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The association between oral health and heart diseases

Submission date	Recruitment status	[_] Prospectively registered
15/04/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
22/04/2021	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
03/05/2022	Circulatory System	

Plain English summary of protocol

Background and study aims
Coronary heart disease (CHD) is still the leading cause of death and morbidity in the Western world. Early diagnosis and treatment of CHD have a positive effect on the outcomes and the consequences of the disease. Spotting patients at risk of CHD and preventing the development of disease would be beneficial.

Periodontitis is a severe gum infection and is the most common mouth disease, affecting 10-30% of the general population depending on age. An association between periodontitis and CHD has been seen, however, the cause of the link between them is not clear.

This study aims to investigate the link between periodontitis and coronary heart disease and whether healthy gums can reduce the risk for CHD. This study also hopes to improve awareness of the importance of oral and periodontal health and the consequences for general health.

Who can participate?
Healthy adult volunteers aged 45-70 years, with 10 or more teeth, and either recently diagnosed periodontitis or no periodontitis.

What does the study involve?
All participants will be asked to fill in questionnaires to gather data on their medical history, perceived health, parental history, lifestyle, socio-economic status, and oral hygiene. Participants will also undergo a physical examination (blood pressure, heart rate, body mass index (BMI), waist to hip ratio, and electrocardiogram), a full mouth examination, oral microbiological samples, and blood tests. To acquire data about the condition of the heart, participants will undergo a CT scan. The function of the lining of the heart and blood vessels will be measured using the EndoPAT. One year later, either after finishing treatment of periodontitis for patients with periodontitis, or one year after inclusion of the participants without periodontitis, these examinations (except the CT scan) will be repeated.

What are the possible benefits and risks of participating?
This is an observational study so no direct benefits or risks are anticipated. However, this study may provide evidence that the extent of heart disease is independently associated with the

presence and extent of periodontitis and that periodontal intervention benefits the cardiovascular system.

Where is the study run from?
Amsterdam University Medical Centers (Netherlands)

When is the study starting and how long is it expected to run for?
From June 2012 to September 2018

Who is funding the study?
Isala Innovation Centre (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NL43083.075.13

Study information

Scientific Title
The association between Periodontitis and Coronary Atherosclerosis (PaCmAn)

Acronym
PaCmAn study

Study objectives
The extent of coronary atherosclerosis is independently associated with the presence and extent of periodontitis. Moreover, periodontal intervention resulting in a reduction of the inflammatory burden in the mouth of CVD patients reduces the extent of coronary atherosclerosis and thereby reduces the risk for cardiovascular events.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/06/2013, amendment approved 04/05/2015, the Medical Ethics Committee, Isala Academy (Mondriaan building, room 0.47, P.O. box 10400, 8000 GK Zwolle, The Netherlands; +31 38 424 3082 / +31 38 424 3054; metc@isala.nl), ref: NL43083.075.13

Primary study design
Observational

Study design
Single-centre prospective cross-sectional study

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Prevention of cardiovascular disease in periodontitis patients

Interventions
This is an observational trial. All participants will be asked to fill in questionnaires to gather data on their age, gender, ethnicity, medical history, perceived health, parental history, lifestyle (smoking, alcohol, drugs, stress), socio-economic status, and oral hygiene.

All participants will undergo a full-mouth periodontal examination performed by two trained periodontists. The Periodontal Inflamed Surface Area (PISA) score was calculated after extensive periodontal examination including periodontal probing pocket depth (PD), plaque score, and bleeding on probing (BOP). All measurements will be performed on all teeth, on six sites per tooth using a manual periodontal standard probe. Microbiological subgingival and oral rinse samples will be obtained.

Participants will undergo a physical examination measuring Blood Pressure (BP), Heart Rate (HR), Body Mass Index (BMI), Waist to Hip ratio (WHR), and Electrocardiogram (ECG). Additionally blood samples measuring High sensitive C-reactive Protein (hsCRP), total cholesterol, High Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglycerides, estimated Glomerular Filtration Rate (eGFR), and Glycated Hemoglobine (HbA1c) will be obtained. An extra blood sample for DNA analysis of risk genes for both periodontitis and coronary heart disease will be taken.

To acquire data about the cardiovascular condition, the Coronary Artery Calcium (CAC) Score will be calculated using a CT-scan. The endothelial function will be measured employing “EndoScore” using the ENDOPAT, a medical device for noninvasive endothelial function assessment. EndoPAT is based on noninvasive Peripheral Arterial Tone (PAT) signal technology. It measures endothelium-mediated changes in vascular tone using unique bio-sensors placed on the

fingertips. These changes in arterial tone are elicited by creating a down-stream hyperemic response induced by a standard 5 min occlusion of the feeding artery (using a standard blood pressure cuff). When the cuff is released, the surge of blood flow causes an endothelium-dependent Flow Mediated Dilatation (FMD). The dilatation, manifested as Reactive Hyperemia, is captured by EndoPAT as an increase in the PAT Signal amplitude. A post-occlusion to pre-occlusion ratio is automatically calculated by the EndoPAT software, thus providing the EndoScore. Measurements from the opposite arm are used to control for concurrent non-endothelial dependent changes in vascular tone. EndoPAT tests can be carried out in both the office and hospital settings, with patients positioned either sitting or supine. The test takes 15 min to complete, is very easy to perform, and is both operator and interpreter independent.

One year after periodontal treatment of the periodontitis patients and one year after inclusion of the control patients, all patients will again undergo the full mouth periodontal examination, physical examination, blood tests and EndoScore.

Intervention Type
Other

Primary outcome(s)
1. Inflammatory and infectious burden of periodontitis measured using Periodontal Inflamed Surface Area (PISA) score calculated after extensive periodontal examination by trained and calibrated examiners from the following measured on all teeth, on six sites per tooth using a manual periodontal standard probe at baseline and 1 year
1.1 Periodontal probing pocket depth (PD) (in mm)
1.2. Gingival recession (in mm)
1.3. Clinical attachment loss (CAL), defined as the distance from the cementoenamel junction to the bottom of the pocket/sulcus and calculated as the mathematical sum of the PD and gingival recession measurements (in mm)
1.4. Plaque score defined as being present or absent at six points on each tooth
1.5. Bleeding on probing (BOP) recorded as either present or absent within 30 s of probing at six sites per tooth
1.6. Number of missing teeth
2. Predicted risk of future cardiovascular events measured using Coronary Artery Calcium Score (CAC) from cardiac computerized tomography scan at baseline
3. Endothelial dysfunction (EndoScore) measured using the EndoPAT at baseline and 1 year

Key secondary outcome(s)
1. Risk of a future heart attack, stroke, or other major cardiovascular events in the next 10 years, measured using the Reynolds Risk Score calculated from the following:
1.1. A demographic information questionnaire (<age 60 years, current smoking, and parental history of a cardiovascular event) at baseline and 1 year
1.2. Blood pressure at baseline and 1 year
1.3. Blood samples (hs-CRP, and total and HDL cholesterol) at baseline and 1 year
2. 10-year risk of coronary artery disease events, measured using Framingham risk score calculated from the following:
2.1. A demographic information questionnaire (age, gender, and smoking status) at baseline and 1 year
2.2. Blood pressure at baseline and 1 year
2.3. Blood samples (total and HDL cholesterol) at baseline and 1 year
3. 10-year risk of cardiovascular disease mortality measured using the SCORE system, which for the Dutch population is calculated according to the algorithm for a low-risk country, calculated

from:
3.1. A demographic information questionnaire (gender, and smoking status) at baseline
3.2. Blood pressure at baseline and 1 year
3.3. Blood samples (total and HDL cholesterol) at baseline and 1 year
4. Risk genes for both periodontitis and coronary heart disease measured using DNA analysis of a blood sample collected at baseline
5. Microbiological analysis of the oral microbiome measured using pyrosequencing of 16S microbial DNA from oral rinse sample and subgingival plaque collected at baseline

Completion date
01/09/2018

Eligibility

Key inclusion criteria
1. Aged between 45 and 70 years
2. ≥10 teeth

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
71

Key exclusion criteria
1. Known cardiovascular diseases
2. Known Diabetes Mellitus
3. Known autoimmune disorders
4. Known immunosuppressive disorders

Date of first enrolment
03/06/2013

Date of final enrolment
01/10/2013

Locations

Countries of recruitment
Netherlands

Study participating centre
Amsterdam UMC
Department of Oral and Maxillofacial Surgery
Location AMC
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Netherlands
1105 AZ

Study participating centre
ACTA
Department of Periodontology
Gustav Mahlerlaan 3004
Amsterdam
Netherlands
1081 LA

Study participating centre
Isala clinics
Department of Cardiology
Dokter van Heesweg 2
Zwolle
Netherlands
8025 AB Zwolle

Study participating centre
Practice for Periodontology Zwolle (PPZ)
Groot Wezenland 15
Zwolle
Netherlands
8011 JV

Sponsor information

Organisation
Amsterdam University Medical Centers

ROR
https://ror.org/05grdyy37

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Isala Innovation Centre

Results and Publications

Individual participant data (IPD) sharing plan
The anonymized datasets generated during and/or analysed during the current study will be available after publication via Figshare.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		15/10/2021	13/01/2022	Yes	No
Results article	1 year follow up results	14/04/2022	03/05/2022	Yes	No
Participant information sheet	version v2.0	27/03/2013	04/05/2021	No	Yes
Participant information sheet	version v3.0	05/12/2014	04/05/2021	No	Yes
Participant information sheet	version v3.0	05/12/2014	04/05/2021	No	Yes
Participant information sheet	version v2.0	27/03/2013	04/05/2021	No	Yes
Protocol file	version v2	27/03/2013	04/05/2021	No	No