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# NUMBER OF TOOTH EXTRACTIONS IS ASSOCIATED WITH INCREASED RISK OF MORTALITY

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## Abstract

### Background

The association of tooth loss with mortality is unclear. The association of a trend in number of tooth extractions and total mortality was examined in the Oslo II-study in 2000 where 6517 men were followed-up for 12 ½ years.

### Method

This prospective cohort study on men aged 48 to 77 years at baseline provided screening data on oral and general health status and several known risk factors. Statistics Norway provided mortality information.

### Results

Total mortality was reported for 2358 men including 742 deaths from cardiovascular diseases (CVD) and 1616 deaths from other causes. Cox's proportional hazard regressions were used to estimate the risk of self-reported tooth extractions on mortality. The number of tooth extractions was stratified as 0, 1-4, 5-9, 10-28, and 29-32, and Kaplan Meier plot illustrates the risk differences in total mortality between these strata. Number of tooth extractions was reported by 4157 men, 673 men had no extractions, and 1687 men did not report the number of extractions. The number of individuals with a history of extractions per category was 2574 for 1-4 extractions, 832 for 5-9, 547 for 10-28, and 204 for 29-32, respectively. Risk factors as age, total cholesterol, systolic blood pressure, daily smoking, diabetes,

education (inversely) and antihypertensive medication were significantly associated with increasing number of tooth extractions. Trend analyses adjusted for CVD confounders were significant for total mortality and non-CVD causes and CVD when age-adjusted. The category of 29-32 extractions (considered to be edentulous persons) versus no extractions was significantly associated with 50% increased risk for non-CVD mortality, 46% for total mortality and a non-significant association of 30% for CVD.

## Conclusions

Increasing number of tooth extractions was independently associated with total mortality and non-CVD mortality in analyses adjusted for CVD confounders. The association with CVD mortality was weaker, but significant in age-adjusted analysis.

## Introduction

Previously, an association between tooth loss and mortality has been reported [1-10]. Oral infections such as periodontitis and dental caries are common disorders worldwide and the prevalence of severe periodontitis is in the order of 5–15% in most population [11]. The prevalence of mild, moderate, and severe periodontitis among adults aged  $\geq 30$  years for the period 2009–10 was reported as 8.7, 30.0 and 8.5%, respectively [12]. Among Norwegian persons aged 67 years or older periodontitis was diagnosed in 33% and 12% had severe periodontitis [13].

The registration of tooth loss in the different studies has either been by a clinical examination or self-reported on a health survey questionnaire. The consistency of the association between tooth loss and mortality across different populations, strengthen the validity of this finding even if the estimated risk levels vary between these studies. The 14-year follow-up of the National Health and Nutrition Examination Survey I (NHANES I)

in 1986 involving 51529 men [1] reported that men with fewer than 25 teeth, self-reported information, were at a higher relative risk of stroke of 1.57 (95% confidence interval (CI) 1.24–1.98). Missing molars and periodontitis, clinical information, have been found to increase the risk of death from neoplasms, cardiovascular diseases (CVDs) and diseases of the digestive system [4]. Results of the National FINNRISK 1997 study showed increased risk for incident cardiovascular events, diabetes and death for  $\geq 9$  missing teeth [6]. The Scottish Health Heart survey reported on tooth loss and CVD mortality [8]. Results showed that edentate people had a hazard rate (HR) of 1.65 (CI=1.31–2.07) for all-cause mortality and 1.76 (CI=1.19–2.59) for CVD mortality. A study on an elderly Japanese population showed that people with  $\geq 20$  teeth had a significantly lower 5-year mortality rate [9]. Different cut off levels of number of extracted teeth have been used varying from edentate participants to more than 6, 9 or 22 teeth, or above the median [2,3,5,7,10]. The risk estimates ranged from 1.13 for total mortality to 3.25 for stroke.

At a health survey in Oslo, Norway in 2000, information on causes of tooth extractions and other health information was recorded using a self-administered questionnaire [14]. The aim of the present study was to study whether we could identify a risk trend according to the number of extracted teeth in three prediction models after adjusting for age, oral health confounders, and CVD confounders and the relation to mortality during 12 ½ years of follow-up.

## Materials and Methods

### Study population

In 2000, all surviving participants of a cohort study undertaken among men in Oslo in 1972–73 were invited to participate in a new health survey [14,15]. Altogether, 12764 men who lived in Oslo or the neighbouring county of Akershus, were invited to participate and 6530

attended the second survey, the Oslo II study, which was carried out from February 2000 to June 2000 (Figure 1). In all 6517 men reported tooth extraction status. The number of extractions was not reported by 1674 men. All participants signed a written statement of consent to take part in the study, authorizing the Norwegian Data Inspectorate and the Regional Committee for Research Ethics to grant permission for future links to disease and death registers, and for analyses of the data recorded and biological samples.

### Survey procedures

Nurses trained in health screening procedures were responsible for the survey. The screening included anthropometric body measurements of height, weight, and waist and hip circumference, and measurement of blood pressure. Serum measurements were total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose in a non-fasting state [16]. High-sensitive C-reactive protein (hs-CRP) was later analysed from frozen serum samples stored at  $-80^{\circ}\text{C}$ . Major items in the questionnaire included medical history, dietary factors, smoking and alcohol use, living conditions, use of medical and dental services, prescribed drugs used in the previous year, physical exercise at leisure and at work, oral health information, mental health and life satisfaction. Figure 1 presents the flow-chart of the Oslo I and II studies.

The reason for tooth extraction was recorded for: (1) infection of the gum, (2) infection in single teeth, (3) trauma or (4) other cause. Results of these analyses are reported on number of teeth irrespective of reason for extraction. Number of teeth is further categorized to 0, 1-4, 5-9, 10-28, and 29-32. This involves a truncation of results at high number of extractions due to the skewed distribution of extractions among participants and to retain power in the analyses. The category 29-32 is considered to include edentulous persons at the time of the screening as it is not uncommon to have a few congenitally missing teeth.

### Health outcome and mortality assessment

The end-points in this cohort study were all deaths recorded during the follow-up time, i.e. from baseline examination until 31. December, 2012. In the analyses, the underlying cause of death was used. Statistics Norway provided the mortality data through linkage to the original cohort data file of the national death register, using the unique Norwegian personal identity numbers. The main outcomes were total mortality, CVD mortality, and mortality from other causes. The Norwegian Data Inspectorate and the Regional Committee for Research Ethics granted permission for the study. The study was carried out according to the Helsinki Declaration. The database was anonymized for researchers. The STROBE guidelines have been followed in the preparation of this manuscript.

### Statistical analyses

Rate of mortality per 1000 person years was calculated for total mortality, CVD and other causes of mortality. The basic characteristics are given as numbers and percentages or means and standard deviations (SDs) when appropriate. Test for trend across extraction categories was by ANOVA for continuous variables and Chi-square test for dichotomous variables. Proportional regression analyses (Cox) were used to estimate the HR from baseline examination to death or end of follow-up by 31. December, 2012. Dates of death were obtained from the National Population Register.

Three models were used to assess the association between oral health (TE, OI) and mortality:

Model 1: adjusted for age

Model 2: adjusted for age, daily smoking, diabetes and education (oral health confounders)

Model 3: adjusted for age, daily smoking, education, total cholesterol, systolic blood pressure, and diabetes (CVD

confounders)

Plot of cumulative hazard for total mortality is stratified by extraction categories (Figure 2). Statistical significance was achieved for  $p < 0.05$ . The statistical package IBM SPSS Statistics version 22 was used for the data analyses.

## Results

### Mortality and oral health

In all, 2358 men died during the follow-up period from July 2000 to December 2012, and the rate of mortality was 33.3 per 1000 person years. Of these men 742 (31.5%) died from CVD mortality and 1616 (68.5%) from other causes and the rate of mortality was 10.5 and 22.8, respectively. CVD mortality accounted for 33% of deaths during this 12 ½ years of follow-up. The largest extraction

category was 1-4 teeth reported by 2574 men, category 5-9 teeth by 832 men, category 10-28 by 547, and 29-32 by 204 men (Table 1). There were 673 men who reported not having extracted teeth and a further 1687 did not report the number of teeth extracted. For several baseline characteristics there was a significant trend with increasing number of tooth extractions, categorized, with age, systolic blood pressure, diabetes, daily smoking, and antihypertensive medication, but education inversely. BMI and cholesterol reducing medication were not associated with a trend for increased risk of mortality.

### Comparison of risk factor models

Three models of Cox proportional regression analyses were applied to total mortality, CVD mortality, and mortality by other causes (non-CVD); model 1) age adjusted, model 2) adjusted for oral health confounders,

**Table 1:** Age, education and cardiovascular risk factors according to Number of Teeth extracted among 6517 men (aged 48-77 years) screened in 2000

	Numbers not reported N=1687 (25.9%) 70.2 (5.6)	Number of Tooth Extractions by Categories					Trend* 0-32 p-value
		0 N=673 (10.3%) 67.3 (7.5)	1-4 N=2574 (39.5%) 68.3 (6.9)	5-9 N=832 (12.8%) 70.0 (5.3)	10-28 N=547 (8.4%) 70.9 (4.2)	29-32 N=204 (3.1%) 71.8 (3.4)	
Age (years) <sup>a</sup>							<0.001
Education (years) <sup>a</sup>	11.4 (3.4)	13.0 (3.3)	12.7 (3.2)	12.3 (3.4)	11.2 (3.4)	10.0 (3.0)	<0.001
Body mass index (kg/m <sup>2</sup> ) <sup>a</sup>	26.5 (3.5)	26.0 (3.1)	26.3 (3.2)	26.4 (3.5)	26.5 (3.8)	26.4 (3.7)	0.307
Total cholesterol (mmol/l) <sup>a</sup>	5.9 (1.1)	5.9 (1.0)	6.0 (1.0)	6.0 (1.1)	5.9 (1.1)	6.0 (1.1)	0.036
Systolic blood pressure (mmHg) <sup>a</sup>	145.4 (21.1)	142.7 (19.5)	143.3 (20.0)	144.4 (19.4)	145.6 (21.3)	147.3 (22.2)	0.003
Diabetes (yes) <sup>b</sup>	123 (7.4%)	32 (4.8%)	136 (5.4%)	60 (7.3%)	53 (9.8%)	21 (10.4%)	<0.001
Smoke daily (yes) <sup>b</sup>	433 (25.7%)	90 (13.4%)	398 (15.5%)	177 (21.3%)	152 (27.8%)	90 (44.1%)	<0.001
Antihyper-tensive medication <sup>b</sup>	538 (32.8%)	182 (27.3%)	696 (27.4%)	262 (31.8%)	170 (32.0%)	77 (38.7%)	<0.001
Cholesterol reducing medication <sup>b</sup>	289 (18.1%)	127 (19.2%)	423 (16.9%)	152 (18.9%)	97 (18.2%)	40 (20.7%)	0.078

<sup>a</sup>Values are mean (SD). <sup>b</sup> Values are n (%)

\*ANOVA for continuous variables and Chi-square-test for dichotomous variables

Figures in bold indicate  $p < 0.05$

**Table 2:** Hazard Ratio (95%CI) of total Mortality after 12.5 years of follow-up, according to Tooth Extraction History in men aged 48-77 years.

	Numbers not reported N=1694	Number of Tooth Extractions by Categories					Trend 0-32  p-value
		0 N=673	1-4 N=2574	5-9 N=832	10-28 N=547	29-32 N=204	
<b>Total mortality</b>							
<b>Age-adjusted</b>							
HR	1.44	1.00 (ref)	<b>1.03(0.87-1.21)</b>	1.09	1.43	1.97	< 0.001
(95% CI)	(1.22-1.69)		<b>0.750</b>	(0.08-1.30)	(1.18-1.73)	(1.56-2.48)	
p-value	<0.001			0.410	<0.0001	<0.0001	
<b>Adjusted for oral health confounders *</b>							
HR	1.25	1.00 (ref)	0.99	0.99	1.23	1.50	< 0.001
(95% CI)	(1.06-1.48)		(0.84-1.16)	(0.82-1.20)	(1.01-1.49)	(1.18-1.91)	
p-value	0.008		0.875	0.933	0.040	0.001	
<b>Adjusted for CVD confounders **</b>							
HR	1.25	1.00 (ref)	1.003	0.96	1.19	1.46	< 0.001
(95% CI)	(1.03-1.50)		(0.84-1.20)	(0.77-1.118)	(0.95-1.48)	(1.11-1.92)	
p-value	0.022		0.977	0.669	0.129	0.006	

\*Oral health confounders are age, daily smoking, education and diabetes

\*\*CVD confounders are Oral health confounder plus total cholesterol, systolic blood pressure, and diabetes

Figures in bold indicate p<0.05

model 3) adjusted for cardiovascular confounders (Table 2 & 3). With regard to total mortality, there was a significant increasing trend across the extraction categories for all three risk factor models. The oral health confounders modified the age-adjusted risk from HR=1.43 (CI=1.18-1.73) to 1.23 (CI=1.01-1.49) for category 10-28 and from 1.97 (CI=1.56-2.48) to 1.50 (CI=1.18-1.91) for category 29-32, respectively. When adjusted for CVD confounders and the oral health confounders the risk for category 10-28 was non-significant, but for category 29-32 HR was 1.46 (CI=1.11-1.92). The group not reporting number of extractions were on level with the category 10-28 with HR of 1.44 (CI=1.22-1.69), 1.25 (CI=1.06-1.48), and 1.25 (CI=1.03-1.50) for the three models.

Cardiovascular mortality showed a significant association to tooth extractions in age-adjusted analyses with HR ranging from 1.50 (CI=1.06-2.11) in category 10-

28 to HR=1.81(CI=1.18-2.77) in category 29-32 and with a significant trend across the categories. Men who had not reported number of extractions, the HR was 1.47 (CI=1.09-1.98) (Table 3). The hazard ratios after adjusting for oral health confounders were of the same order as for total mortality, but not significant. Adjusting for CVD confounders further reduced the HR for these two categories.

The results of mortality for other causes showed a significant trend across the categories for all three models (Table 3). Significant results were seen for category 29-32 in all three models; model 1) HR=2.05 (CI=1.55 – 2.69), model 2) HR=1.53 (CI=1.15-2.04), and model 3) HR=1.50 (CI=1.12-2.00). Significant results were observed for numbers of teeth not reported in models 1 and 2.

**Table 3:** Hazard Ratio (95%CI) of total all CVD combined and other Causes of Mortality after 12.5 years of follow-up, according to Tooth Extraction History in men aged 48-77 years.

	Numbers not reported N=1694	Number of Tooth Extractions by Categories					Trend 0-32 p-value
		0 N=673	1-4 N=2574	5-9 N=832	10-28 N=547	29-32 N=204	
<b>All CVD</b>							
Age adjusted	1.47 1.09-1.985 0.011 1.30	1.00 (ref)	1.12 0.83-1.50 0.466	1.102 0.72-1.43 0.933	1.50 1.06-2.11 0.022	1.81 1.18-2.77 0.006	0.005
Oral health RF adjusted	0.975-1.76 0.084 1.22	1.00 (ref)	1.08 0.81-1.46 0.590	0.95 0.67-1.34 0.778	1.30 0.92-1.85 0.142	1.43 0.92-2.23 0.113	0.167
CVD RF adjusted	0.90-1.65 0.197	1.00 (ref)	1.08 0.80-1.45 0.612	0.91 0.64-1.28 0.576	1.20 0.84-1.70 0.326	1.30 0.83-2.03 0.258	0.348
<b>All other causes</b>							
Age adjusted	1.42 1.17-1.730 <0.001 1.23	1.00 (ref)	0.99 0.820-1.20 0.908	1.11 0.89-1.39 0.346	1.40 1.11-1.76 0.005	2.07 1.55-2.69 <0.001	<0.001
Oral health confounders adjusted	1.01-1.50 0.040 1.22	1.00 (ref)	0.95 0.78-1.15 0.577	1.01 0.81-1.26 0.916	1.19 0.94-1.51 0.141	1.53 1.15-2.04 0.004	0.001
CVD confounders adjusted	0.999-1.48 0.052	1.00 (ref)	0.95 0.77-1.14 0.497	1.001 0.80-1.25 0.992	1.17 0.92-1.48 0.202	1.50 1.12-2.00 0.006	0.002

\*Oral health confounders are age, daily smoking, education, and diabetes

\*\*CVD confounders are Oral health confounder plus total cholesterol, systolic blood pressure, and diabetes

Figures in bold indicate p<0.05

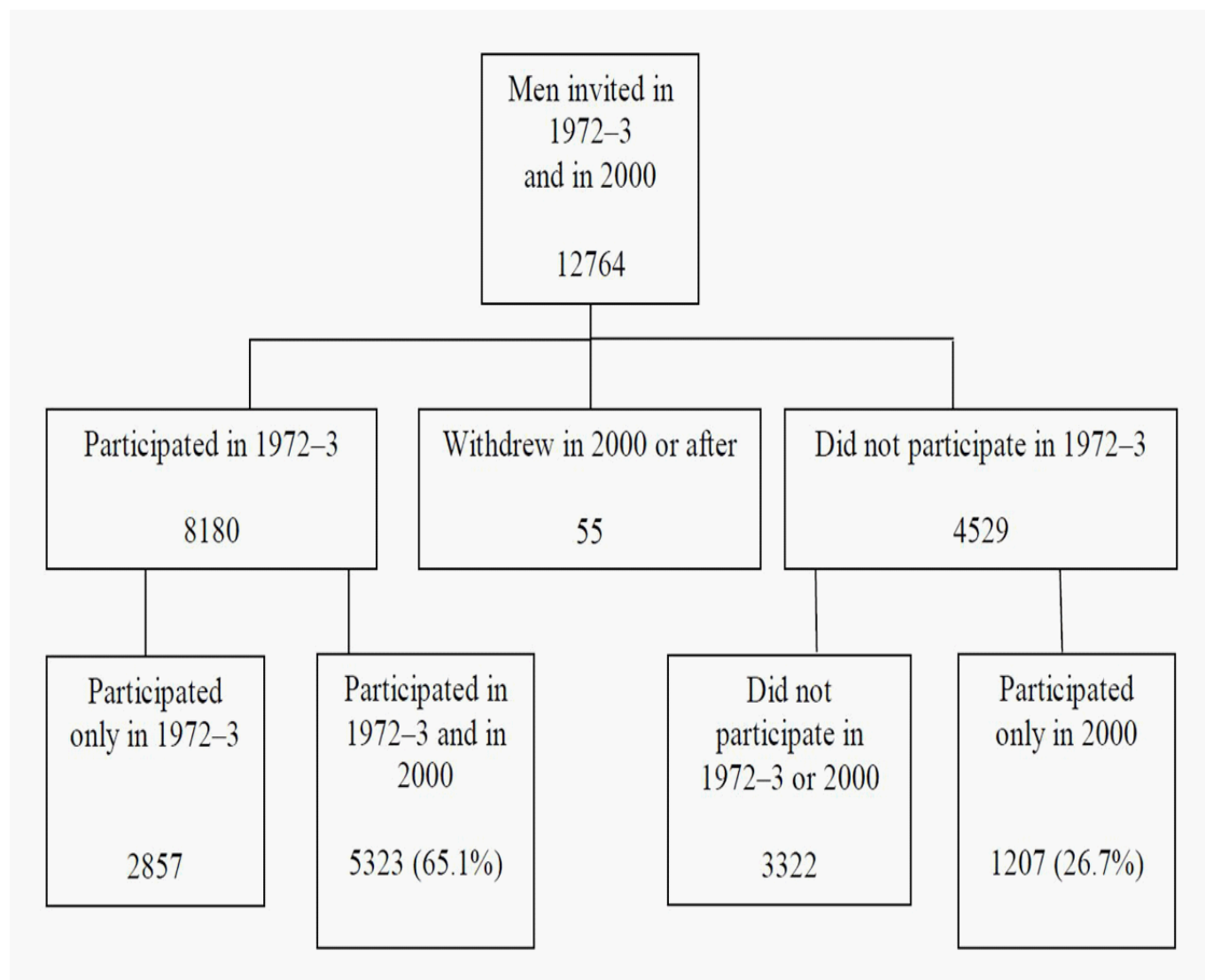
The plot of the cumulative hazard shows increasingly distinct differences between the extraction categories with regard to total mortality in the 12 ½ years of follow-up (Figure 2).

## Discussion

Our data support the hypothesis that the association between tooth extraction and total mortality is not only associated with age. The data also show that the age-adjusted risk estimate for total mortality was reduced

after including oral health variables in the equation, but only slightly affected by further adding of cardiovascular risk factors. The association between tooth extraction and cardiovascular mortality became insignificant when adjusting for cardiovascular risk factors, pointing at the association between these variables and tooth extractions. However, about a third of the men were treated by antihypertensive medication and/or about twenty percent by cholesterol reducing medication. The results suggest that there is more to tooth extractions and mortality than can be explained by the confounding



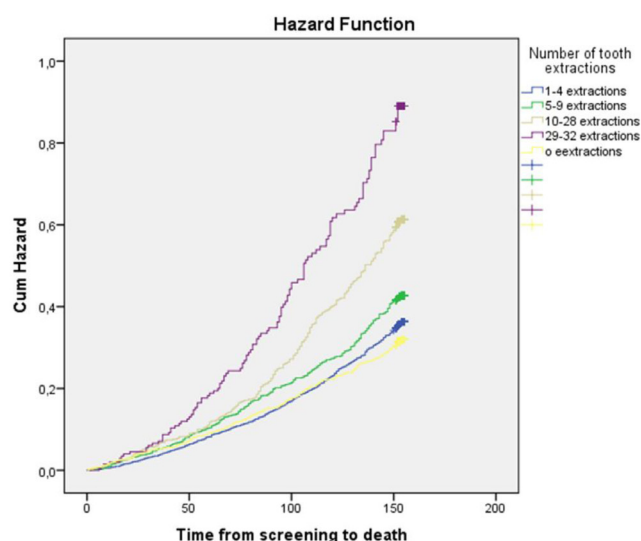


**Figure 1:** Flowchart of the Oslo II study screening in 2000 in relation to the first screening in 1972–3.

variables included in this study. This may be due to residual confounding but also to so far unknown factors. Tooth extractions reflect to a greater degree a history of oral infection and in particular periodontal infections and dental caries rather than orthodontic treatment or trauma in elderly men [17,18].

**Prospective cohort studies give support for causal associations as the risk factors are measured before and independent of the outcomes. Possible known confounding factors must be measured at start of the study and be included in the statistical analyses.**

**It must also be a plausible explanation as to how oral infections can indeed cause atherosclerosis and/or thrombosis, two main factors in mortality. In the large pool of bacteria in the oral cavity many possess the ability to evade host immunology, invade epithelial cells, cause periodontal ligament destruction, and alveolar bone loss. In this process bacteria and their virulence factors enter the blood stream and are identified in atherosclerosis, atheroma, stenosed heart valves, and affect thrombotic activity. The characteristic of periodontitis is the often long standing low grade level**



**Figure 2:** Cumulative hazard for total mortality by tooth extraction categories, Oslo II study, 2000.

**of infection as people are not always able to keep the level of biofilm low in the oral cavity through hygienic measures and the infection proceeds at a few or several sites in the mouth.**

Oral infections can be considered important in non-oral disease originating from oral infections [19]. They relate oral infections to three broad categories: first as metastatic dissemination of oral bacteria, second by bacterial toxins and third through immunological manifestations of oral disease due to a range of pathophysiologic mechanisms. The plausibility for the association between oral infection and CVD is based on several studies. There is evidence for periodontal pathogens contributing to atherosclerosis [20]. In their extensive review, the authors presented a 7-point list of biological mechanisms confirmed by scientific evidence. Pathological reports have identified oral bacteria in distant tissues and organs supporting the plausibility of oral bacteria being involved in atherothrombosis [21-25]. The interaction of bacteria with platelets, increasing the risk of thrombosis and embolism, is also important here [26]. A former analysis of the Oslo II study showed that

bacterial antigens of four oral periodontopathogens being associated with a history of myocardial infarction at the time of screening, odds ratio (OR) of 1.30 (CI=1.01 - 1.68) [27]. The present study based the oral health information on self-reports from questionnaires and not detailed clinical data, but previous studies have confirmed the reliability of such reports [28].

Much of the evidence for an association between oral infection and mortality has been related to total CVD and different sub-categories as myocardial infarction and stroke. This study showed a weak non-significant association with CVD compared to mortality from other causes in analyses adjusted for CVD-confounders. A possible explanation is statistical (lack of power) as the risk estimates are of similar magnitude to previous studies but with wider confidence intervals. Hence, our study does not negate the findings of potential associations in other studies. These analyses do not show clearly an association to CVD mortality by number of extracted teeth. The risk estimates (HR) are, however, not of great differences. It can therefore be argued that the results possibly reflect a difference in power in the analyses as there were less than half the number of CVD deaths (742 deaths) compared to non-CVD deaths (1616 deaths).

Participants with a high risk of disease are expected to have undergone or are currently on treatment of known risk factors thus attenuating the health risk from oral infections, treatment for hypertension and hyperlipidaemia during follow-up. The long follow-up of 12 ½ years may either have attenuated or strengthened the risk relations to future mortality. The clear trend by number of tooth extractions (categorized) as observed in this study is indicative of a “stable” risk factor for predictive analyses regarding mortality.

**The current study looks at the predictivity of tooth extractions for mortality as this is an important aspect for understanding one of causal factors for mortality and hence their prevention. In terms of generalisability,**



**it is a limitation that women were not included in the study. However, when the Oslo-study of 1972/73 was planned and of which the Oslo II-study is a follow-up study, the problem of acute myocardial infarctions was a major health problem among men in Norway. Periodontal disease is of equal importance in men and women, and the disease as such is not considered to be different between the genders.**

In conclusion, this study shows that increasing number of tooth extractions are independently associated with total mortality. The results on non-CVD-mortality may indicate a negative association to specific causes of mortality. This needs to be explored in future analyses in view of the general high prevalence of oral infections world wide.

## Author Contributions

Lund Håheim L, was the initiator and project leader for the Oslo II-study, analysed the acquired data, and drafted the manuscript; Rønningen KS was responsible and facilitated the storage of serum samples, and critically revised the manuscript; Nafstad P facilitated the hs-CRP analyses, and critically revised the manuscript; Schawartze PE facilitated serum analyses, and critically revised the manuscript; Thelle DS was instrumental in the conception of the Oslo II-study, and critically revised the manuscript; Olsen I was instrumental in the follow-up of the Oslo-II study, facilitated serum analyses, and critically revised the manuscript.

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The data collection was carried out in cooperation with but before the Oslo Health Study in 2000-1 in collaboration with the National Health Screening Service of Norway - now part of the Norwegian Institute for Health, Ullevål University Hospital - now Oslo University Hospital, the University of Oslo, and The City of Oslo.

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