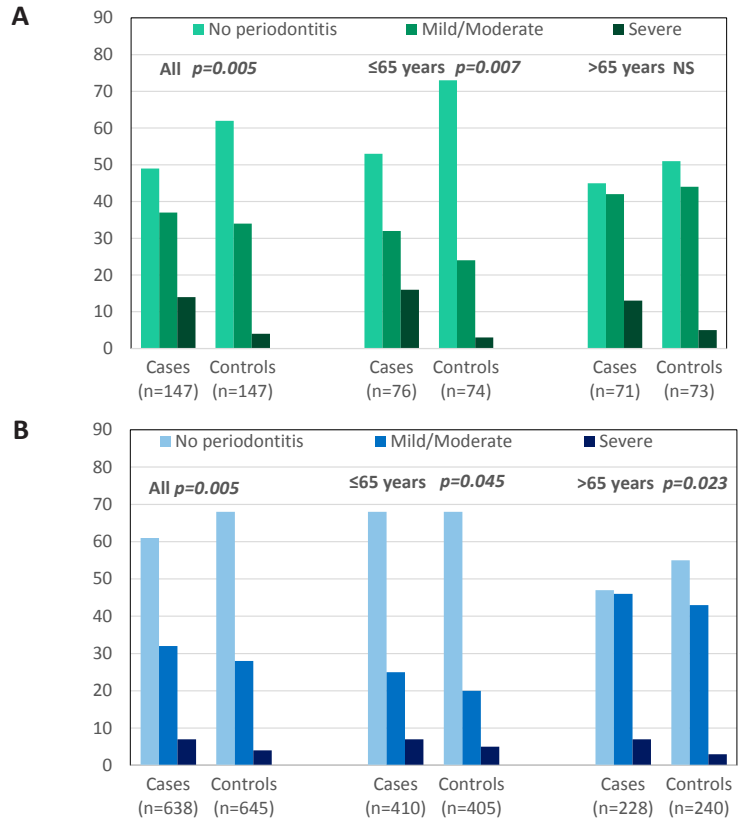

Figure 15. Frequency (%) of periodontal status by gender. **(A)** Women. **(B)** Men. Data are shown for all participants and for participants stratified by age: ≤65 and >65 years.(Study II)

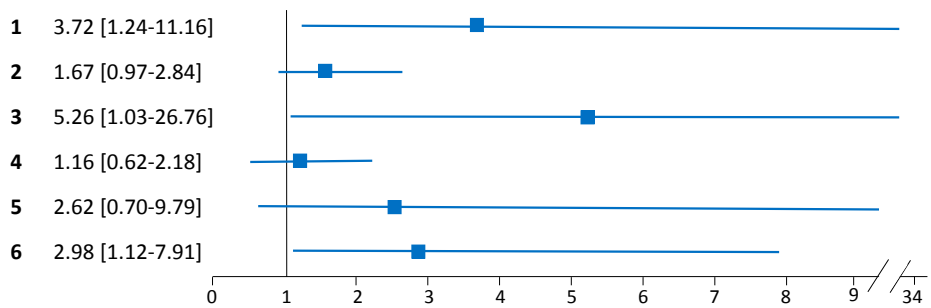

Figure 16. Associated risks (Odds ratios with 95% CIs) between severe periodontitis and a first myocardial infarction by gender and age-groups. All analyses were adjusted for age, smoking, diabetes, education, and marital status. **(1)** Women: cases [126/21] vs. controls [141/6]; **(2)** Men: cases [593/45] vs. controls [620/25]; **(3)** Women ≤65: cases [65/12] vs. controls [72/2]; **(4)** Men ≤65: cases [382/28] vs. controls [386/19]; **(5)** Women >65: cases [62/9] vs. controls [69/4]; **(6)** Men >65: cases [211/17] vs. controls [234/6]. (Study II)

Table 8. Clinical characteristics in Study II of women ≤65 and >65 years separated by group. Data are mean±SD or n (%). Information on pharmacological treatment and smoking habits in patients were registered at the time for hospital admission.

	Women ≤ 65 years of age			Women > 65 years of age		
Characteristics	**Cases n=76**	**Controls n=74**	***P***	**Cases n=71**	**Controls n=73**	***P***
Age (years)	59±6	58±6	NS	69±3	69±3	NS
Family history of CVD	28 (37)	23 (31)	NS	33 (46)	19 (26)	*0.031*
Medical history						
Hypertension	25 (33)	18 (25)	NS	37 (53)	26 (36)	*0.038*
Diabetes	13 (17)	3 (4)	*0.010*	21 (30)	9 (12)	*0.010*
Pulmonary disease	12 (16)	8 (11)	NS	18 (26)	8 (11)	*0.020*
Rheumatic disease	21 (28)	23 (32)	NS	31 (44)	28 (3)	NS
Pharmacological treatment						
Renin-angiotensin inhibitors	4 (5)	4 (5)	NS	10 (14)	8 (11)	NS
Aspirin	7 (9)	5 (7)	NS	16 (23)	5 (6)	*0.008*
Beta-blockers	14 (19)	6 (8)	NS	18 (25)	10 (14)	NS
Statins	18 (24)	5 (7)	*0.004*	13 (18)	16 (22)	NS
Number of teeth	24±5	25±5	NS	22±5	24±5	NS
Smoking habits						
Current/Previous	54 (73)	44 (59)	NS	39 (56)	39 (53)	NS
Never	20 (27)	30 (41)		31 (44)	34 (47)	

CVD = cardiovascular disease

The over 65-year age group of women had a higher frequency of hypertension, diabetes, and pulmonary disease compared to their matched controls (Table 8). Severity of periodontitis did not differ significantly between the two groups (13 vs. 5%; p=0.313; Figure 15). Among women over 65 years, the association between severe periodontitis and a first myocardial infarction was non-significant (adjusted OR 2.50; 95% CI: 0.73−8.54; Figure 16).

Case-control comparison among men

Among men, family history of cardiovascular disease, diabetes and divorce were seen more often among men cases compared to controls (Table 7). Severe periodontitis was more common in men cases compared to controls (7 vs. 4%; p=0.005; Figure 15). Among men, the association between severe periodontitis and a first myocardial infarction was not significant after adjustments (OR 1.67; 95% CI: 0.97−2.84; Figure 16).

Case-control comparison among men by age group ≤65 and >65 years

Among men aged ≤65 years, cases had more of a family history of cardiovascular disease, were more often smoking at the time of hospital admission and divorced or widowed in comparison with men controls (Table 9). The proportion of severe periodontitis was higher among cases compared to controls (7 vs. 5%; p=0.045; Figure 15).

The association between severe periodontitis and myocardial infarction was non-significant between men cases and controls ≤65 years (adjusted OR 1.16; 95% CI: 0.62−2.18; Figure 16).

In the over-65 age group of men, compared to controls, cases had more of a family history of cardiovascular disease and rheumatic disease (Table 9). Severe periodontitis was more frequent among cases compared to men controls (7 vs. 3%; *p*=0.023; Figure 15). Among men over 65 years, the association between severe periodontitis and myocardial infarction was significant (OR 3.14; 95% CI: 1.22−8.12), and remained after adjusting for relevant confounders (OR 2.98; 95% CI: 1.12−7.91; Figure 16).

Table 9. Clinical characteristics in Study II of men ≤65 and >65 years separated by group. Data are mean±SD or n (%). Information on pharmacological treatment and smoking habits in patients were registered at the time for hospital admission.

	Men ≤ 65 years of age			Men > 65 years of age		
Characteristics	**Cases**	**Controls**	***P***	**Cases**	**Controls**	***P***
	n=410	**n=405**		**n=228**	**n=240**	
Age (years)	57±7	58±7	NS	69±3	69±3	NS
Family history of CVD	166 (40)	97 (24)	*<.001*	65 (29)	40 (17)	*0.007*
Medical history						
Hypertension	122 (30)	105 (26)	NS	96 (42)	115 (48)	NS
Diabetes	62 (15)	49 (12)	NS	54 (24)	43 (18)	NS
Pulmonary disease	36 (9)	40 (10)	NS	35 (16)	24 (10)	NS
Rheumatic disease	54 (13)	48 (12)	NS	54 (24)	35 (15)	*0.010*
Pharmacological treatment						
Renin-angiotensin inhibitors	50 (12)	42 (10)	NS	39 (17)	44 (18)	NS
Aspirin	35 (9)	23 (6)	NS	30 (13)	46 (19)	NS
Beta-blockers	48 (12)	38 (9)	NS	34 (15)	50 (21)	NS
Statins	53 (13)	56 (14)	NS	32 (14)	54 (23)	*0.020*
Number of teeth	25±4	26±4	NS	23±6	23±5	NS
Smoking habits						
Current/Previous	249 (62)	222 (55)	*0.036*	132 (59)	143 (60)	NS
Never	152 (38)	183 (45)		93 (41)	97 (40)	

CVD = cardiovascular disease

STUDIES III & IV

The total study population comprised 51,880 cases and 246,978 controls. Nineteen percent (n=10,076) of the cases and 16% (n=40,637) of the controls had no record of dental visits during the study period. Mean ages were 72.6±13.0 years for cases and 72.3±13.0 for controls (Table 10). The gender ratios were 62 (men):38 (women) among cases and 61 (men):39 (women) among controls (Table 10).

Characteristics of cases and controls (Studies III & IV)

Diabetes, fewer teeth, lower education level, and lower income were more frequent among cases than controls (Table 10). Cases with no record of dental treatment during the study period had lower education and a higher frequency of diabetes compared to controls.

Diabetes and previous cardiovascular disease (heart failure, atrial fibrillation, angina pectoris, and stroke) were more common among cases than controls (Table 10). Cases also had more

prescribed cardiovascular drug treatment (antihypertensives, statins, low-dose aspirin, and beta-blockers) than controls (Table 10). Education level and income were lower among cases compared to controls (Table 10).

Periodontal treatments (Study III)

Cases had received more non-advanced periodontal treatment than controls (14.8 vs. 14.6%; $p<0.001$), yet advanced periodontal treatment was more common among controls (19.8 vs. 19.2%; $p<0.001$). The annual frequency of advanced periodontal treatment was higher among cases compared to controls (1.5 vs. 1.4%; $p<0.001$).

Table 10. Clinical characteristics in Study III and IV of cases and controls. Data are presented as mean±SD or number (%), p-values compare cases and controls.

	Cases	Controls	*P*
Characteristics	**n=51,880**	**n=246,978**	
Gender			
Women	19,773 (38.0)	95,342 (39.0)	NS
Men	32,107 (62.0)	151,636 (61.0)	
Mean age (years)	73±13	72±13	*<0.001*
Geographic area[a]			
North	11,834 (22.8)	56,150 (22.7)	
Middle	16,652 (32.1)	79,538 (32.2)	NS
South	23,394 (45.1)	111,290 (45.1)	
Education			
Primary school	22,130 (42.7)	95,432 (38.6)	
High school	20,377 (39.3)	94,333 (38.2)	*<0.001*
College/University	8,204 (15.8)	51,129 (20.7)	
Post graduate degree	338 (0.7)	2,596 (1.0)	
Missing data	831 (1.6)	3,488 (1.4)	
Income (SEK/year)			
≤ 99,000	7,567 (14.8)	3,3328 (13.6)	
100,000-299,000	38,232 (74.5)	178,173 (72.9)	*<0.001*
≥ 300,000	5,508 (10.7)	32,992 (13.5)	
No. of teeth (mean (± SD))	20 (±9)	21 (±8)	*< 0.001*
Comorbidities			
Diabetes[b]	9,931 (19.1)	26,707 (10.8)	*< 0.001*
Type 1[c]	1,181 (2.3)	1,924 (0.8)	
Type 2[d]	8,753 (16.9)	24,899 (10.1)	
Previous CVD	25,374 (48.9)	57,100 (23.1)	*<0.001*
Heart failure	8,265 (15.9)	12,716 (5.2)	*<0.001*
Atrial fibrillation	6,609 (12.7)	23,465 (9.5)	*<0.001*
Angina pectoris	14,102 (27.2)	15,272 (6.2)	*<0.001*
Stroke	6,286 (12.1)	21,754 (8.8)	*<0.001*
Diabetes treatment[e]			
Insulin (A10A)	5,033 (9.7)	10,590 (4.3)	*< 0.001*
Oral (A10B)	6,110 (11.8)	18,821 (7.6)	
CVD drug treatment	35,355 (68.2)	139,054 (56.3)	*<0.001*
Antihypertensive	27,395 (52.8)	104,063 (42.1)	*<0.001*
Statins	14,156 (27.3)	51,871 (21.0)	*<0.001*
Low dose aspirin	17,866 (34.4)	57,143 (23.1)	*<0.001*
Beta blockers	19,552 (37.7)	65,785 (26.6)	*<0.001*

[a]North = counties of Värmland, Dalarna, Gävleborg, Västernorrland, Jämtland, Västerbotten, Norrbotten. Middle = Stockholm, Uppsala, Södermanland, Östergötland, Örebro, Västmanland. South = Jönköping, Kronoberg, Kalmar, Gotland, Blekinge, Skåne, Halland, Västra Götaland.

[b]Diabetes was defined based on the ICD-10 codes, E.10-E.14, or if the history noted a glucose-lowering therapy with an Anatomical Therapeutic Chemical (ATC) code of A10A or A10B. [c]ICD code for type 1 diabetes E10 + ATC code short acting insulin A10AB 6 months before the MI event. [d]Patients who didn't fit the criteria for type 1 diabetes were classified as having type 2 diabetes. [e]regardless of type of diabetes

CVD = cardiovascular disease

In a conditional logistic regression analysis, individuals with no record of dental treatment had an increased risk of a first myocardial infarction (adjusted OR 1.15; 95% CI: 1.12−1.18; Figure 17). In individuals receiving dental treatment, non-advanced periodontal treatment increased the risk of myocardial infarction (adjusted OR 1.06; 95% CI: 1.03−1.09; Figure 17). However, risk of a myocardial infarction did not increase among individuals who underwent advanced periodontal treatment, with or without surgery (adjusted OR 1.02; 95% CI: 1.00−1.05; Figure 17). A high annual frequency of advanced periodontal treatment (≥3 visits for advanced treatment and/or ≥1 periodontal surgery per year) increased the risk of myocardial infarction (crude OR 1.16; 95% CI: 1.02−1.30), but after adjustments, the risk was non-significant (adjusted OR 1.14; 95% CI: 1.00−1.29; Figure 17).

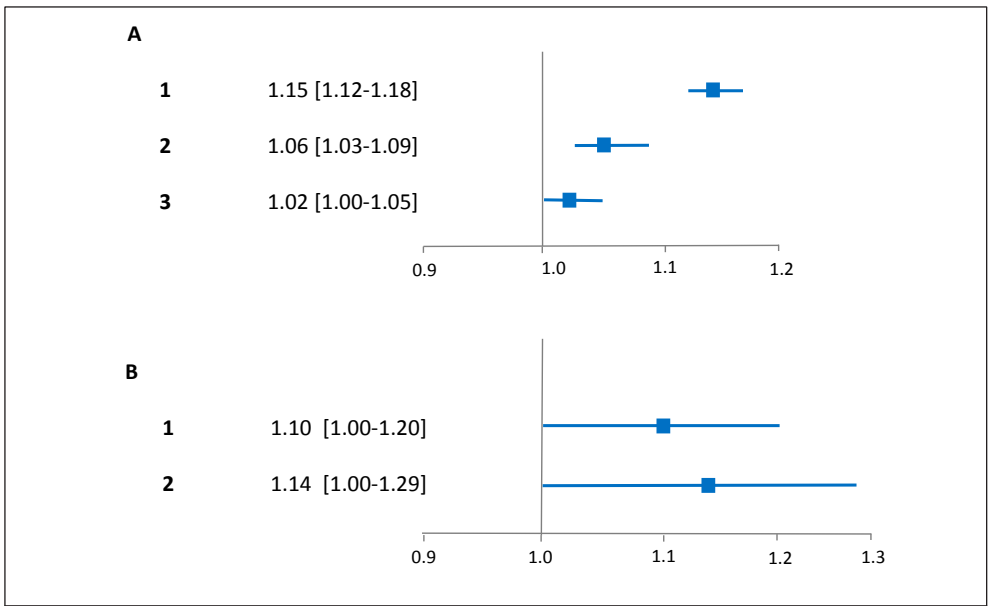

Figure 17. Association between periodontal treatment and myocardial infarction presented as Odds ratios with 95% CIs. All analyses were adjusted for diabetes, income and education.
(A) Periodontal treatment within 3 years, prior to index event. No periodontal treatment was used as reference: cases n=24,174 and controls n=121,467; **(1)** No record of dental treatment: cases [10,076/24,174] vs. controls [40,637/121,467]; **(2)** ≥one non-advanced periodontal treatment: cases [7,686/24,174] vs. controls [35,948/121,467]; **(3)** ≥one advanced periodontal treatment with or without periodontal surgery: cases [9,944/24,174] vs. controls [48,926/121,467].
(B) Number of periodontal treatment per year, prior to index event. One visit with advanced periodontal treatment without periodontal surgery was used as reference: cases n=7,294 and controls n=36,833 ; **(1)** Two visits with advanced periodontal treatment without periodontal surgery: cases [1,656/7,294] vs. controls [7,561 /36,833]; **(2)** Three visits with advanced periodontal treatment with periodontal surgery: cases [773/7,294] vs. controls [3,469/36,833]. (Study III)

Dental treatments (Study IV)

The exposure, dental treatment, was analyzed at three time intervals: 4 weeks, 2 weeks, and 2 days before the index event.

During the *4 weeks* preceding the myocardial infarction, the frequency of invasive dental treatment was similar for cases and controls (1.8 vs. 1.8%; p=0.571; Table 11), the only exception was implant surgery, which was more frequent among cases (Table 11). General dental procedures and interventions; dental examinations, temporary treatments, caries treatment, supra-gingival scaling/prophylaxis, fillings, root canal treatment, and fixed prosthodontics were less frequently performed in cases compared to controls (Table 11).

Invasive dental treatments during the *2 weeks* prior to the myocardial infarction were similar for cases and controls (0.9 vs. 1.0%; p=0.150; Table 11). The frequency of invasive dental treatment performed *2 days* before the myocardial infarction event was lower in cases compared to controls (0.1 vs. 0.2%; p=0.004; Table 11).

Table 11. Dental treatments 4 and 2 weeks, and 2 days before the case patient's myocardial infarction diagnosis and the corresponding index date for control subjects. Data are presented as numbers (%)

Time interval	**4 weeks**			**2 weeks**			**2 days**		
	Cases	**Controls**	***P***	**Cases**	**Controls**	***P***	**Cases**	**Controls**	***P***
Characteristics	n=51,880	n=246,978		n=51,880	n=246,978		n=51,880	n=246,978	
Invasive dental treatments*	**934 (1.8)**	**4,537 (1.8)**	**0.571**	**474 (0.9)**	**2,425 (1.0)**	**0.150**	**70 (0.1)**	**483 (0.2)**	**0.004**
Sub-gingival scaling	492 (52.7)	2,498 (55.0)		246 (51.9)	1,301(53.7)		39 (55.7)	251 (52.0)	
Surgery**	414 (44.3)	1,947 (42.9)		213 (44.9)	1,039 (42.9)		29 (41.4)	210 (43.5)	
Implant surgery	38 (4.1)	115 (2.5)		18 (3.8)	65 (2.7)		1 (1.4)	12 (2.5)	
Periodontal surgery	12 (1.3)	66 (1.5)		5 (1.1)	35 (1.4)		1 (1.4)	8 (1.7)	
Apical surgery	5 (0.5)	29 (0.6)		1 (0.2)	13 (0.5)		1 (1.4)	6 (1.2)	
Other dental treatments									
Dental examination	3,059 (5.9)	16,578 (6.7)	<.001	1,548 (3.0)	8,693 (3.5)	<.001	261 (0.5)	1,759 (0.7)	<.001
X-ray examination	839 (1.6)	4,113 (1.7)	0.434	427 (0.8)	2,159 (0.9)	0.253	67 (0.1)	415 (0.1)	0.045
Temporary treatment	432 (0.8)	2,337 (1.0)	0.014	221 (0.4)	1,206 (0.5)	0.061	38 (<0.1)	251 (0.1)	0.059
Caries treatment	605 (1.2)	3,819 (1.6)	<.001	315 (0.6)	2,008 (0.8)	<.001	48 (<0.1)	410 (0.2)	<.001
Supra-gingival scaling/ prophylaxis	1,084 (2.1)	6,315 (2.6)	<.001	520 (1.0)	3,256 (1.3)	<.001	73 (0.1)	645 (0.3)	<.001
Fillings	1,661 (3.2)	9,369 (3.8)	<.001	862 (1.7)	5,060 (2.1)	<.001	148 (0.3)	1,072 (0.4)	<.001
Root canal treatment	183 (0.4)	1,145 (0.5)	<.001	90 (0.2)	618 (0.3)	0.001	13 (<0.1)	123 (<0.1)	0.016
Fixed prosthodontics	378 (0.7)	1,981 (0.9)	0.085	203 (0.4)	1,049 (0.4)	0.284	31 (<0.1)	220 (<0.1)	0.036
Removable prosthodontics	157 (0.3)	635 (0.3)	0.067	86 (0.2)	335 (0.14)	0.096	14 (<0.1)	65 (<0.1)	0.932
Temporomandibular disorder treatment	18 (<0.1)	90 (0.1)	0.849	6 (<0.1)	52 (<0.1)	0.158	1 (<0.1)	12 (<0.1)	0.357

*Each individual could have more than one recorded procedure **Including tooth extractions

Figure 10 presents the association between invasive dental treatment and a first myocardial infarction. The invasive dental treatments performed *4 weeks* before the myocardial infarction event were not associated with an increased risk of myocardial infarction (adjusted OR 0.98; 95% CI: 0.91−1.06; Figure 18); neither was treatment performed during the *2 weeks* before the myocardial infarction event (adjusted OR 0.92; 95% CI: 0.83−1.02; Figure 18). Treatment performed *2 days* before the myocardial infarction event was associated with a decreased risk of experiencing a myocardial infarction (adjusted OR 0.71; 95% CI: 0.55−0.93; Figure 18).

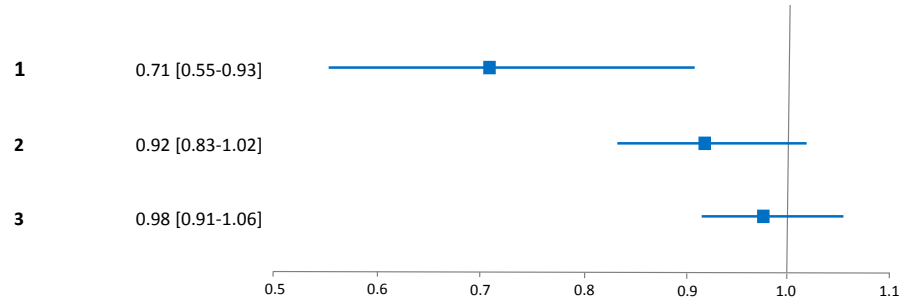

Figure 18. Association between invasive dental treatments before the myocardial infarction diagnosis presented as Odds ratios with 95% CIs. All analyses were adjusted for diabetes, previous cardiovascular disease, cardiovascular drug treatment, education and income. Shown in brackets [cases/controls]. **(1)** 2 days before the myocardial infarction [70/483]; **(2)** 2 weeks before the myocardial infarction [470/2,410]; **(3)** 4 weeks before the myocardial infarction [934/4,537]. (Study IV)

DISCUSSION

Cardiovascular disease and periodontitis, two major global health problems, cause considerable pain and suffering and are substantial burdens on the individual and society. The diseases are closely related, and the most probable link is a leakage of inflammatory mediators from the local periodontal lesion, driving a systemic low-grade inflammation and development of atherosclerosis.[120] Research in this field has been ongoing for over 30 years, but whether this relation is causal is still unclear.[83] To be able to offer men and women who are suffering from periodontitis and cardiovascular disease the best possible treatment, it is fundamentally important to understand the risks and relations.

The major objective of this thesis was to improve our knowledge of the relation between oral health and cardiovascular disease, in particular concerning the association between periodontitis, invasive dental treatment, and myocardial infarction. This was explored by including prospectively collected cases and controls as well as contemporary and large study populations. Even though the results of this thesis allow no definitive conclusion on whether the relationship between periodontitis and cardiovascular disease is causal, the studies were designed to yield results with more comprehensive reliability compared to previous reports.

Study I concluded that periodontitis is a risk factor for myocardial infarction (OR 1.28) based on objectively verified radiographic bone loss, after adjustment for several confounders. This agrees with previous studies of varying design that have had myocardial infarction as an outcome.[42,43,56,58,60,62,63,68,73,75] One Swedish study reported a higher OR (2.69) when clinical and periodontal bone loss were combined as the exposure.[42] Interestingly, this association was only seen in 40−60-year-old individuals, which is in line with the results of *Study II*: where periodontitis was more strongly associated to a myocardial infarction in women below age 65 (OR 3.72) than in men or older women. Another study reported an even higher OR (3.77) when the exposure was clinically judged attachment loss in a younger population of mean age 55 years.[43] This suggests that the association between periodontitis and myocardial infarction might be higher at younger ages, which would explain the lower OR in *Study I* compared to previous studies and *Study II*. Furthermore, one could speculate if this suggests that severe periodontitis at younger ages reflects a hyper-inflammatory response which could put individuals at an increased risk of developing both periodontitis and atherosclerosis.

Oral health has improved considerably in the last 20 years in Sweden (Figure 3), with a parallel reduction in incidence and mortality of myocardial infarction (Figure 5).[13,27] This is an achievement of a social health care system with high standards in dental care and secondary prevention programs for cardiovascular disease.[158] In epidemiological studies, one important factor appears to be the years of enrollment of the patients, which seems to affect the relationship between periodontitis and cardiovascular disease. Stronger associations have been reported by earlier studies[42,43,47,60,62,63,73] while more recent studies such *Study I* and others more often report a less strong or no association.[75-78] Two studies conducted in high-income countries where patients were enrolled in 2007−2009 reported no associated risk.[77,78] However, several methodological shortcomings might explain their results, for example, there was no matched control population and the definitions of periodontitis were vague. It is, however, interesting to speculate whether the association between the diseases is decreasing compared to reports from earlier studies.

The lack of association in *Study III* and the rather low OR in *Study I* could be a result of improving health trends and may explain the lower association compared to older data.[42,43,47,60,62,63,73] Thus, if the results of *Studies I* and *III* accurately reflect the association between severe periodontitis and myocardial infarction in a contemporary Swedish setting, the results emphasize the importance of access to both preventive dental care and preventative cardiovascular care. The results of *Studies 1* and *III* might not be generalizable to populations with other types of health care systems.

Study III did not confirm an association between periodontitis and myocardial infarction. This was unexpected and surprising, since *Study III* included over 50,000 cases during the same time period as *Study 1*. Several possible explanations for this discrepancy come to mind. Firstly, *Study III* used a surrogate marker for periodontitis, a procedure code for periodontal treatment, that had not been previously validated. This treatment code was chosen as the exposure since it was the best available national registry code with information on periodontitis. However, it must be noted that these registry codes have not been validated against patient records. There is a risk that individuals who actually did not have periodontitis were given periodontal treatment and *vice versa*, thus diluting the OR toward null. Secondly, *Study 1* might have introduced a selection bias towards more healthy controls, since those with worse oral health might have declined participation to a larger extent, thus strengthening the association. However, looking at *Study III* data again, cases with a high annual frequency of advanced periodontal treatments in combination with periodontal surgery presented a slightly increased risk of myocardial infarction (OR 1.14). Even though this result was non-significant, it indicates that an association might still be present in individuals with a severe level of periodontitis. *Studies I* and *II* present the level of periodontitis differently; *Study I* combined moderate to severe periodontitis, and *Study II* presented severe periodontitis only, indicating that severe periodontitis is a greater risk factor.

S*tudy II* found a strong association between severe periodontitis and myocardial infarction in women (OR 3.72) and an even stronger association at ages below 65 years (OR 5.26). The corresponding associations in men were lower. These findings are novel since gender aspects in the relation of periodontitis and cardiovascular disease are sparely studied. Women experience myocardial infarction later in life, and because upper age limits are often utilized to avoid a multiplicity of concomitant disorders, women are less represented in studies.[28,88,94] One study investigating both women and men found clinical attachment loss to be more associated with a myocardial infraction in women (OR 2.08) compared to men (OR 1.34), supporting the findings in *Study II*.[58] In the Women's Health Study, a large prospective cohort study, myocardial infarction events were more common in women with self-reported periodontitis.[68] In *Study II*, the associated risk was more obvious in women (OR 3.72) than in men (OR 1.67), and was only present in women 65 years or younger. One explanation for a stronger association in women than in men might be due to gender differences in susceptibility to risk factors. Diabetes is known to affect men and women differently thereby increasing the risk for myocardial infarction more in women than in men.[28,88,119] Perhaps this is also true for severe periodontitis, and needs further investigation. Surprisingly, there were no differences in smoking habits between cases and controls among women or among men in *Study II.* This rules out smoking as an explanatory reason for the association between severe periodontitis and myocardial infarction in *Study II*. Diabetes, on the other hand, was more common in all cases regardless of gender, and in all four S*tudies* (*Studies I–IV)* compared with the controls. This indicates that diabetes is an

important risk factor to periodontitis and myocardial infarction and emphasizes that individuals with diabetes need special attention. A limitation in *Study II* was the low number of included women, and the gender-related results might thus be coincidental. As already discussed, the findings that severe periodontitis seems to be a stronger risk factor at younger ages in women could perhaps reflect a susceptible individual with a hyper-inflammatory response, and with an increased risk of developing periodontitis and atherosclerosis.

Invasive dental treatments, such as dental extraction and sub-gingival curettage, are routinely performed in dental practice. *Study IV* found no evidence for an increased risk of a first myocardial infarction after invasive dental procedures. Experimental clinical evidence linking invasive dental treatment and vascular dysfunction suggests a strong association within the first seven days after dental treatment.[131] Although this relationship is important, it has not been well studied, which is surprising. One reason could be that it is challenging to investigate such an association, as invasive dental procedures are common, and it would be difficult to find a comparable group that has not received this type treatment. The study by Minassian et al. reported an increased risk of vascular events, myocardial infarction and stroke, in the first four weeks following an invasive dental procedure; however, no association with myocardial infarction events was observable.[139] *Study IV*, done during the same time period as the Minassian et al. study, used a 4-week follow-up period beginning the day after the dental procedure and a much larger study population, and found no clear association. More recently, Chen et al. have confirmed the result of *Study IV*.[159]

Study IV conclusions, along with the results of *Studies I–III*, send strong messages. *Studies I–III* emphasize a possible, slightly increased risk for individuals with severe periodontitis to experience a first myocardial infarction, but the treatment or examination *itself*, as *Study IV* indicates, does not elevate this risk. As these are common procedures in general dental clinics, this finding should be reassuring.

METHODOLOGICAL CONSIDERATIONS

Study designs

Observational studies are important study designs in medical research as experimental studies are not always are possible. At the start of this thesis, several designs for investigating the relation between periodontitis, invasive dental treatment, and myocardial infarction were discussed. Because periodontitis develops over several decades, a longitudinal cohort study was judged to be difficult as it would be not only extremely time consuming but also expensive. The ideal study design for providing evidence of a causal relation would have been a prospective randomized clinical trial, the best of all designs in the hierarchy of study designs.[160] However, randomly recruiting individuals with periodontitis free of cardiovascular disease and then offering dental treatment to only some of them, over a long period of time, would have been unethical. The case-control design which was chosen for all four studies, is a type of observational study in which two groups of outcome are identified; in contrast, a cohort study follows certain exposures over time and measures and compares risks of disease between different exposures. The major strengths of case-control studies are that they are relatively inexpensive compared with cohort studies and often have a more ethical design for studying diseases that develop over long time.

Internal and external validity

Internal validity is an important consideration in epidemiological studies. It determines to what degree the measurement actually measures what it was intended to measure,[161] and is an indication of the strength of the study method. A study with high internal validity has a low frequency of selection bias, measuring bias, and confounding. In *Studies I* and *II*, this was considered when defining exposure and periodontitis and throughout the radiographic analysis. Radiographic measurements of periodontist have previously been used with a high correlation[162-166] and it provides blinded evaluations by calibrated examiners. The outcome, the myocardial infarction diagnosis, was set by a physician according to standardized international criteria on myocardial infarction that are used throughout Sweden and which were used in all four studies.[144]

External validity is another important consideration; it helps determines the generalizability of the results to another population. To achieve high external validity, internal validity must also be high. By including cases and controls from 17 different hospitals across Sweden, resulting in a study population of 1610 well-examined participants, *Studies I* and *II* were able to achieve high internal and external validity. *Studies III* and *IV* included all individuals in Sweden who had experienced a first myocardial infarction, both fatal and non-fatal, between 2011 and 2013, together with matched controls. This makes generalizability reasonably high in high-income populations similar to the Swedish population, where cardiovascular disease prevention is widespread and general oral health, good.

Bias

Bias, a systematic tendency in data collection resulting in misleading results, is important to consider when designing studies.[161] Selection bias can occur in the method used to recruit study participants, for example, if an enrolled individual has a different association to the exposure and outcome compared to those who were eligible to participate but declined. Even though this was taken into consideration in *Studies I* and *II* by matching the study population with a control group, participation in the case and control groups was voluntary and if possible to reach by telephone. If healthier controls with better oral status were included, a selection bias might have been introduced, since more patients with a severely compromised oral status might have declined participation.

Measurement bias or information bias is a misclassification of the level of exposure or of the outcome itself. To diminish the risk of introducing measurement bias in *Studies I* and *II*, the definition of the exposure was stated before the outcome, the myocardial infarction, which strengthens these measures. In addition, trained and blinded dentists examined all radiographs. However, radiographs as a measure could have been misclassified as they can be a historic picture of a now stabile periodontitis, with no ongoing inflammatory response; stable patients might be misclassified as having active periodontitis. However, considering that both diseases develop over decades, the actual activity of the periodontitis at the time of examination was deemed less important.

When gathering data from registers, there is always a risk of introducing misclassification bias. This could be the case in *Studies III* and *IV* if an individual reported as having received dental treatment had an incorrect diagnosis. It could be claimed that using periodontal treatment as a proxy for the exposure periodontitis is less robust in *Study III* compared to *Studies I* and

II. However, it is unlikely that an individual receiving three or more advanced periodontal treatments annually in combination with surgery does not have periodontitis. In this setting, if it occurred, it would appear as a non-differential misclassification bias, a bias toward null. In other words, the misclassification would be equal in both groups, leading to a faded result. The risk of selection bias being introduced in *Studies III* and *IV* would be likely if the individuals receiving dental treatment were healthier and had easier access to dental care, which would explain some of the lack of association. However, this is very speculative. In *Study IV*, it could be speculated that the lack of association in the group where an invasive dental treatment had been performed two days prior to the myocardial infarction was related to protopathic bias;[167] if true, this would suggest that in the days preceding the myocardial infarction, the cases were less likely to attend dental health appointments due to weakness or sickness related to the coming myocardial infarction.

Confounding

Confounding is a variable that influences both the exposure variable and the outcome variable, causing a false association; for instance, although the analysis may unveil an association between exposure and outcome, it may actually be due to a shared external factor associated with the two (Figure 8).[161] For a variable to be categorized as a confounder, three criteria must be fulfilled: *(i)* It must be a risk factor external to the outcome variable, *(ii)* It must be associated with the exposure in the source population during the study, and *(iii)* It cannot be affected by the exposure or the outcome. Importantly, the confounder should not be an intermediate step in the causal pathway between exposure and outcome (Figure 8). Confounding can be managed in several ways, through randomization, restriction, stratification, regression analyses, and matching.

To distribute the basic cofounding factors in *Studies I* and *II* − such as age, gender, and geographic location − each case was matched with one control. The study participants were recruited from throughout Sweden, with the intention of including participants from the broadest possible spectrum of educational and socioeconomic conditions. To be able to control for relevant confounders in *Studies I* and *II*, variables such as family history of cardiovascular disease, smoking, diabetes, education, and marital status had to be accurately known for all participants. Cardiovascular risk factors such as hypertension, dyslipidemia, and known diabetes were treated similarly in both groups, which thereby limited their confounding. In *Studies III* and *IV*, the study population was also matched for age, gender, and geographic area, and information on possible confounders was obtained though register data. Information on one possible confounder, which probably would have had a strong impact on the results of *Studies III* and *IV* − smoking − was not retrieved. To manage confounding in all four studies, relevant confounders were adjusted for in regression models.

IMPLICATIONS AND FUTURE RESEARCH

Dental practitioners strive to maintain oral health by treating and preventing oral disease. As populations are becoming more elderly globally and in Sweden, there is reason to believe that people will have more complex medical histories as well as more complex oral health demands. This highlights the need for improved dialogues between the treating physician and dental care, where dentists serve as an important link to the health care system. The results of this thesis suggest that severe periodontitis may be a risk factor for myocardial infarction in susceptible individuals and younger women and underlines the need for improving such

collaborations. Thus, it is vital that we truly verify the role and the breadth of oral disease and its effect on systemic conditions.

In the near future, the prospective follow-up of the PAROKRANK cohort may be able to provide some evidence. Hitherto, the association between periodontal and cardiovascular disease has mostly been explored in observational studies; thus mainly generating large numbers of hypotheses. One could question whether more research with such designs will provide any additional information. Instead, perhaps future research should focus on study designs that can provide definitive information on causality or effective prevention.

A randomized intervention study would be desirable, however, it is outside the realm of possibilities if it includes a control group that will not be offered existing evidence-based periodontal treatments. Another way to attack the problem would be to broaden our understanding of the underlying inflammatory mechanisms of periodontitis. Individuals who are most susceptible to the disease could then be detected, and custom intervention programs could be designed to reduce the inflammatory response. This could be important since the association between periodontitis and myocardial infarction appears to be gender related. In an era where the pharmaceutical industry is developing novel anti-inflammatory and immune-modulating therapies, this is of special interest. If such personalized intervention programs could be designed, and if light is then shed on the causal pathway, novel treatment strategies might be possible. A new research design that has become more common is the genome-wide association study, which is an observational study design where the genome-wide set of genetic variants in different individuals is tested to detect disease associated variants. As an example, an association between periodontitis and hypertension was recently shown by using periodontal-linked single nucleotide polymorphisms (SNPs) and hypertension phenotypes.[168] This study design may be a future tool for elucidating the association between periodontitis and myocardial infarction.

Research in this field will continue, but hopefully in a different direction, and the future will certainly provide us with clearer information and better answers. However, for dental practitioners and most patients, the main goal is still to treat oral diseases and to maintain a high level of oral health, because these are important in themselves. In addition, the present thesis can conclude that such measures will not harm, but will probably ameliorate, the cardiovascular risk in our patients.

CONCLUSIONS

Based on the four thesis studies, it can be concluded that:

I. Periodontitis is more common in patients surviving a first myocardial infarction compared to controls and increases the risk of experiencing a first myocardial infarction.

II. Severe periodontitis is more strongly associated with a first myocardial infarction in women compared to men, particularly in women aged 65 years and under.

III. When periodontal treatment is used as a surrogate marker, there is no evidence that an association between periodontitis and a first myocardial infarction has any significance in the general Swedish population.

IV. Invasive dental treatment, including dental surgery and tooth extraction, is not associated with an increased risk of a first myocardial infarction in the general Swedish population.

ACKNOWLEDGEMENTS

A Ph.D. thesis is a challenging a task, and without the support and encouragement of the people around you, would never be accomplished. I am genuinely and deeply thankful to everyone who has contributed to this research project.

My journey as a Ph.D. student began in September 2013, when I received a phone call from Professor Anders Gustafsson. Still today, I do not know the reason why Anders chose to call me; however, I am extremely grateful to him for giving me the opportunity and privilege of being a Ph.D. student at Karolinska Institutet.

I wish to express special thanks to:

My dedicated, primary supervisor, Professor **Anders Gustafsson**, for giving me this chance and for always believing in me. Thank you for your guidance and encouragement throughout this research project. I am thankful and glad for your always so calm and steady character, which has had a positive impact on me. Moreover, for always finding time for discussion and help in your full schedule. Thank you!

My dedicated co-supervisor, Professor **Anna Norhammar**, for sharing with me your great knowledge of cardiovascular medicine and diabetes, and for always coming with wise comments and meaningful discussions.

My devoted co-supervisor, Associate Professor **Barbro Kjellström**, for being strong where I am weak, for always being enthusiastic about my ideas and believing in me, for all the hours you have spent revising my manuscripts, and for all your warm and encouraging words.

My enthusiastic co-supervisor Associate Professor **Michael Fored**, for explaining the world of epidemiology to me and for always leaving me with positive, encouraging feelings after discussions.

My passionate mentor, Professor **Anders Ekbom**, for pushing me to think outside the box and making me less anxious. I always carry with me your words from our walk in Central Park: "Eva, remember, if you ask for permission for something, then you must always consider to the answer; if you don't ask, you can do as you wish".

Tobias Svensson, for all the help you have given me in constructing the database and carrying out the analyses in *Studies III* and *IV*, and to Associate Professor **Fredrik Granath** for helping me structure the analysis in S*tudy III*.

All my co-workers in the PAROKRANK study, Professor **Lars Rydén**, Associated Professor **Kåre Buhlin**, Professor **Ulf de Faire**, Professor **Bertil Lindahl**, Professor Åke **Nygren**, Statistician **Per Näsman**, PhD **Nilminie Rathnayake**, Professor **Elisabet Svenungsson**, and Professor **Björn Klinge**, all of you have contributed to my scientific upbringing.

Associate Professor, **Margaret Sällberg Chen**, Director of Doctoral Studies, for all the assistance and guidance with the never-ending details of the Ph.D. studies, as well as always taking time to help and to encourage me when I knocked on your door.

Heli Vänskä, research administrator at the Department of Dental Medicine, for always being so kind and helpful every time I knocked at your door or sent you an e-mail.

Gabriella Bröms, Director of Studies at the Research School for Clinicians in Epidemiology, and to all my colleagues at the Research School. A particular special thanks to my study colleagues and dear friends **Louise Ziegler** and **Gry Johansen,** for all your cheering and being constantly supportive. I would never have made this without you.

My friend and colleague, **Aron Naimi-Akbar**, for helping me improve my knowledge in epidemiology and statistics.

Associate Professor, **Leif Jansson**, Head of the Department of Periodontology at Eastmaninstitutet, for being so supportive and truly generous and flexible with my working schedule.

Anita Johansson at Eastmaninstitutet, for always being so helpful with administrative work and flexible when planning my schedule.

My mentors, **Carolina Modin** and **Lottie Adler**, for all the clinical guidance with my patients and all the support you have given me.

All my wonderful colleagues at Eastmaninstitutet for being supportive and always helpful with assistance.

All my brilliant former and new "ST colleagues": **Marjan Najafzade**, **Tom Guan**, **Ali Faham**, **Caroline Dolk Rinon**, **Freha Niazi**, **Jacob Holmer**, and **Natalie Stempa**

My dear and loyal dental assistant, **Terhi Karvonen**, for all the help with the administrative work regarding our patients and for being so loving and caring.

All my wonderful friends and colleagues: **Amelie Hjortsjö**, **Nina Johansson**, **Maria Andersson**, and **Loisette Diaz**, for always being so positive and encouraging.

Professor **Panos Papapanou**, for being such an inspiring researcher and for always giving me generous attention at every international congress I have attended.

All my beloved friends, **Corinne Engellau, Elise Avsan**, **Emma Hernström**, **Jenny Hedqvist**, **Kim Nersing**, **Louise Rey**, **Madeleine Beyer**, **Malin Mazeret, Margareta Borg** and **Mickaela Rosén**, for being who you are and for providing an "outer world", and for giving me all your love. I am so lucky to have you all in my life!

Kay Bjørgengen, for providing me with a peaceful working space this summer.

My dear **Augustina Bengtstelius**, for all the love and joy you have given Olivia and brought into our family. Jacob and I are truly grateful for all our help!

My deeply beloved family, **Mamma**, **Pappa**, **Jens**, **Lena**, and **Göran**, for all your endless encouragement and love, and for always being there for me. You have supported and believed in me through this whole journey, I would never have managed this without you. I love you all from the bottom of my heart!

My husband, **Jacob**, for all the love and support while walking through life together. You complement me and give me the opportunity constantly to learn new things. For always including me in your passion for life. I love you!

Our adorable daughter, **Olivia**, for being the light and meaning of my life.

This research was made possible through contributions from **AFA Insurance**, the **Swedish Heart-Lung Foundation**, the **Swedish Research Council**, the **Swedish Society of Medicine**, **Stockholm County Council** (ALF project and Steering committee KI/SLL for odontological research), and **The Baltic Child Foundation**.

REFERENCES

1. Miller WD. The Human Mouth as a Focus of Infection. *The Lancet* 1891; **138**: 340-42.
2. Hunter W. The coming of age of oral sepsis. *Br Med J* 1921; **1**: 859.
3. Garcia RI, Henshaw MM, Krall EA. Relationship between periodontal disease and systemic health. *Periodontol 2000* 2001; **25**: 21-36.
4. Reimann HA, Havens WP. Focal infection and systemic disease: A critical appraisal: The case against indiscriminate removal of teeth and tonsils clinical lecture at St. Louis seseeion. *JAMA* 1940; **114**(1): 1-6.
5. Mattila KJ, Nieminen MS, Valtonen VV, et al. Association between dental health and acute myocardial infarction. *BMJ* 1989; **298**: 779-81.
6. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996; **67**(10): 1123-37.
7. Rocha e Silva M. A brief survey of the history of inflammation. 1978. *Agents Actions* 1994; **43**(3-4): 86-90.
8. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet* 2005; **366**(19): 1809-20.
9. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers* 2017; **3**: 1-14.
10. Lang NP, Lindhe J. Clinical periodontology and implant dentistry. Vol. 1, Basic concepts. Oxford: Wiley-Blackwell; 2015.
11. Lang NP, Lindhe J. Clinical periodontology and implant dentistry. Vol. 2, Clinical concepts. Oxford: Wiley-Blackwell; 2015.
12. Albandar JM, Rams TE. Global epidemiology of periodontal diseases: an overview. *Periodontol 2000* 2002; **29**: 7-10.
13. Norderyd O, Koch G, Papias A, et al. Oral health of individuals aged 3-80 years in Jönköping, Sweden during 40 years (1973-2013). II. Review of clinical and radiographic findings. *Swed Dent J* 2015; **39**(2): 69-86.
14. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol* 2018; **45**: 162-70.
15. Armitage G. 1999 International Workshop for a Classification of Periodontal Diseases and Conditions. Papers. Oak Brook, Illinois, October 30-November 2, 1999. *Ann Periodontol* 1999; **4**(1): 1-6.
16. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. *J Periodontol* 2007; **78**: 1387-99.
17. Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J, Sardo-Infirri J. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). *Int Dent J* 1982; **32**(3): 281-91.
18. Kassebaum NJ, Bernabe E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *J Dent Res* 2014; **93**(11): 1045-53.

19. Eke PI, Dye BA, Wei L, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. *J Periodontol* 2015; **86**(5): 611-22.
20. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. *Nat Rev Immunol* 2015; **15**(1): 30-44.
21. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. *Periodontol 2000* 2015; **69**(1): 7-17.
22. Stabholz A, Soskolne WA, Shapira L. Genetic and environmental risk factors for chronic periodontitis and aggressive periodontitis. *Periodontol 2000* 2010; **53**: 138-53.
23. Albandar JM. Global risk factors and risk indicators for periodontal diseases. *Periodontol 2000* 2002; **29**: 177-206.
24. Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol* 2017; **70**(1): 1-25.
25. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* 2017; **390**: 2643-54.
26. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016; **37**(42): 3232-45.
27. The National Board of Health and Welfare. Statistik om hjärtinfarkter 2017. 2018-12-13. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2018-12-42.pdf (accessed October 15 2019).
28. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**: 937-52.
29. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**(16): 1685-95.
30. Ross R. Atherosclerosis - An Inflammatory Disease. *N Engl J Med* 1999; **340**(2): 115-26.
31. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001; **104**(3): 365-72.
32. Libby P. Inflammation in atherosclerosis. *Nature* 2002; **420**: 868-74.
33. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011; **473**: 317-25.
34. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**(9): 1135-43.
35. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; **40**(3): 237-69.
36. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; **36**(3): 959-69.
37. Schenck-Gustafsson K. Diagnosis of cardiovascular disease in women. *Menopause Int* 2007; **13**(1): 19-22.

38. Elter JR, Champagne CM, Offenbacher S, Beck JD. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. *J Periodontol* 2004; **75**(6): 782-90.

39. Buhlin K, Gustafsson A, Håkansson J, Klinge B. Oral health and cardiovascular disease in Sweden. *J Clin Periodontol* 2002; **29**(3): 254-9.

40. Gotsman I, Lotan C, Soskolne WA, et al. Periodontal destruction is associated with coronary artery disease and periodontal infection with acute coronary syndrome. *J Periodontol* 2007; **78**(5): 849-58.

41. Accarini R, de Godoy MF. Periodontal disease as a potential risk factor for acute coronary syndromes. *Arq Bras Cardiol* 2006; **87**(5): 539-43.

42. Holmlund A, Holm G, Lind L. Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. *J Periodontol* 2006; **77**(7): 1173-8.

43. Arbes SJ, Jr., Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. *J Dent Res* 1999; **78**(12): 1777-82.

44. Persson RE, Hollender LG, Powell VL, et al. Assessment of periodontal conditions and systemic disease in older subjects. II. Focus on cardiovascular diseases. *J Clin Periodontol* 2002; **29**(9): 803-10.

45. Buhlin K, Gustafsson A, Håkansson J, Klinge B. Self-reported oral health, dental care habits and cardiovascular disease in an adult Swedish population. *Oral Health Prev Dent* 2003; **1**(4): 291-9.

46. Yu H, Qi LT, Liu LS, et al. Association of Carotid Intima-media Thickness and Atherosclerotic Plaque with Periodontal Status. *J Dent Res* 2014; **93**(8): 744-51.

47. Starkhammar Johansson C, Richter A, Lundström A, Thorstensson H, Ravald N. Periodontal conditions in patients with coronary heart disease: a case-control study. *J Clin Periodontol* 2008; **35**(3): 199-205.

48. Amabile N, Susini G, Pettenati-Soubayroux I, et al. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. *J Intern Med* 2008; **263**(6): 644-52.

49. Nonnenmacher C, Stelzel M, Susin C, et al. Periodontal microbiota in patients with coronary artery disease measured by real-time polymerase chain reaction: a case-control study. *J Periodontol* 2007; **78**(9): 1724-30.

50. Briggs JE, McKeown PP, Crawford VL, et al. Angiographically confirmed coronary heart disease and periodontal disease in middle-aged males. *J Periodontol* 2006; **77**(1): 95-102.

51. Spahr A, Klein E, Khuseyinova N, et al. Periodontal infections and coronary heart disease: role of periodontal bacteria and importance of total pathogen burden in the Coronary Event and Periodontal Disease (CORODONT) study. *Arch Intern Med* 2006; **166**(5): 554-9.

52. Geismar K, Stoltze K, Sigurd B, Gyntelberg F, Holmstrup P. Periodontal disease and coronary heart disease. *J Periodontol* 2006; **77**(9): 1547-54.

53. Buhlin K, Gustafsson A, Ahnve S, Janszky I, Tabrizi F, Klinge B. Oral health in women with coronary heart disease. *J Periodontol* 2005; **76**(4): 544-50.

54. Geerts SO, Legrand V, Charpentier J, Albert A, Rompen EH. Further evidence of the association between periodontal conditions and coronary artery disease. *J Periodontol* 2004; **75**(9): 1274-80.

55. Meurman JH, Janket SJ, Qvarnström M, Nuutinen P. Dental infections and serum inflammatory markers in patients with and without severe heart disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**(6): 695-700.
56. Andriankaja O, Trevisan M, Falkner K, et al. Association between periodontal pathogens and risk of nonfatal myocardial infarction. *Community Dent Oral Epidemiol* 2011; **39**(2): 177-85.
57. Lund Håheim L, Olsen I, Nafstad P, Schwarze P, Rönningen KS. Antibody levels to single bacteria or in combination evaluated against myocardial infarction. *J Clin Periodontol* 2008; **35**(6): 473-8.
58. Andriankaja OM, Genco RJ, Dorn J, et al. Periodontal disease and risk of myocardial infarction: the role of gender and smoking. *Eur J Epidemiol* 2007; **22**(10): 699-705.
59. Rech RL, Nurkin N, da Cruz I, et al. Association between periodontal disease and acute coronary syndrome. *Arq Bras Cardiol* 2007; **88**(2): 185-90.
60. Cueto A, Mesa F, Bravo M, Ocana-Riola R. Periodontitis as risk factor for acute myocardial infarction. A case control study of Spanish adults. *J Periodontal Res* 2005; **40**(1): 36-42.
61. Ryden L, Buhlin K, Ekstrand E, et al. Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study. *Circulation* 2016; **133**(6): 576-83.
62. Lopez R, Oyarzun M, Naranjo C, Cumsille F, Ortiz M, Baelum V. Coronary heart disease and periodontitis -- a case control study in Chilean adults. *J Clin Periodontol* 2002; **29**(5): 468-73.
63. Andriankaja OM, Genco RJ, Dorn J, et al. The use of different measurements and definitions of periodontal disease in the study of the association between periodontal disease and risk of myocardial infarction. *J Periodontol* 2006; **77**(6): 1067-73.
64. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ* 1993; **306**: 688-91.
65. Hung HC, Joshipura KJ, Colditz G, et al. The association between tooth loss and coronary heart disease in men and women. *J Public Health Dent* 2004; **64**(4): 209-15.
66. Ajwani S, Mattila KJ, Narhi TO, Tilvis RS, Ainamo A. Oral health status, C-reactive protein and mortality--a 10 year follow-up study. *Gerodontology* 2003; **20**(1): 32-40.
67. Dietrich T, Jimenez M, Krall Kaye EA, Vokonas PS, Garcia RI. Age-dependent associations between chronic periodontitis/edentulism and risk of coronary heart disease. *Circulation* 2008; **117**(13): 1668-74.
68. Yu YH, Chasman DI, Buring JE, Rose L, Ridker PM. Cardiovascular risks associated with incident and prevalent periodontal disease. *J Clin Periodontol* 2015; **42**(1): 21-8.
69. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. *Int Dent J* 2009; **59**(4): 197-209.
70. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J* 2007; **154**(5): 830-7.
71. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. *J Dent Res* 1996; **75**(9): 1631-6.

72. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol* 2001; **37**(2): 445-50.

73. Persson RG, Ohlsson O, Pettersson T, Renvert S. Chronic periodontitis, a significant relationship with acute myocardial infarction. *Eur Heart J* 2003; **24**(23): 2108-15.

74. Tuominen R, Reunanen A, Paunio M, Paunio I, Aromaa A. Oral health indicators poorly predict coronary heart disease deaths. *J Dent Res* 2003; **82**(9): 713-8.

75. Beukers NG, van der Heijden GJ, van Wijk AJ, Loos BG. Periodontitis is an independent risk indicator for atherosclerotic cardiovascular diseases among 60 174 participants in a large dental school in the Netherlands. *J Epidemiol Community Health* 2017; **71**(1): 37-42.

76. Jung YS, Shin MH, Kim IS, et al. Relationship between periodontal disease and subclinical atherosclerosis: the Dong-gu study. *J Clin Periodontol* 2014; **41**(3): 262-8.

77. Kodovazenitis G, Pitsavos C, Papadimitriou L, Vrotsos IA, Stefanadis C, Madianos PN. Association between periodontitis and acute myocardial infarction: a case-control study of a nondiabetic population. *J Periodontal Res* 2014; **49**(2): 246-52.

78. Willershausen I, Weyer V, Peter M, et al. Association between chronic periodontal and apical inflammation and acute myocardial infarction. *Odontology* 2014; **102**(2): 297-302.

79. Dorn JM, Genco RJ, Grossi SG, et al. Periodontal disease and recurrent cardiovascular events in survivors of myocardial infarction (MI): the Western New York Acute MI Study. *J Periodontol* 2010; **81**(4): 502-11.

80. Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. *J Periodontol* 2010; **81**(6): 870-6.

81. Heitmann BL, Gamborg M. Remaining teeth, cardiovascular morbidity and death among adult Danes. *Prev Med* 2008; **47**(2): 156-60.

82. Senba T, Kobayashi Y, Inoue K, et al. The association between self-reported periodontitis and coronary heart disease--from MY Health Up Study. *J Occup Health* 2008; **50**(3): 283-7.

83. Lockhart PB, Bolger AF, Papapanou PN, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation* 2012; **125**(20): 2520-44.

84. Li C, Lv Z, Shi Z, et al. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. *Cochrane Database Syst Rev* 2017; **11**: Cd009197.

85. Bergström J, Eliasson S, Dock J. A 10-year prospective study of tobacco smoking and periodontal health. *J Periodontol* 2000; **71**(8): 1338-47.

86. Albandar JM, Streckfus CF, Adesanya MR, Winn DM. Cigar, pipe, and cigarette smoking as risk factors for periodontal disease and tooth loss. *J Periodontol* 2000; **71**(12): 1874-81.

87. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998; **316**(7137): 1043-7.

88. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008; **29**(7): 932-40.

89. Ryder MI. The influence of smoking on host responses in periodontal infections. *Periodontol 2000* 2007; **43**: 267-77.

90. Bergström J, Eliasson S, Dock J. Exposure to tobacco smoking and periodontal health. *J Clin Periodontol* 2000; **27**(1): 61-8.

91. Palmer RM, Wilson RF, Hasan AS, Scott DA. Mechanisms of action of environmental factors--tobacco smoking. *J Clin Periodontol* 2005; **32**: 180-95.
92. Leite FRM, Nascimento GG, Scheutz F, Lopez R. Effect of Smoking on Periodontitis: A Systematic Review and Meta-regression. *Am J Prev Med* 2018; **54**(6): 831-41.
93. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368**: 647-58.
94. Maas AH, van der Schouw YT, Regitz-Zagrosek V, et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J* 2011; **32**(11): 1362-8.
95. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nat Rev Endocrinol* 2011; **7**(12): 738-48.
96. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol 2000* 2007; **44**: 127-53.
97. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. *Oral Dis* 2008; **14**(3): 191-203.
98. Soskolne WA, Klinger A. The relationship between periodontal diseases and diabetes: an overview. *Ann Periodontol* 2001; **6**(1): 91-8.
99. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; **54**(6): 1615-25.
100. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia* 2012; **55**(1): 21-31.
101. Strain WD, Paldanius PM. Diabetes, cardiovascular disease and the microcirculation. *Cardiovasc Diabetol* 2018; **17**(1): 57.
102. Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 2000; **23**(7): 962-8.
103. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. *Circulation* 2007; **115**(12): 1544-50.
104. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332**: 73-8.
105. Norhammar A, Schenck-Gustafsson K. Type 2 diabetes and cardiovascular disease in women. *Diabetologia* 2013; **56**(1): 1-9.
106. Norhammar A, Stenestrand U, Lindback J, Wallentin L. Women younger than 65 years with diabetes mellitus are a high-risk group after myocardial infarction: a report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). *Heart* 2008; **94**(12): 1565-70.
107. Löwel H, Koenig W, Engel S, Hörmann A, Keil U. The impact of diabetes mellitus on survival after myocardial infarction: can it be modified by drug treatment? Results of a population-based myocardial infarction register follow-up study. *Diabetologia* 2000; **43**(2): 218-26.
108. Norderyd O, Hugoson A. Risk of severe periodontal disease in a Swedish adult population. A cross-sectional study. *J Clin Periodontol* 1998; **25**(12): 1022-8.

109. Dolan TA, Gilbert GH, Ringelberg ML, et al. Behavioral risk indicators of attachment loss in adult Floridians. *J Clin Periodontol* 1997; **24**(4): 223-32.

110. Drury TF, Garcia I, Adesanya M. Socioeconomic disparities in adult oral health in the United States. *Ann N Y Acad Sci* 1999; **896**: 322-4.

111. Naimi-Akbar A, Kjellström B, Ryden L, et al. Attitudes and lifestyle factors in relation to oral health and dental care in Sweden: a cross-sectional study. *Acta Odontol Scand* 2019; **77**(4): 282-9.

112. Klinge B, Norlund A. A socio-economic perspective on periodontal diseases: a systematic review. *J Clin Periodontol* 2005; **32**: 314-25.

113. Lynch JW, Everson SA, Kaplan GA, Salonen R, Salonen JT. Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *Am J Public Health* 1998; **88**(3): 389-94.

114. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. *Circulation* 2006; **114**(24): 2619-26.

115. Ohm J, Skoglund PH, Discacciati A, et al. Socioeconomic status predicts second cardiovascular event in 29,226 survivors of a first myocardial infarction. *Eur J Prev Cardiol* 2018; **25**(9): 985-93.

116. Haytac MC, Ozcelik O, Mariotti A. Periodontal disease in men. *Periodontol 2000* 2013; **61**(1): 252-65.

117. Shiau HJ, Reynolds MA. Sex differences in destructive periodontal disease: a systematic review. *J Periodontol* 2010; **81**(10): 1379-89.

118. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011; **124**(19): 2145-54.

119. Schenck-Gustafsson K. Risk factors for cardiovascular disease in women. *Maturitas* 2009; **63**(3): 186-90.

120. Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"--epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. *J Dent Res* 2010; **89**(9): 879-902.

121. Terheyden H, Stadlinger B, Sanz M, Garbe AI, Meyle J. Inflammatory reaction - communication of cells. *Clin Oral Implants Res* 2014; **25**(4): 399-407.

122. D'Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. *J Clin Periodontol* 2013; **40**: S85-105.

123. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and atrial fibrillation: a nationwide cohort study. *Int J Cardiol* 2013; **168**(3): 2300-3.

124. Higashi Y, Goto C, Hidaka T, et al. Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. *Atherosclerosis* 2009; **206**(2): 604-10.

125. Kholy KE, Genco RJ, Van Dyke TE. Oral infections and cardiovascular disease. *Trends Endocrinol Metab* 2015; **26**(6): 315-21.

126. Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. *J Clin Periodontol* 2013; **40**: S51-69.

127. Herzberg MC, Weyer MW. Dental plaque, platelets, and cardiovascular diseases. *Ann Periodontol* 1998; **3**(1): 151-60.

128. Dorn BR, Dunn WA, Jr., Progulske-Fox A. Invasion of human coronary artery cells by periodontal pathogens. *Infect Immun* 1999; **67**(11): 5792-8.

129. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000; **71**(10): 1554-60.

130. Lowe G, Woodward M, Rumley A, Morrison C, Tunstall-Pedoe H, Stephen K. Total tooth loss and prevalent cardiovascular disease in men and women: possible roles of citrus fruit consumption, vitamin C, and inflammatory and thrombotic variables. *J Clin Epidemiol* 2003; **56**(7): 694-700.

131. Tonetti MS, D'Aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007; **356**(9): 911-20.

132. Elter JR, Hinderliter AL, Offenbacher S, et al. The effects of periodontal therapy on vascular endothelial function: a pilot trial. *Am Heart J* 2006; **151**(1): 47.

133. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000; **71**(10): 1528-34.

134. Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT. Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *Am J Epidemiol* 2000; **151**(3): 273-82.

135. Teeuw WJ, Slot DE, Susanto H, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. *J Clin Periodontol* 2014; **41**(1): 70-9.

136. Beck JD, Couper DJ, Falkner KL, et al. The Periodontitis and Vascular Events (PAVE) pilot study: adverse events. *J Periodontol* 2008; **79**(1): 90-6.

137. Offenbacher S, Beck JD, Moss K, et al. Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *J Periodontol* 2009; **80**(2): 190-201.

138. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol* 2010; **192**(19): 5002-17.

139. Minassian C, D'Aiuto F, Hingorani AD, Smeeth L. Invasive dental treatment and risk for vascular events: a self-controlled case series. *Ann Intern Med* 2010; **153**(8): 499-506.

140. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation* 2008; **117**(24): 3118-25.

141. Olsen I. Update on bacteraemia related to dental procedures. *Transfus Apher Sci* 2008; **39**(2): 173-8.

142. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006; **367**: 1075-9.

143. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012; **126**(16): 2020-35.

144. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation* 2007; **116**(22): 2634-53.

145. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; **24**(11): 659-67.

146. The National Board of Health and Welfare. Klassifikationen ICD-10. 2019-10-03. https://www.socialstyrelsen.se/utveckla-verksamhet/e-halsa/klassificering-och-koder/icd-10/ (accessed October 14 2019).

147. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart* 2010; **96**(20): 1617-21.

148. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382-9.

149. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.

150. Arwidsson Hansen A, Cederlund A, Sjödin L. Social Insurance Report, 2012.

151. Ljung R, Lundgren F, Appelquist M, Cederlund A. The Swedish dental health register - validation study of remaining and intact teeth. *BMC Oral Health* 2019; **19**(1): 116.

152. The Dental and Pharmaceutical Benefits Agency. Föreskrifter om ändring i Tandvårds- och läkemedelsförmånsverkets föreskrifter och allmänna råd (TLVFS 2008:1) om statligt tandvårdsstöd 2018-10-22. https://www.tlv.se/download/18.37dae4591665e2ff1c218b6b/1540902022671/HSLF_FS_2018_23_konsoliderad.pdf (accessed October 14 2019).

153. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; **16**(7): 726-35.

154. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol* 2016; **119**(5): 464-9.

155. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017; **32**(9): 765-73.

156. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016; **31**(2): 125-36.

157. Statistics Sweden. Background Facts 2016:1, Integrated database for labour market research. 2016. https://www.scb.se/contentassets/f0bc88c852364b6ea5c1654a0cc90234/dokumentation-av-lisa.pdf (accessed October 14 2019).

158. Jernberg T. SWEDEHEART Annual report 2018. 2018; (2019).

159. Chen TT, D'Aiuto F, Yeh YC, Lai MS, Chien KL, Tu YK. Risk of Myocardial Infarction and Ischemic Stroke after Dental Treatments. *J Dent Res* 2019; **98**(2): 157-63.

160. Greenhalgh T. Assessing the methodological quality of published papers. *BMJ* 1997; **315**: 305-8.

161. Rothman KJ, Greenland S, Lash TL. Modern epidemiology; 2013.

162. Kaimenyi JT, Ashley FP. Assessment of bone loss in periodontitis from panoramic radiographs. *J Clin Periodontol* 1988; **15**(3): 170-4.

163. Rohlin M, Åkesson L, Håkansson J, Håkansson H, Näsström K. Comparison between panoramic and periapical radiography in the diagnosis of periodontal bone loss. *Dentomaxillofac Radiol* 1989; **18**(2): 72-6.

164. Kilic AR, Efeoglu E, Yilmaz S, Orgun T. The relationship between probing bone loss and standardized radiographic analysis. *Periodontal Clin Investig* 1998; **20**(1): 25-32.

165. Eickholz P, Hausmann E. Accuracy of radiographic assessment of interproximal bone loss in intrabony defects using linear measurements. *Eur J Oral Sci* 2000; **108**(1): 70-3.

166. Graetz C, Plaumann A, Wiebe JF, Springer C, Salzer S, Dorfer CE. Periodontal probing versus radiographs for the diagnosis of furcation involvement. *J Periodontol* 2014; **85**(10): 1371-9.

167. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol* 1999; **149**(11): 981-3.

168. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, et al. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J* 2019.

Appendix 1. Information on data source in Study III from: the National Inpatient Register, the Swedish Prescribed Drug Register and the Dental Health Register	
Variables	**Codes**
Comorbidities	*ICD-10 and ATC code*
Diabetes overall	E.10-E.14 or A10A or A10B
Diabetes type 1	E.10+ A10AB
Diabetes type 2	(E.10-E.14 or A10A or A10B) – (E.10+A10AB)
Diabetes treatment regardless of type of diabetes	
Treatment insulin	A10A
Treatment oral	A10B
Periodontal treatments within 3 years, prior to index event	*The Dental and Pharmaceutical Benefits Agency codes system (In Sweden)*
No record of dental treatment	No registered code
No periodontal treatment	≠ 311, 312, 341, 342, 343, 441, 442, 444
≥one non-advanced periodontal treatment	(311, 312, 341) + 3043
≥one advanced periodontal treatment with or without periodontal surgery	(342, 343, 441, 442, 444) + 3043
Numbers of periodontal treatment per year, prior to index event	
one advanced periodontal treatment without periodontal surgery	(342, 343, 441, 442, 444) + 3043
two advanced periodontal treatments without periodontal surgery	(342, 343, 441, 442, 444) + 3043
≥three advanced periodontal treatments and/or ≥one periodontal surgeries	(342, 343, 441, 442, 444) + 3043

Appendix 2. Information on data sources in Study IV from: the National Inpatient Register, the Swedish Prescribed Drug Register and the Dental Health Register

Variables	**Codes**
Comorbidities	*ICD-10 and ATC code*
Diabetes	E.10-E.14 or A10A or A10B
Heart failure	I50
Atrial fibrillation	I48
Angina pectoris	I20
Stroke	I60–64 , G45, I63–64, I60–62
CVD drug treatment	*ATC code*
Antihypertensive	C09_CD, C09_AB, C08C, C03A_x
Statins	C10AA
Low dose aspirin	B01AC06_x
Beta blockers	C07_x
Dental treatments	*The Dental and Pharmaceutical Benefits Agency codes system (In Sweden)*
Sub-gingival scaling	342, 343
Surgery*	401-405
Implant surgery	421-436
Periodontal surgery	441, 442, 444
Apical surgery	541, 542
Dental examination	101-116
X-ray examination	121-128, 131-134
Temporary treatment	301-303
Caries treatment	322
Supra-gingival scaling/prophylaxis	311, 312, 341
Fillings	701-708
Root canal treatment	501-523
Fixed prosthodontics	801-815, 845-848
Removable prosthodontics	821-839
Temporomandibular disorder treatment	601-691

*Including extractions