UiT The Arctic University of Norway

Faculty of Medical Sciences / Department of community medicine

Sex-specific associations between oral health and cardiovascular risk profile in the population-based Tromsø Study 7.

Cross-sectional study

Ahmed Elawady

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Supervisor: Ekaterina Sharashova

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a. List of abbreviation:

- Body mass index (BMI)
- Cardiovascular disease (CVD)
- Decayed Missed Filled Teeth score (DMFT score)
- high-density lipoprotein (HDL)
- low-density lipoprotein (LDL)
- Non communicable disease (NCD)
- Framingham risk score (FRS)

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c. Acknowledgment

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d. Abstract:

Introduction: cardiovascular disease (CVD) is one of the major causes of death in the world. Many studies have linked CVD with periodontitis which is oral inflammatory disease. But those studies didn´t take into consideration the overall oral health as one confounder that can be linked to CVD, not just periodontitis.

Objective: the main aim was to study the sex-specific association between variables that describe oral health and CVD risk profile.

Materials and methods: cross-sectional study design has been performed using data from Tromsø study 7. In Tromsø study 7, a random sample was selected to undergo a dental examination before the study begins. This randomized sample had been used after excluding cases with missing data to do a complete analysis. The final sample comprised 3374 subjects: 1736 women and 1638 men. Sex-specific association between oral health describing variables (decayed missed filled teeth (DMFT), number of teeth and number of decayed teeth) and CVD risk profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes, obesity and hypertension) was assessed in univariable and multivariable models. Age, Smoking and number of dentist visits were used as possible confounders. Furthermore, the association between oral health describing variables and Framingham risk score (FRS) which describes 10 years risk of developing CVD has been assessed in univariable and multivariable models both with linear and binary logistic statistical models.

Results: DMFT which is unfavourable for oral health when increased is associated with unfavourable total cholesterol, LDL cholesterol and obesity in women. And

unfavourable HDL and obesity in men. Furthermore, DMFT had an unfavourable association with FRS only in men. Teeth number which is favourable for oral health when increased is associated with favourable obesity and hypertension for women and favourable HDL and obesity in men. But in contrast, it has an unfavourable association with total cholesterol and LDL cholesterol in both men and women. Furthermore, teeth number was associated with favourable FRS in both men and women.

Conclusion: favourable oral health is generally associated with the favourable CVD risk profile. oral health is associated with different CVD risk profile variables with different grades in men and women. Furthermore, compromised oral health is associated with increased 10 years risk of CVD incidence in both men and women but with different grades. Therefore, any future studies or preventive strategies regarding this topic should be also sex-specific.

1. Introduction

I. Cardiovascular disease epidemiology

Cardiovascular disease (CVD) is a group of diseases that affects heart and cardiovascular system. This includes ischemic heart disease, stroke, and other diseases. CVD is the leading cause of death in the world (1). It was the cause of 17.9 million deaths in 2015. In Europe about 45% of all deaths are caused by CVD. This represents over 3.9 million deaths every year only in Europe (2). CVD is one of the major causes of death also in Norway (3) & (4) . Because of the huge burden, CVD became one of the most demanding public health issues. Thus, World Health Organization launched 25*25 global action plan in 2013 (5). This global action plan is aiming to reduce the premature death caused by non-communicable diseases (NCDs) by 25% in 2025. The global action plan is focusing on the four major causes of premature deaths in NCDs including CVD, cancer, diabetes, and chronic respiratory diseases. Furthermore, United Nations have outlined the reduction of NCDs including CVD as one of its sustainable development goals. The target is to reduce the premature mortality rates of NCD by one third in 2030 (6). To achieve the aimed reduction of CVD, prevention strategies should be applied. Those strategies should be based upon sound evidence-based studies that clarify the etiological and predisposing factors for CVDs.

Age, sex, smoking, unhealthy diet, elevated blood pressure, obesity, dyslipidaemia, and diabetes mellitus are known to be major risk factors for developing atherosclerotic CVD such as coronary heart disease, stroke, peripheral vascular disease, and heart failure. These risk factors represent individual cardiovascular risk profile and are usually included in a general CVD risk assessment tool that is used in primary care to identify high-risk candidates for developing atherosclerotic CVD (7). Some of those risk factors correlate with each other. For example, unhealthy diet can predispose to obesity, dyslipidaemia, and diabetes mellitus. Thus, CVD risk factors can be drawn in causality cascade that appears as a net of correlated factors which all together affect the incidence of CVD (Figure 1).

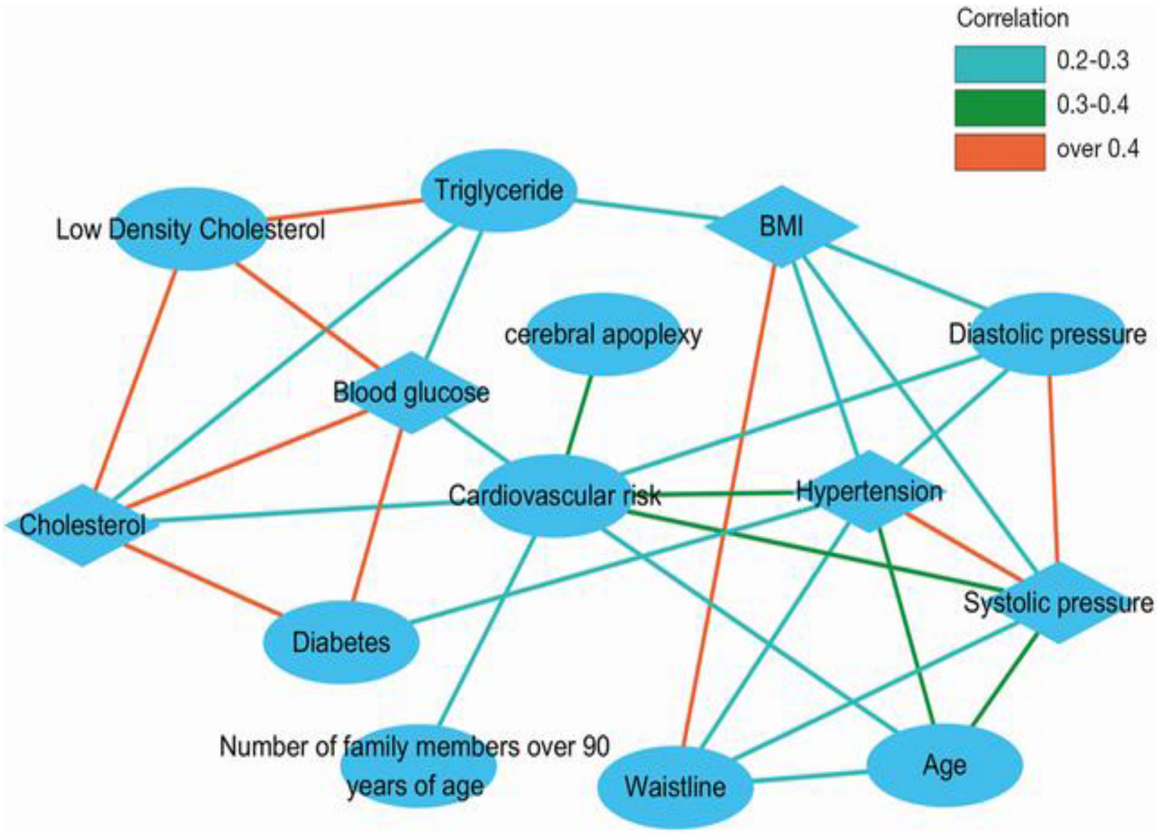


Figure 1: Factors that affect incidence of cardiovascular diseases.

Source: (8)

II. Cardiovascular disease and oral health

In addition to the traditional cardiovascular risk factors there is an increasing evidence that links CVD with periodontitis (9). Periodontitis is an inflammatory oral disease that affects the tooth supporting structures (periodontium). It is characterized by formation of microbial plaque on the teeth, inflammation of periodontium and loss of attachment and alveolar bone. The progression of periodontitis is evaluated by extension of attachment and alveolar bone loss. This progression is usually slow in chronic cases. However, smoking and systematic conditions such as diabetes and stress alter tissue response to the microbial plaque and thus, it becomes dramatically faster (10).

The main etiological factor that causes periodontitis is microbial biofilm that form dental plaque. Accumulation of this dental plaque triggers inflammatory destructive reaction in the periodontal tissue which is translated clinically by the loss of attachment and destruction of a part of alveolar bone (10).

The link between periodontitis and CVD has been documented in many studies. In a cohort study which operated by DeStefano et al, subjects were followed up for 14 years to examine the association between periodontitis and CVD. Possible confounders have been taken into consideration. Those confounders were age, gender, race, education, marital status, systemic blood pressure, total cholesterol levels, body mass index (BMI), diabetes, physical activity, alcohol consumption, poverty, and cigarette smoking. They found 25% increasing in possibility for having CVD in subjects with periodontist. More surprisingly males under 50 years who had periodontitis were 72% more likely to develop CVD (11).

The mechanism that links periodontitis with CVD is not totally clarified yet. Some studies stated that bacteria in dental plaque like Streptococcus Sanguis and Porphyromona Gingivalis causes the aggregation and activation of platelets. Those aggregated proteins cause thromboembolic events which directly results in CVD (12).

But is this the full picture?! Periodontitis is just one branch of a larger tree of the oral health. To our knowledge all the studies that linked periodontitis with CVDs did not take into consideration the most important confounder which may cause both periodontitis and increased risk of CVDs (13) (14). This confounder is compromised oral health (Figure 2). Oral health describes the wider range of diseases in the oral cavity like dental caries, periodontal health, oral trauma, tooth loss, oral cancer and others (15).

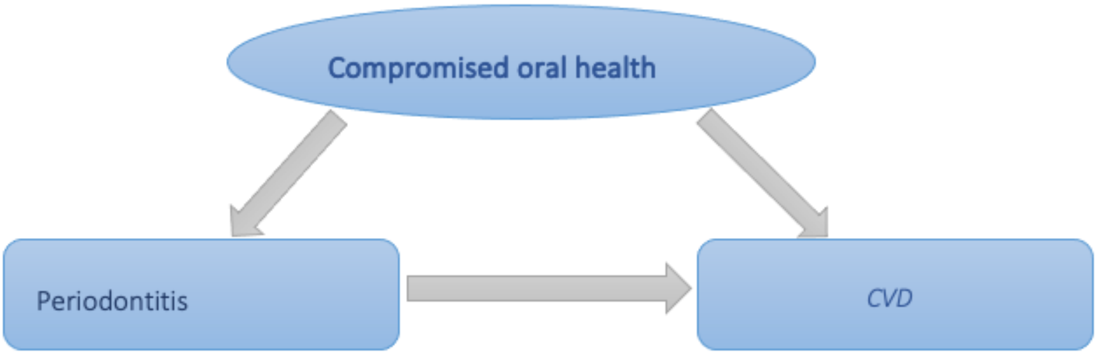


Figure 2: The possible effect of oral health as a confounder

According to the Global Burden of Disease 2016, about half of the world's population (3.58 million people) have oral disease (3). Dental caries is one of the most epidemic lesions in the world (16). Oral disease can cause pain, discomfort, compromised chewing function and even death (15). Dental caries and compromised oral health could have reasonable pathologic pathways to increase CVD risk. For example, impairment of chewing function caused by oral disease could affect the patients' diet. Furthermore, chronic inflammation caused by oral lesions, tooth abscess or periodontitis has pathological pathways for atherosclerosis progression and CVD development (17). Also stress and anxiety secondary to unconfident smile is a predisposing factor for CVD (17).

To draw a correlation cascade between oral health and CVDs, we aim to explore sex-specific associations between oral health and cardiovascular risk profile which includes age, smoking, elevated blood pressure, obesity, dyslipidaemia, and diabetes mellitus. This will outline the possible mechanisms that relate oral health to the CVD.

III. <u>Hypothesis</u>

Compromised oral health is associated with unfavourable cardiovascular risk profile. Oral health is expressed by Decayed Missed Filled Teeth score (DMFT score), number of teeth, and decayed teeth number. Variables that describe cardiovascular risk profile are age, smoking, elevated blood pressure, obesity, dyslipidaemia, diabetes mellitus and Framingham risk score (FRS).

IV. Research question

Is there any association between oral health and cardiovascular risk profile in women and men from the population-based Tromsø Study 7 conducted in 2015-2016?

V. Aim

The aim of the study was to explore sex-specific associations between variables that describe oral health and cardiovascular risk profile as possible mechanism for atherosclerosis progression and increased risk of CVD development.

2. Materials and methods

I. The Tromsø Study

The Tromsø Study is a population-based study which was initiated in 1974 to explore reasons behind high cardiovascular mortality in Northern Norway. In total, seven consecutive surveys have been conducted in the municipality of Tromsø between 1974 and 2016. In our study we used data from the Tromsø Study 7 (first visit) which is the most recent survey and conducted in 2015-2016. The first visit of the study was composed of both questionnaires and clinical examinations. Questionnaire Q1 had a paper version and a digital version using username and password and included questions on lifestyle, medications and medical history. Many of the participants preferred to fill the questionnaire in the examination site. Clinical examination at the first visit included physical examinations, measurement of blood pressure and heart rate, and taking biological samples. Blood samples were processed immediately after collection and the laboratory tests were performed in the same day to determine lipid profile and other biomarkers. This analysis has been performed at the department of laboratory medicine, university hospital of northern Norway (ISO certification NS-EN ISO 15 189:2012). (18) Furthermore, dental examination was conducted on a subsample that has been randomly selected before the first visit.

II. Study population

In the Tromsø Study 7 all residents of the Tromsø municipality above the age of 40 years were invited to participate using mail invitation (n=32,591). Out of these, 21,803 subjects participated in the study (65% response rate). Of those participated, 3858 underwent dental examination. Individuals with missing data on the variables used in this study were excluded to do a complete case analysis. The final sample comprised 3374 subjects: 1736 women and 1638 men (Figure 3).

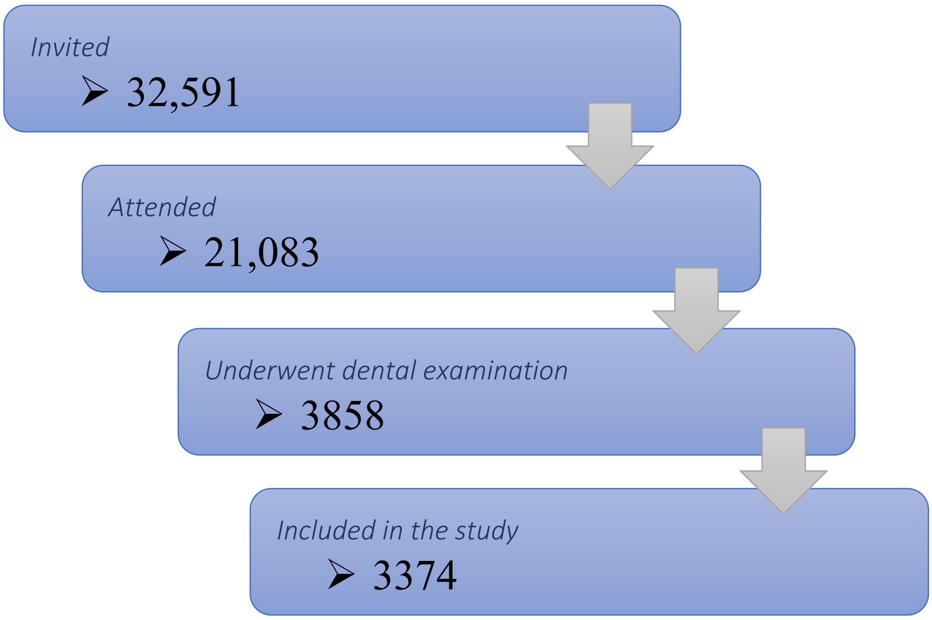


Figure 3: Flow chart of the participants.

III. <u>Study design</u>

This is a cross-sectional study. The association between oral health expressed by DMFT score and teeth number has been assessed in relation to cardiovascular risk profile as would be described in variable description and analysis sections.

<u>Variables description</u>

Variables describing oral health

1. <u>Decayed Missed Filled Teeth score</u>

DMFT score is common and standardized expression of dental caries in dental public health systems (19). In DMFT score every decayed, missed and/or filled tooth is given the score 1. Totally intact tooth is expressed by value 0 in the score. DMFT depicts not only the present active carious lesions, but also the old treated carious lesions. In one hand active lesions is expressed by decayed teeth. On the other hand, old lesions expressed by filled and missed teeth that has been already treated by restorations or extraction respectively.

The oral cavity is composed of four quadrants. Each quadrant has 7 teeth in adults in addition to the wisdom tooth that is not considered in DMFT score. Thus, the score is ranged from 0 to 28. Since this is a wide range, the scale of DMFT was changed by dividing DMFT by 7. This shows the odds ratio for decayed or missed or filled 7 teeth (one quadrant) rather than just one tooth. The new variable is called quadrant DMFT. This made it easier to report and interpret the odds ratios and regression coefficients. This is like we do for age in epidemiological studies to show the odds ratio for 10 years increase rather than only one-year.

2. Number of teeth

DMFT score involves a drawback. It describes the carious lesions only, but not the oral function. For example, it gives the tooth with filling and functioning well the same value as the tooth which has been totally missed. So, it was crucial to add another parameter into our analysis that describes the functions of oral cavity. This parameter is “teeth number”. Because the tooth is the unite of function in oral cavity, so increased number of teeth would allow the subject to perform healthier masticatory and other stomatognathic functions. Number of teeth has been changed also in scale by dividing teeth number by 7. The new variable is called quadrant number of teeth.

3. Number of decayed teeth:

It describes the number of teeth that has decay. This number doesn´t depict the teeth that has been treated nor the teeth that are missed.

4. Number of dentist visits:

This is self-reported variable in Tromsø study 7. The subjects have been asked do you go regularly to dentist/ dental care. The answer was categorized into six groups yes once a year, yes (every year), yes (every second year), yes (with longer intervals than two years), No (only for acute problems), No (never goes) groups. This variable has been dichotomised into at least a visit every year group and more than a year interval group. The statistical analysis was adjusted to this variable. The main aim for that is to element the effect of deferent degrees of dental care on results.

Variables describing cardiovascular risk profile

1. Blood lipids

Serum levels of blood lipids were analysed using enzymatic colorimetric test (18). Total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels are continuous variables that expresses the lipid profile for the subject. Total cholesterol describes how much cholesterol subjects have in their blood. Cholesterol levels tends to be unfavourable when elevated. (20) Cholesterol level would be dichotomised into normal and elevated cholesterol subgroups. Values equal to or lesser than 5 mmol/L were considered normal. (21) LDL cholesterol level expresses “bad” proportion of the total cholesterol level. Thus, elevated LDL cholesterol level increases the risk of CVD development. (20) LDL cholesterol has also been dichotomised into normal and elevated subgroups. If LDL cholesterol was equal to 3 mmol/L or lesser it was considered normal. (21) On contrast, HDL cholesterol expresses the “good” proportion of the subject´s total cholesterol. (20). Higher HDL cholesterol values express lower risk of CVD development. In this study HDL cholesterol level had been dichotomised into low and normal subgroups. If HDL cholesterol was 1 mmol/L or above it was considered normal. (21)

2. Diabetes

Diabetes is a self-reported variable. In a questionnaire subjects had to choose if they had diabetes at the time of examination, had had diabetes previously or had never had diabetes. Those who have had diabetes previously and those who have never had diabetes were combined into one group. Thus, variable had been dichotomised to only having diabetes currently (yes/no).

3. Obesity

BMI was calculated by dividing body weight (kg) on the square value of the body height (m). Hight and weight were gauged without shoes and with light clothes. Hight was measured to the nearest millimetre by electronic stadiometer (DS-103, Dongsahn JENIX Co. Ltd) while weight was measured to the nearest 100gm electronic digital scale (DS-B02, Dongsahn JENIX Co.Ltd). (22)

BMI is a continuous variable. In the present study we used BMI to diagnose obesity (BMI≥30 kg/m^2; yes/no) and used this binary variable in the analyses. (23).

4. Blood pressure

Systolic and diastolic blood pressure were measured three times using Dinamap (ProCare 300, GE Healthcare) (22). Dinamap usage for measuring blood pressure has been validated (24). The mean of the second and the third measurements was the final blood pressure value.

Systolic and diastolic blood pressure are continuous variables and would be dichotomised into elevated systolic (>140 mmHg) and diastolic (>90 mmHg) variables (yes/no) based on the European Society of Cardiology recommendations (25).

We also would use systolic and diastolic blood pressure variables together with the information on taking antihypertensive medications to examine if a patient had hypertension or not. Information on taking antihypertensive medications (yes/no) was self-reported. Participant was considered to have hypertension if systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥ 90 mmHg and/or participant was taking antihypertensive medications (25).

5. Smoking

Information on smoking was self-reported. Individuals had three options to describe their smoking status: never smoked, smoking now and smoked previously. In this study, never smoking group was combined with the previously smoking group into not smoking group. Thus, current smoking would be used as a binary variable.

6. Framingham Risk Score

Framingham risk score (FRS) is a sex-specific algorithm that is used to predict the 10-years probability of developing CVD. This score was based on the data obtained from Framingham Heart Study. (26) The main advantage of using this score in our study is that it would give us a description of cumulative risk of developing CVD in addition to using the risk factors separately one by one. The cardiovascular risk factors (dyslipidaemia, diabetes, obesity, hypertension, and smoking) are combined in one sex-specific algorithm to give Framingham risk points (27).(table 1.) Risk points range between (-4 to 30) in men and (-5 to 29) in women. Afterword, Framingham risk points are translated to 10-years probability of CVD developing, or FRS (table 2.). FRS ranges from <1 to 30. In this study FRS has been used in two different statistical models. First it was used as continuous variable. Second it was dichotomised. Dichotomisation was done by two different cut points (FRS ≥ 30%; yes/no) and (FRS ≥ 20%; yes/no)

Table1. Step 1 for FRS calculation (each subcategory is valued with specific risk point)

<table>
<tr><th colspan="2">Risk factor</th><th colspan="4">Risk points</th><th>points</th></tr>
<tr><td colspan="2"></td><td colspan="2">women</td><td colspan="2">men</td><td></td></tr>
<tr><td colspan="7">Age</td></tr>
<tr><td colspan="2">30-34</td><td colspan="2">0</td><td colspan="2">0</td><td></td></tr>
<tr><td colspan="2">35-39</td><td colspan="2">2</td><td colspan="2">2</td><td></td></tr>
<tr><td colspan="2">40-44</td><td colspan="2">4</td><td colspan="2">5</td><td></td></tr>
<tr><td colspan="2">45-49</td><td colspan="2">5</td><td colspan="2">7</td><td></td></tr>
<tr><td colspan="2">50-54</td><td colspan="2">7</td><td colspan="2">8</td><td></td></tr>
<tr><td colspan="2">55-59</td><td colspan="2">8</td><td colspan="2">10</td><td></td></tr>
<tr><td colspan="2">60-64</td><td colspan="2">9</td><td colspan="2">11</td><td></td></tr>
<tr><td colspan="2">65-69</td><td colspan="2">10</td><td colspan="2">12</td><td></td></tr>
<tr><td colspan="2">70-74</td><td colspan="2">11</td><td colspan="2">14</td><td></td></tr>
<tr><td colspan="2">75+</td><td colspan="2">12</td><td colspan="2">15</td><td></td></tr>
<tr><td colspan="7">HDL (mmol/l)</td></tr>
<tr><td colspan="2">>1.6</td><td colspan="2">-2</td><td colspan="2">-2</td><td></td></tr>
<tr><td colspan="2">1.3-1.6</td><td colspan="2">-1</td><td colspan="2">-1</td><td></td></tr>
<tr><td colspan="2">1.2-1.29</td><td colspan="2">0</td><td colspan="2">0</td><td></td></tr>
<tr><td colspan="2">0.9-1.19</td><td colspan="2">1</td><td colspan="2">1</td><td></td></tr>
<tr><td colspan="2"><0.9</td><td colspan="2">2</td><td colspan="2">2</td><td></td></tr>
<tr><td colspan="7">Total cholesterol(mmol/l)</td></tr>
<tr><td colspan="2">< 4.1</td><td colspan="2">0</td><td colspan="2">0</td><td></td></tr>
<tr><td colspan="2">4.1-5.19</td><td colspan="2">1</td><td colspan="2">1</td><td></td></tr>
<tr><td colspan="2">5.2-6.19</td><td colspan="2">3</td><td colspan="2">2</td><td></td></tr>
<tr><td colspan="2">6.2-7.2</td><td colspan="2">4</td><td colspan="2">3</td><td></td></tr>
<tr><td colspan="2">>7.2</td><td colspan="2">5</td><td colspan="2">4</td><td></td></tr>
<tr><td colspan="7">Systolic blood pressure (mmHg)</td></tr>
<tr><td colspan="2"></td><td>Not treated</td><td>treated</td><td>Not treated</td><td>treated</td><td></td></tr>
<tr><td colspan="2"><120</td><td>-3</td><td>-1</td><td>-2</td><td>0</td><td></td></tr>
<tr><td colspan="2">120-129</td><td>0</td><td>2</td><td>0</td><td>2</td><td></td></tr>
<tr><td colspan="2">130-139</td><td>1</td><td>3</td><td>1</td><td>3</td><td></td></tr>
<tr><td colspan="2">140-149</td><td>2</td><td>5</td><td>2</td><td>4</td><td></td></tr>
<tr><td colspan="2">150-159</td><td>4</td><td>6</td><td>2</td><td>4</td><td></td></tr>
<tr><td colspan="2">160+</td><td>5</td><td>7</td><td>3</td><td>5</td><td></td></tr>
<tr><td rowspan="2">smoker</td><td>yes</td><td colspan="2">4</td><td colspan="2">3</td><td rowspan="2"></td></tr>
<tr><td>no</td><td colspan="2">0</td><td colspan="2">0</td></tr>
</table>

Table 2. Step 2 for sum of points from previous step is translated in 10-years CVD Risk (FRS) by the following algorithm

Total points	10 years CVD Risk (%)	
	women	men
-3 or less	<1	<1
-2	<1	1.1
-1	1	1.4
0	1.2	1.6
1	1.5	1.9
2	1.7	2.3
3	2	2.8
4	2.4	3.3
5	2.8	3.9
6	3.3	4.7
7	3.9	5.6
8	4.5	6.7
9	5.3	7.9
10	6.3	9.4
11	7.3	11.2
12	8.6	13.3
13	10	15.6
14	11.7	18.4
15	13.7	21.6
16	15.9	25.3
17	18.51	29.4
18	21.5	>30
19	24.8	>30
20	27.5	>30
21+	>30	>30

Statistical analyses:

All analyses would be sex-specific because of sex differences regarding risk of developing CVD (28). All individuals with missed data related to the study variables would be removed in order to run complete case analyses. The baseline characteristics for the sample would be compared using independent sample t-test for total cholesterol, LDL cholesterol, HDL cholesterol, systolic blood pressure and diastolic blood pressure variables. For age groups, hypertension, diabetes and smoking Chi square test would be used. For discrete variables such as FRS, DMFT, number of teeth, and number of decayed teeth, Mann Whitney statistical test would be used.

We used binary logistic regression models to examine the association of DMFT, number of teeth and number of decayed teeth (used as predictors one by one) with total cholesterol, LDL cholesterol, HDL cholesterol, diabetes, obesity and hypertension (dichotomised and used as the outcome one by one). These associations were explored in both univariable and multivariable models. In multivariable models the estimates were adjusted for age, smoking and number of dentist visits which are important potential confounders.

Then the associations between FRS and oral health variables (DMFT score, number of teeth, number of decayed teeth) were examined using liner regression analysis. Both crude and adjusted models have been used. Furthermore, association of FRS≥20 and FRS≥30 with dental parameters has been analysed using univariable and multivariable logistic regression models. Differences between men and women that has been noted were examined by interaction tool on SPSS for regression tests. SPSS statistical package (SPSS 26 - Mac) was used to run the analyses. A 5% level of significance was applied.

IV. Ethical approval and data handling

According to the new regulations for ethical approval for research projects that use data from the Tromsø Study, it is not needed to have ethical approval from the Regional Committees for Medical and Health Research Ethics (REC) for small research projects that uses anonymise data file with up to 20 variables. It is the situation in this study so we wouldn’t need REC approval. The application has been already approved for this protocol and the data has been collected by the researchers.

4. Results

I. Baseline characteristics

Cardiovascular risk profile

After inclusion and exclusion criteria the study population comprised 3374 individuals, 1736 women and 1638 men. Age distribution did not differ between women and men (Table 1). In women, 29.7% were younger than 50 years, 55.9% were aged 50-69 years and 14.4% were 70 years or older; in men the corresponding proportions were 28.7%, 54.7% and 16.6%, respectively. The mean value of total cholesterol was higher in women compared to men: 5.59 mmol/L versus 5.38 mmol/L, respectively. LDL cholesterol level did not differ between women and men (p=0.48), while HDL cholesterol was higher in women compared to men. Mean levels of systolic and diastolic blood pressure as well as the proportion of those with hypertension were higher in men compared to women. Furthermore, obesity and diabetes were more prevalent in men than in women: 26.6% and 21.5%, respectively. In contrast, smoking was more prevalent in women than in men. Proportion of smokers was 14.6% in women and 11.9 % in men. Finally, FRS was almost three times higher in men compared to women: 15.6% versus 5.3%, respectively, p<0,01. To sum up, cardiovascular risk profile factors were more favourable in women than in men.

Oral health variables

The medians for DMFT were 18 and 19 for women and men, respectively, p=0.19 (Table1). The medians (quartiles) for teeth number were 26 (24; 28) in women but 26 (23;28) for men p=0.01. median for decayed teeth was 0 in both men and women but the third quartile median was higher in men p< 0.01.

Table 3. Descriptive characteristics of the study population. The Tromsø Study 2015-2016.

	Women (n=1736)	Men (n=1638)	P value
Age[a]			0.22
<50 years	515 (29.7%)	470 (28.7%)	
50-69 years	971 (55.9%)	896 (54.7%)	
≥70 years	250 (14.4%)	272 (16.6%)	
Serum total cholesterol[b]**, mmol/L**	5.59 (1.04)	5.38 (1.10)	< 0.01
LDL cholesterol[b]**, mmol/L**	3.59 (0.98)	3.62 (1.00)	0.48
HDL cholesterol[b]**, mmol/L**	1.75 (0.49)	1.39 (0.40)	< 0.01
Systolic blood pressure[b]**, mmHg**	127.0 (20.8)	133.4 (18.4)	< 0.01
Diastolic blood pressure[b]**, mmHg**	72.8 (9.6)	78.7 (9.7)	< 0.01
Hypertension[a]	628 (36.2%)	780 (47.6%)	< 0.01
Obesity[a]	374 (21.5%)	435 (26.6%)	< 0.01
Diabetes[a]	80 (4.6%)	108 (6.6%)	0.01
Smoking[a]	254 (14.6%)	195 (11.9%)	0.01
Framingham Risk Score[c]**, %**	5.3 (2.8; 11.7)	15.6 (7.9; 25.3)	< 0.01
DMFT score[c]	18 (13; 22)	19 (13; 22)	0.19
Number of Teeth[c]	26 (24; 28)	26 (23; 28)	0.01
Number of Decayed Teeth[c]	0 (0; 0)	0 (0; 1)	< 0.01

DMFT indicates Decayed Missed Filled Teeth; HDL high-density lipoprotein; LDL low-density lipoprotein.

Values in the table are: [a]number (%) for categorical variables, [b]means (standard deviations) for continuous variables, and [c]medians (Q1; Q3) for discrete variables.

II. Association between quadrant Decayed Missed Filled Teeth Score and cardiovascular risk profile

Univariable and multivariable logistic regression analyses were performed to examine the crude and adjusted ORs of each of the cardiovascular risk factors (dichotomized) for quadrant DMFT (Table 2). In adjusted models, increasing DMFT score was associated with elevated total cholesterol and LDL cholesterol levels in women, but not in men. In women, one unit increase in quadrant DMFT (7 decayed, missed or filled teeth) was associated with 1.22- and 1.21-times higher odds of having elevated total cholesterol and elevated LDL cholesterol, respectively. In contrast, increasing DMFT score was associated with lower odds of having normal HDL cholesterol level in men, but not in women. One unit increase in quadrant DMFT in men was associated 24% lower odds of having normal HDL. Furthermore, there was no independent association between quadrant DMFT and diabetes neither in women nor in men. However, we discovered an association between quadrant DMFT and obesity in both sexes. One unit increase in quadrant DMFT was associated with 1.25- and 1.33-times higher odds of having obesity in women and men, respectively. Finally, quadrant DMFT was not independently associated with hypertension neither in women nor men. In conclusion, higher DMFT score which indicates unfavourable oral health was associated with unfavourable total cholesterol and LDL cholesterol levels in women, unfavourable HDL cholesterol levels in men, and higher odds of obesity in both women and men.

Table 4. Sex-specific crude and adjusted odds ratios of cardiovascular risk factors for quadrant DMFT. The Tromsø Study 2015-2016.

	Women (n=1736)		**Men** (n=1638)	
Dependent variables	**OR (95% CI)[a]**	**OR (95% CI)[b]**	**OR (95% CI)[a]**	**OR (95% CI)[b]**
Elevated total cholesterol	**1.52 (1.36- 1.70)**	**1.22 (1.05 – 1.41)**	**0.82 (0.74-0.92)**	0.95 (0.83 – 1.09)
Elevated LDL cholesterol	**1.38 (1.24 – 1.54)**	**1.21 (1.04 – 1.39)**	**0.76 (0.67 - 0.86)**	0.99 (0.85 – 1.14)
Normal HDL cholesterol	.0.93 (0.60 – 1.43)	0.92 (.51– 1.64)	0.95 (0.79 – 1.14)	**0.76 (0.61 – 0.96)**
Diabetes	1.09 (0.86 – 1.40)	0.78 (0.57 – 1.05)	**1.68 (1.32 – 2.15)**	1.30 (0.97 – 1.72)
Obesity	1.10 (0.97 – 1.25)	**1.25 (1.06 – 1.48)**	1.09 (0.97 – 1.23)	**1.33 (1.14 – 1.55)**
Hypertension	**2.19 (1.93 – 2.48)**	1.08 (0.92 – 1.26)	**1.63 (1.45 – 1.82)**	1.04 (0.90 – 1.19)

CI indicates confidence interval; DMFT Decayed Missed Filled Teeth; HDL high-density lipoprotein; LDL low-density lipoprotein; OR odds ratio.

Quadrant DMFT is calculated as DMFT score divided by 7 and used as the main predictor in logistic regression models. Each of the cardiovascular risk factors (dichotomized) was used as a dependent variable in a corresponding logistic regression model. [a] Crude OR (95% CI). [b]OR (95% CI) adjusted for age, smoking and dentist follow up.

III. Association between quadrant teeth number and cardiovascular risk profile

In adjusted models, there was significant association between teeth number and elevated total cholesterol level in both women and men (Table 3). One unit increase in quadrant teeth number (7 teeth increase) is associated with 1.42- and 1.21-times higher odds of having elevated cholesterol in women and men, respectively. Moreover, there was significant association between quadrant teeth number and LDL cholesterol in both men and women. One unit increase in the quadrant teeth number was associated with 1.33- and 1.49-times higher odds of having elevated LDL cholesterol level. However, quadrant teeth number was associated with HDL cholesterol in men only. One unit increase in quadrant teeth number was associated with 1.48 times higher odds of having normal HDL cholesterol level. Quadrant teeth number was not significantly associated with diabetes neither in women nor in men. Moreover, there was a significant association between quadrant teeth number and obesity in both women and men. One unit increase of quadrant teeth number was associated with 19.0% and 31.0% lower odds of having obesity in women and men, respectively. Finally, quadrant teeth number was associated with having hypertension in women. One unit increase in quadrant teeth number was associated with 28.0% lower odds of having hypertension in women. To sum up, teeth number (favourable for oral health) has favourable association with HDL cholesterol in men, hypertension in women, and obesity in both genders. However, the association with total and LDL cholesterol was unfavourable in both women and men: those with more teeth had higher total and LDL cholesterol levels.

We have not found any association between decayed teeth number and cardiovascular risk profile variables (data is not shown).

Table 5. Sex-specific crude and adjusted odds ratios of cardiovascular risk factors for quadrant teeth number. The Tromsø Study 2015-2016.

	Women (n=1736)		**Men** (n=1638)	
Dependent variables	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Elevated total cholesterol	0.93 (0.81- 1.06)	**1.42 (1.20 - 1.68)**	**1.35 (1.19- 2.52)**	**1.21 (1.05- 1.40)**
Elevated LDL cholesterol	0.96 (0.84 - 1.10)	**1.33 (1.13 – 1.57)**	**1.49 (1.32 - 1.69)**	**1.23 (1.06 – 1.43)**
Normal HDL cholesterol	1.01 (0.59 – 1.69)	0.97 (0.52 – 1.83)	1.16 (0.96 – 1.41)	**1.48 (1.18 – 1.85)**
Diabetes	0.78 (0.61 – 1.01)	1.01 (0.73 – 1.37)	**0.66 (0.55- 0.80)**	0.83 (0.66 – 1.05)
Obesity	0.88 (0.77 – 1.02)	**0.81 (0.68 – 0.96)**	**0.84 (0.74 – 0.96)**	**0.69 (0.59 – 0.81)**
Hypertension	**0.39 (0.34 – 0.46)**	**0.72 (0.60 – 0.85)**	**0.55 (0.47 – 0.63)**	0.87 (0.74 – 1.02)

CI indicates confidence interval; HDL high-density lipoprotein; LDL low-density lipoprotein; OR odds ratio.

Quadrant teeth number is calculated as teeth number divided by 7 and used as the main predictor in logistic regression models. Each of the cardiovascular risk factors (dichotomized) was used as the dependent variable. [a] Crude OR (95% CI). [b]OR (95% CI) adjusted for age, smoking and dentist follow up.

IV. Association between oral health parameters and Framingham risk score

Using linear regression, we found significant association between quadrant DMFT and FRS in men, but not in women (Table 4). One unit increase in quadrant DMFT was associated with 0.57 units increase in FRS in men. Moreover, there was significant association between quadrant teeth number and FRS in both women and men. One unit increase of quadrant teeth number was associated with 1.09 and 0.44 units decrease in FRS in women and men respectively. There was no significant association between decayed teeth number and FRS in neither women nor men. To sum up, quadrant DMFT (unfavourable for oral health) had unfavourable association with FRS in men, but quadrant teeth number (favourable for oral health) had favourable association with FRS in both sexes.

Table 6. Sex-specific crude and adjusted regression coefficients of Framingham risk score for oral health parameters. The Tromsø Study 2015-2016.

	Women (n=1736)		**Men** (n=1638)	
	b^a p-value	b^b, p-value	b^a, p-value	b^b, p-value
Quadrant DMFT	**3.63 (p<.01)**	-0.03 (p=0.86)	**4.86 (p<.01)**	**0.57 (p<0.01)**
Quadrant teeth number	**-4.51 (p<0.01)**	**-1.09(P<0.01)**	**-5.05 (p<0.01)**	**-0.44 (p=0.02)**
Decayed teeth number	**-6.95 (p<0.01)**	1.32 (p=0.27)	**-3.89 (p<0.01)**	0.34 (p =0.71)

DMFT indicates Decayed Missed Filled Teeth.

Framingham risk score was used as the dependent variable in linear regression models. [a]Crude regression coefficients, b. [b]Regression coefficients, b, adjusted for age, smoking and dentist follow up.

Using binary logistic regression, we found significant independent association between quadrant DMFT and FRS ≥ 30% in men, but not in women (Table 5). One unit increase in quadrant DMFT in men was associated with 1.44 times higher odds of having FRS ≥ 30%. Moreover, there was significant independent association between quadrant teeth number and having FRS ≥ 30% in men, but not in women also. One unit increase of quadrant teeth number was associated with 23% lower odds of having FRS ≥ 30%. There was no significant statistical association between decayed teeth number and FRS in neither women nor men. To sum up, in men quadrant DMFT (unfavourable for oral health) had unfavourable association with having FRS≥30%, while quadrant teeth number (favourable for oral health) had favourable association with FRS ≥ 30%. Decayed teeth number had no independent association with FRS in both sexes. The p-values for interaction between sex and quadrant DMFT and between sex and quadrant teeth number for having FRS ≥ 30% were <0.01.

Table 7. Sex-specific crude and adjusted odds ratios of high Framingham risk score ≥ 30% for oral health parameters. The Tromsø Study 2015-2016.

	Women (n=1736)		**Men** (n=1638)	
	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Quadrant DMFT	**4.35 (2.33 – 8.10)**	1.36 (0.69 – 2.67)	**3.57 (2.87 – 4.44)**	**1.44 (1.11 – 1.87)**
Quadrant teeth number	**0.41 (0.31 – 0.56)**	.90 (0.59 – 1.36)	**0.38 (0.32 – 0.44)**	**0.77 (0.64 – 0.93)**
Decayed teeth	0.18 (0.01 – 25.32)	2.04 (0.01 – 411.24)	**0.28 (0.08 –0.95)**	0.57 (0.12 – 2.59)

DMFT indicates Decayed Missed Filled Teeth.

Framingham risk score was dichotomized (those with high cardiovascular risk had score≥30%) and used as the dependent variable in logistic regression models. [a] Crude OR (95% CI). [b]OR (95% CI) adjusted for age, smoking and dentist follow up.

Using logistic regression models there was no independent association of quadrant DMFT and decayed teeth number with having FRS ≥ 20% (Table 6). However, quadrant teeth number had significant association with having FRS ≥ 20 in women. One unit increase in quadrant teeth number was associated with 28.0% lower odds of having FRS ≥ 20 in women. P-value for interaction between sex and quadrant teeth number on odds of having FRS ≥ 20 was <0.01. This confirms that association of quadrant teeth number with odds of having FRS ≥ 20 differs by sex.

Table 8. Sex-specific crude and adjusted odds ratios of high Framingham risk score ≥ 20% for oral health parameters. The Tromsø Study 2015-2016.

	Women (n=1736)		**Men** (n=1638)	
	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[a]	OR (95% CI)[b]
Quadrant DMFT	**3.82 (2.94 – 2.98)**	1.12 (0.82- 1.55)	**2.87 (2.47 – 3.32)**	0.99 (0.81 – 1.20)
Quadrant teeth number	**0.33 (0.28 – 0.39)**	**0.72 (0.59 – 0.89)**	**0.32 (0.27- 0.38)**	0.95 (0.79 – 1.15)
Decayed teeth	0.21 (.03 – 1.62)	2.82 (0.24 – 33.65)	0.54 (0.26 – 1.14)	1.26 (0.50 – 3.16)

DMFT indicates Decayed Missed Filled Teeth.

Framingham risk score was dichotomized (those with high cardiovascular risk had score ≥2 0%) and used as the dependent variable in logistic regression models. [a] Crude OR (95% CI). [b]OR (95% CI) adjusted for age, smoking and dentist follow up.

The description of direction for associations of DMFT score and teeth number with cardiovascular risk profile is shown in table 9.

Table 9. Direction of associations of DMFT and teeth number with cardiovascular risk factors and Framingham risk score.

	Women (n=1736)		Men (n=1638)	
Dependent variables	**DMFT** (unfavourable for oral health)	**Teeth number** (favourable for oral health)	**DMFT** (unfavourable for oral health)	**Teeth number** (favourable for oral health)
Elevated total cholesterol	Unfavourable	Unfavourable		
Elevated LDL cholesterol	Unfavourable	Unfavourable		
Normal HDL cholesterol			Unfavourable	Favourable
Diabetes				
Obesity	Unfavourable	Favourable	Unfavourable	Favourable
Hypertension		Favourable		
FRS		Favourable	Unfavourable	Favourable
FRS ≥ 30%			Unfavourable	Favourable
FRS ≥ 20%		Favourable		

DMFT indicates Decayed Missed Filled Teeth.; FRS Framingham risk score; HDL high-density lipoprotein; LDL low-density lipoprotein.

Favourable associations are marked by green, unfavourable associations are marked by red.

5. Discussion

I. Results summary

This study showed that increased number of DMFT had unfavourable associations with total cholesterol and LDL in women, HDL in men and obesity in both men and women. Increased number of teeth had favourable association with HDL in men, hypertension in women and obesity in both men and women. In contrast, number of teeth had unfavourable association only with total cholesterol and LDL in women. DMFT had unfavourable association with FRS in men, but not in women. Increased teeth number had favourable association with FRS in both men and women but with different grades as described in the results.

ii. Discussion of the results in the light of present evidence

Our results coincide with the present evidence. For example, the link between periodontitis and hyperlipidaemia had been proved in humans and also in non-human primates (13) (14) (29), but again, as we described in the introduction chapter most of those studies analysed the association with periodontitis only which is a very narrow branch of the oral health. Those studies had neglected the most important confounder which is oral health itself that could cause both periodontitis and increase CVD risk. The association between oral health and cardiovascular risk profile has been proved through this study. This confirms that the associations are not restricted to only periodontitis, but also overall health of the oral cavity and stomatognathic masticatory functions. Thus, periodontitis would be used in this context as one variable that describes oral health like DMFT score and number of teeth. In contrast to the studies mentioned above we found that compromised oral health (higher DMFT score) was associated with total and LDL cholesterol in women only. However, higher DMFT score was associated with lower levels of HDH cholesterol only in men. Interestingly, we found that number of teeth was associated with higher total and LDL cholesterol in both women and men in our study. This might be due to the fact that some of the teeth in those individuals who had more teeth could be decayed or filled, and therefore would increase odds of dyslipidaemia.

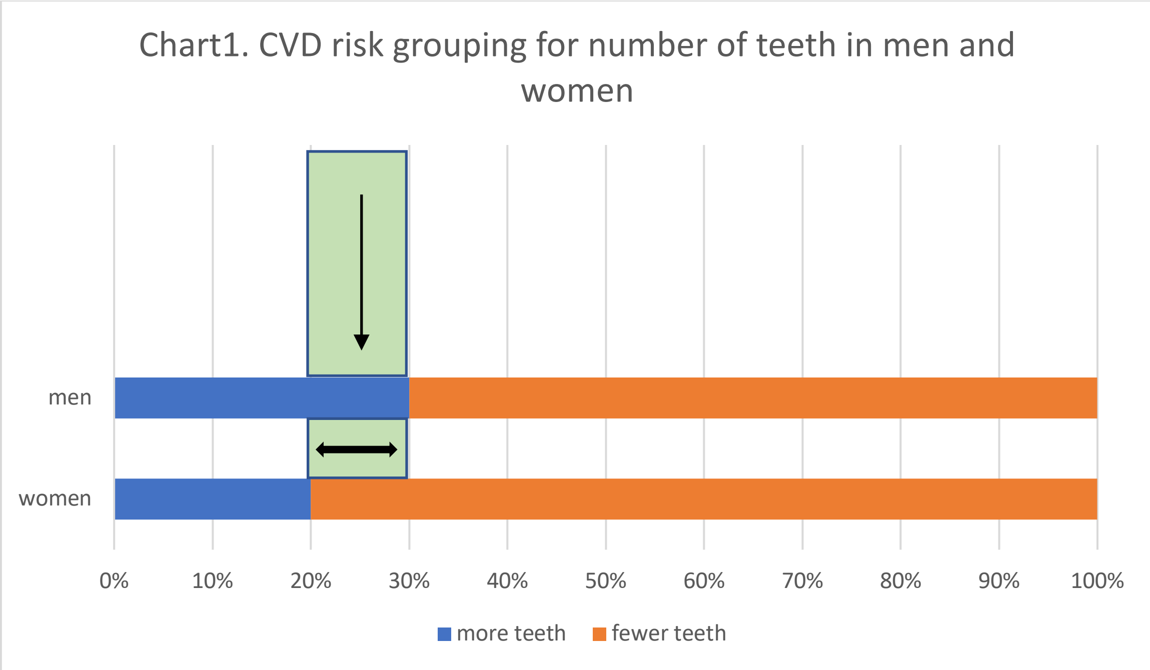
Association of compromised oral health with obesity had been proved in our study. These findings could be criticised as the diet could be a confounder. High carbohydrate diets increase the risk of carious lesions (30). But the association of high carbohydrate level and obesity itself is questionable topic with very weak evidence (31). Furthermore, even if there was an association between high carbohydrates diet and obesity this will lead us to the chicken or the egg causality dilemma. Is the compromised oral health changes the subjects´ choice to eat more carbohydrates because it is easier to chew or it is high carbohydrate food causes both obesity and compromised oral health?! This dilemma would be relevant for obesity, but not for the association between higher number of teeth and decreased odds of hypertension, for example.

There are many studies that linked periodontitis (oral disease) with increased odds of hypertension (32). Moreover, studies showed that it is more difficult to treat hypertension in patients with periodontitis and treating periodontitis increases the efficiency of antihypertensive drugs (32)& (33). This could support the hypothesis that that the compromised oral health causes hypertension, not the other way around. We also found that higher number of teeth was associated with decreased odds of hypertension, but in women only.

III. Discussion of differences between linear and logistic regression models with Framingham risk score as the outcome.

Regarding teeth number, in linear regression models association between number of teeth and favourable FRS was found in both women and men, but the association was stronger in women. In logistic regression models with FRS ≥ 30%, yes/no as the dependent variable it was noted only for men only. In contrast, in the logistic regression models with FRS ≥ 20%, yes/no as the dependent variable it was only noted only in women.

These differences in findings between the regression models can be explained by gender differences in risk of developing CVD. The group of those with 20 < FRS < 30 was more likely to have fewer teeth in women, but more teeth in men (Figure 4). In another words, if the theory that states that compromised oral health increases the risk of CVD development is true, the effect of having compromised oral health would have more negative impact in men than in women. This coincides with the available evidence which confirms that the incidence of CVD is higher in men than women (28). Thus, those findings could to some extent support the theory of causality. N.B. This is just an assumption because this study confirms the association not the causation because of the cross-sectional nature of the data.



This difference in the nature of association according to different grouping method is also noted for DMFT variable. In linear regression, DMFT ws associated with unfavourable FRS only in men. In binary logistic regression (FRS ≥ 30%; yes/no) it is also noted only in men. In binary logestic regression model (FRS ≥ 20% yes/no) no association noted.

To sum up, the linear regression statistical method was identical to the addition of the two binary logistic statistical methodes that differs only in categorization of FRS (Table 8). Thus , (FRS ≥ 30%; yes/no) were noted to be more suitable categorization method for men and (FRS ≥ 20%; yes/ no) were noted to be more suitable categorization method for women.

Table 10. addition of positive results from two binary logestic regression model will form the results from the linear regression model.

	Women (n=1736)		Men (n=1638)	
Dependent variables	**DMFT** (unfavourable for oral health)	**Teeth number** (favourable for oral health)	**DMFT** (unfavourable for oral health)	**Teeth number** (favourable for oral health)
FRS ≥ **30% (yes,no)**			Unfavourable	favourable
FRS ≥ **20% (yes, no)**		favourable		
FRS (linear regression)		favourable	Unfavourable	favourable

DMFT indicates Decayed Missed Filled Teeth.; FRS Framingham risk score; HDL high-density lipoprotein; LDL low-density lipoprotein.

Favourable associations are marked by green, unfavourable associations are marked by red.

iv. Methodological discussion

Generalization of association to overall oral health rather than periodontitis.

As mentioned in the introduction, many studies linked CVD with oral health expressed by periodontitis. The mechanism was thought to be the inflammatory condition caused by periodontitis that exacerbates atherogenesis (34). In this study, the aim was to link the oral health and its function to the development of CVD, and not just a single inflammatory oral disease inside the human body (periodontitis) that could cause serological changes that lead eventually to CVD. In this study we did not do the same. The association is studied from another prospect. We used DMFT and number of teeth variables to describe the oral health state rather than periodontitis. Number of teeth variable describes the masticatory function of the oral cavity not the inflammatory state. This is because the tooth is the unit of function in the oral cavity. Thus, the findings of this study that links number of teeth with increased CVD risk in both men and women confirms that masticatory function itself could be preventive factor for CVD and its compromising either by periodontitis or any other oral lesion could increase the CVD risk.

Why we studied the association of oral health with cardiovascular risk profile not cardiovascular disease incidence

This study did not link oral health directly with CVD incidence because this would not help us to see the possible pathway in which compromised oral health could be etiological factor for increased CVD. But instead, we linked oral health describing variables to the cardiovascular risk profile. This would help to investigate which of CVD risk variables is associated with compromised oral health. Thus, those variables can be considered as a possible branch of CVD etiological cascade that begins with compromised oral function and ends with CVD incidence. Those suspected variables can be assessed further in prospective studies either biological or epidemiological, that will be able establish causality, like cohort or case-control studies.

Additionally, linking oral health with CVD risk factors would support to some extent the theory of causality. It is more likely to think that compromised oral health could cause dyslipidaemia or hypertension than the other way around. Specially for hypertension which have evidence that having an oral lesion like periodontitis have bad consequences on the efficiency of antihypertensive drugs (32)& (33). On the other hand, if CVD incidence was used directly there would be more uncertainty of the direction of the corelation.

Framingham risk score

FRS was categorised and dichotomised in two different methods (FRS ≥ 30%; yes/no) and (FRS ≥ 20%; yes/no). Catigorization itself was not simple process and we desided to use to different cutpoints because of two reasons. First, categorization used in the Framingham risk tool is arbitrary. Second and the most important is that FRS translates risk points diffrently in men and in women. For example in one hand, if we considered FRS ≥20% as high CVD risk group, then subjects with 15 to 30 risk points in men would be valued the same which can affect the results. Specially taking into account that age in men has a very big impact on the risk points (from 0 to 15). But for women if we used the same cutpoint, it would be narrower and more suitable range from 18 to 29 points. Considering that the impact of age in women is not as strong (from 0 to 12).

On the other hand, if we consider FRS ≥ 30% as the high risk group, the range of risk points would be more suitable for men (from 18 to 30 risk points), but it could be problematic for women because the range would be very narrow (from 21 to 29 only).

Thus, both categorization methods were used. This also supports what had been discussed about investigation of different results in the different categorization methods.

V. Implementation of the study findings and future prospects

This study confirms strong association between compromised oral health and increased risk of developing CVD. The importance of prevention and treatment of oral disease had been doubled through those findings. Missing a tooth is no more seems like just missing of masticatory surface but also as a step for getting CVD (either as indicative factor or etiological factor).

Another prospect is the difference between women and men in the corelated CVD risk factors with Oral health. In women the association was mainly with total cholesterol, LDL, obesity and hypertension, but in men association was mainly with HDL and obesity. This reveals one important fact if the causality was stablished in the future so the preventive measure should be sex specific according to the findings of this study and other studies that could be based upon it.

Moreover, this study findings open a new horizon to assess the link between oral health and CVD from another prospect. The new prospect is oral function and not just inflammatory oral lesions like periodontist. Here appears the need to conduct other prospective studies that are based on these findings. Those studies should investigate the nature of association of oral health and its masticatory function with CVD risk factors either by biological studies or epidemiological studies that could establish causality. Those studies should investigate if compromised oral health and function causes increasing in significantly associated CVD risk variables in current study or not. The most important variables in this sense are dyslipidaemia, obesity and hypertension.

VI. strength and limitations:

In this study we had enough power to separate men and women during the analysis. This allowed us to probe the difference between both genders in all aspects of the study question.

But in the other hand the main limitation for this study is the nature of cross-sectional design. Cross sectional study design cannot stablish the temporal relation between the exposure and the outcome. (35) This is mainly because exposure and outcome have been evaluated in the same point of time.

Additionally, we took in consideration all suspected confounder, however we are not sure if it is all possible confounders or not. For example, diet can be possible confounder but we didn´t adjust for it for two main reasons. First, it can be on the causal pathway where we don´t know if oral health can affect diet or the other way around. Second Diet is very complicated term that composed of dozens of variables and very hard to adjust for it in this study.

VI. Recommendation about future studies on cardiovascular disease

CVD etiological cascade is like jig saw puzzle. It is composed of small pieces of associated and corelated factors that if put together we can see the whole picture of aetiology for CVD. To solve this puzzle, we collect the similar pieces together that would form small portions of the whole picture. Those portions can be added together to form the final image. This is the same of what can be done with CVD.

To properly understand CVD risk factors, we should get tangles between those factors decrypted. This can be done by separating CVD risk factors into subgroups which describes the origin of risk. This strategy aims to decreasing the number of confounding and corelated factors. For example, those risk factors that originated from systemic conditions that affects each other can put together in the same group, etc. This is just a recommendation that if would be applied would need finalization and experts review about proper categorization that can be performed.

6. Conclusion

favourable oral health is generally associated with favourable CVD risk profile. Compromised oral health and stomatognathic function is a risk factor for CVD and needs more investigation if it is a direct causative factor or not.

This association is presenting in both genders but with different natures. Teeth number (which depicts oral function and when increases shows better oral health) had a favourable association with obesity, hypertension and FRS in women. Furthermore, it has favourable association with HDL cholesterol, obesity and FRS in men. However, it had unfavourable association with total cholesterol and LDL in women.

DMFT score (when increases expresses more compromised oral health) had an unfavourable association with total and LDL cholesterol, and obesity in women. Additionally, it had an unfavourable association with HDL cholesterol, obesity and FRS in men.

Those sex specific differences should be taken in consideration in any future studies or in any preventive strategies that is concerned with the link between oral health and CVD. The main concern should be in which gender oral health is associated with which CVD risk variable with which grade.

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