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Oral Condition and Incident Coronary Heart Disease: A Clustering Analysis

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Abstract

Poor oral health has been linked to coronary heart disease (CHD). Clustering clinical oral conditions routinely recorded in adults may identify their CHD risk profile. Participants from the Paris Prospective Study 3 received, between 2008 and 2012, a baseline routine full-mouth clinical examination and an extensive physical examination and were thereafter followed up every 2 y until September 2020. Three axes defined oral health conditions: 1) healthy, missing, filled, and decayed teeth; 2) masticatory capacity denoted by functional masticatory units; and 3) gingival inflammation and dental plaque. Hierarchical cluster analysis was performed with multivariate Cox proportional hazards regression models and adjusted for age, sex, smoking, body mass index, education, deprivation (EPICES score; Evaluation of Deprivation and Inequalities in Health Examination Centres), hypertension, type 2 diabetes, LDL and HDL serum cholesterol (low- and high-density lipoprotein), triglycerides, lipid-lowering medications, NT-proBNP and IL-6 serum level. A sample of 5,294 participants (age, 50 to 75 y; 37.10% women) were included in the study. Cluster analysis identified 3,688 (69.66%) participants with optimal oral health and preserved masticatory capacity (cluster 1), 1,356 (25.61%) with moderate oral health and moderately impaired masticatory capacity (cluster 2), and 250 (4.72%) with poor oral health and severely impaired masticatory capacity (cluster 3). After a median follow-up of 8.32 y (interquartile range, 8.00 to 10.05), 128 nonfatal incident CHD events occurred. As compared with cluster 1, the risk of CHD progressively increased from cluster 2 (hazard ratio, 1.45; 95% CI, 0.98 to 2.15) to cluster 3 (hazard ratio, 2.47; 95% CI, 1.34 to 4.57; $P < 0.05$ for trend). To conclude, middle-aged individuals with poor oral health and severely impaired masticatory capacity have more than twice the risk of incident CHD than those with optimal oral health and preserved masticatory capacity (ClinicalTrials.gov NCT00741728).

Keywords: coronary disease, cardiovascular diseases, biomarkers, oral health, primary prevention, cluster analysis

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Introduction

Oral disorders are highly prevalent, affecting 3.47 billion people worldwide (James et al. 2018). Investigating the association between oral conditions and cardiovascular diseases (CVDs) may have important implications for CVD prevention. Previous studies on oral health and incident CVD mainly dealt with tooth loss (Seitz et al. 2019; Sanz et al. 2020). The pathologic progression of periodontal disease and dental decay is the leading cause of tooth loss. Thus, tooth loss captures the history of oral diseases, which indeed is a lengthy process of low-grade inflammatory burden that has been already associated with systemic inflammation leading to increased CVD risk (Vedin et al. 2017). Therefore, it is not surprising that untreated periodontitis (Sanz et al. 2020) and the infectious sequelae of untreated dental caries (Liljestrand et al. 2016; Garrido et al. 2019) have been associated with detrimental CVD parameters. To the best of our knowledge, there has been no study on the combined effect of periodontal diseases and dental caries on cardiovascular conditions.

Oral pathology encompasses not only a biological aspect but also a major functional dimension: the ability to chew, which is evaluated by the masticatory capacity, an accurate proxy for masticatory efficiency. We previously displayed the detrimental role of impaired masticatory capacity on hypertension (Darnaud et al. 2015), cardiovascular health (Rangé et al. 2019), all-cause mortality (Adolph et al. 2017), and CVD mortality (Darnaud et al. 2020).

So far however, the contribution of the oral function dimension to the risk of incident coronary heart disease (CHD) is yet to be investigated. Such an association may rely on the corruption of healthy dietary patterns whereby an impaired masticatory capacity leads to an imbalanced diet that fosters cardiometabolic risk factors contributing to atherosclerosis development and CHD occurrence (Kikui et al. 2017).

One can hypothesize that poor oral health's inflammatory potential and the effect of impaired masticatory capacity can increase the risk of CHD events. Therefore, CHD risk may be evaluated by its oral-systemic links through a novel integrative approach combining oral health and function indicators. In this context, cluster analysis may be relevant as it detects similar patterns of oral health while accounting for collinearity among indicators. We are unaware of any previous studies examining the association between clusters of oral health conditions and incident CHD events. Therefore, the study's objectives are 1) to identify and characterize clusters based on characteristics commonly recorded during clinical examinations in adults and 2) to investigate the associations of the clusters with incident CHD events as well as the distribution of CHD risk factors among them.

Materials and Methods

The Paris Prospective Study 3 is an ongoing longitudinal cohort study investigating the determinants of sudden cardiac death and other CVD phenotypes in initially healthy participants (World Health Organization international trial registry, ClinicalTrials.gov NCT00741728; Empana et al. 2011). From June 13, 2008, to May 31, 2012, 10,157 participants aged 50 to 75 y were recruited in a large preventive medical center, the Centre d'Investigations Préventives et Cliniques, Paris, France. The center offers a free medical examination every 5 y to working and retired employees and their families registered in the French National Insurance System. The target population of the center includes 11 million inhabitants from Paris and its suburbs. The Paris Prospective Study 3 protocol was approved by the Ethics Committee of the Cochin Hospital, and all participants provided informed consent for participation in the study.

Oral Health Indicators

At the preventive health center, the policy is that participants who have not attended a dental visit during the last year are eligible for an oral examination. Therefore, from the initial 10,157 recruited participants, 5,430 who had not attended a dental visit during the previous year received a full-mouth examination by trained dentists. The dental and periodontal examinations have been detailed previously (Darnaud et al. 2015; Rangé et al. 2019). Briefly, missing, decayed, and healthy teeth were recorded with a detailed dental chart. Dental plaque and gingival inflammation were visually assessed. A modified gingival index was used to evaluate gingival inflammation, distinguishing between no inflammation and moderate or severe inflammation affecting the gingival marginal or papillae (erythema, edema, or spontaneous bleeding). A modified plaque index based on the Silness-Löe index was used to evaluate the presence of dental plaque and was denoted by 0 if plaque could not be seen and 1 if plaque could be seen or if an abundance of soft matter was present on the tooth structure or gingival margin. Masticatory capacity was evaluated by the number of functional masticatory units, defined by pairs of natural or prosthetic units opposing premolars and molars; impaired masticatory capacity was denoted by having <5 units (Ueno et al. 2010; Rangé et al. 2019).

Blood Biomarkers

Blood samples were collected following overnight fasting. Total and high-density lipoprotein (HDL) cholesterol and fasting glycemia were measured on-site at the medical laboratory of the preventive medical center with standardized methods. Thereafter, blood samples were aliquoted and stored at −80°C at the Paris Prospective Study 3 biobank at the Georges Pompidou European Hospital, Paris, France. Centralized measurements of hs-CRP, IL-6, and NT-proBNP were performed on plasma EDTA (Chatzopoulou et al. 2021). High-sensitivity CRP was assessed with the V-PLEX Human CRP Kit (K151STD; Meso Scale Discovery); the lower limit of detection was 2.63 pg/mL. IL-6 and NT-ProBNP were quantified with a MSD MULTI-SPOT® 4 Spot Special Order Human triplex of customized kit (N45JA-1; Meso Scale Discovery), including IL-6 and NT-ProBNP. The limit of detection was

0.107 pg/mL for IL-6 and 0.945 pg/mL for NT-ProBNP. The study participants had not visited a dental office in the year preceding the baseline recruitment, and blood draw was systematically taken before the dental checkup at the health center, making it unlikely that a dental checkup or masticatory examination itself affected inflammatory biomarkers IL-6 and hs-CRP.

Covariates

At baseline, the participants received a detailed physical examination and completed a series of questionnaires on sociodemographic factors and health behaviors. Participants' use of medication was validated during a face-to-face interview with a physician. Body mass index (BMI; kg/m^2) was calculated. Type 2 diabetes was defined as a fasting glucose concentration ≥126.0 mg/dL (7.0 mmol/L), a nonfasting glucose concentration ≥200.0 mg/dL (11.1 mmol/L), or a self-reported history of antidiabetic medication. Blood pressure measurements were conducted after 10 min of rest. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or intake of antihypertensive medication. Smoking status distinguishes between current and noncurrent smoker (i.e., nonsmoker, trying to quit <1 y, or former smoker). Education level distinguishes between those with and without university-level education or equivalent (minimum, bachelor and graduate level). The EPICES score (Evaluation of Deprivation and Inequalities in Health Examination Centres) estimates individuals' material and psychosocial deprivation based on an 11-item score, varying from 0 to 100, with higher values indicating greater deprivation (Labbe et al. 2015).

Follow-up and Event Ascertainment

Every 2 y, participants self-reported via questionnaires any hospitalizations for CHD events. As of September 2020, the retention rate varies between 84% and 92%, according to the month of follow-up. Hospitalizations for CHD events were adjudicated by 1 epidemiologist and 1 cardiologist, who were blinded with respect to oral health status, after a critical review of hospital records and contact of treating physicians and next of kin. CHD events include acute coronary syndrome, myocardial infarction, hospitalized angina pectoris requiring coronary revascularization procedures, and sudden cardiac arrest. Mortality status was obtained from the mortality records at the National Institute of Statistics and Economic Studies. At the time of analysis, we had not yet been granted access to the national French registry of the causes of death; thus, cause-specific mortality and CVD mortality could not be investigated.

Statistical Methods

Hierarchical cluster analysis was used to identify patterns of oral conditions to maximize the similarities of oral indicators within each cluster while minimizing their similarities across clusters. The oral health variables were first processed by dimensionality reduction (factor analysis) to correct for multicollinearity and reduce data noise. The number of dimensions to retain was based on the diminution of the explained variance gain. Five dimensions were retained, explaining 80.2% of the multidimensional variance or total inertia (Appendix Fig. 2). The resulting dimensions were used as input for hierarchical agglomerative clustering via an algorithm with Euclidean distance measures and Ward's linkage criterion (Sharma et al. 2018). The final clustering solution was *k*-means consolidated; the Dunn index and silhouette method were used to select the optimal number of clusters (Dalton et al. 2009). A V-test score ≥1.96 was considered the statistical significance threshold of 0.05. The V-test evaluates statistical difference in means (for discrete variables) or proportions (for categorical variables) in each cluster as compared with the total. It also ranks the importance of variables in each cluster: a positive V-score indicates that the cluster is positively associated with the oral variable, while a negative V-score indicates an inverse association. Statistical trends were assessed for continuous variables, with linear regression for the normally distributed and Jonckheere-Terpstra for the nonnormally distributed, and the chi-square trend test was used to estimate the proportional trends of categorical variables.

Survival Description and Modeling

The Nelson-Aalen nonparametric estimator was used to plot the cumulative hazard function of incident CHD across the clusters. The log-rank test was used to compare survivor function equality. Survival trends were tested with the log-rank trend test and the proportional hazard regression trend estimating the per-cluster increase in the log (hazard). Cox proportional hazards regression models with the exact method to handle events occurring on the same date were used to estimate the hazard ratios (HRs) associated with clusters of oral conditions for CHD events. Time-to-event analysis was censored at the date of the CHD event or the last questionnaire answered for those without an event. The proportionality assumption was assessed via log-log (survival) versus log (time) plots and Schoenfeld's residual test. The regression models were sequentially adjusted for age, sex, smoking, BMI, education, EPICES score (social deprivation), hypertension, type 2 diabetes, LDL (low-density lipoprotein) and HDL serum cholesterol, triglycerides, lipid-lowering medications, and NT-proBNP and IL-6 serum levels. Missing data for covariates (n = 504) were imputed via multiple imputation by chained equations, with logistic models for binary variables and linear models for continuous ones, adjusting for age, sex, and BMI. The data analyses were performed with Stata version 16 (StataCorp) and R version 3.5 (R Foundation).

Results

Figure 1 summarizes the sampling steps. From the 10,157 participants recruited, 4,727 were ineligible for dental assessment, and 136 had prevalent CVD, leaving a sample of 5,294 participants for the descriptive analysis. Among them, 340 had no

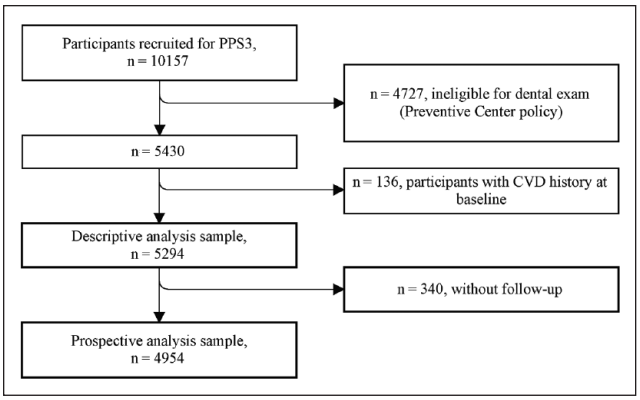

Figure 1. Study sample flowchart depicting the descriptive and prospective study samples. CVD, cardiovascular disease; PPS3, Paris Prospective Study 3.

follow-up data, yielding a sample of 4,954 participants for the prospective analysis. The baseline characteristics of excluded and included participants are compared in Appendix Table 1, which does not show clinically meaningful differences between the groups.

Oral Health Clusters

As shown in Table 1, 3 clusters were identified, corresponding to optimal oral health and preserved masticatory capacity (n = 3,688, 69.66%; cluster 1), moderate oral health and moderately impaired masticatory capacity (n = 1,356, 25.61%; cluster 2), and poor oral condition and severely impaired masticatory capacity (n = 250, 4.72%; cluster 3). In addition, there was a gradient in the distribution of oral variables from cluster 1 to cluster 3, with a decrease in the average number of healthy teeth and filled teeth and an increase in the average number of missing teeth, decayed teeth, proportions of dental plaque, gingival inflammation, and impaired masticatory capacity. Appendix Table 2 depicts the V-test scores characterizing oral conditions for each cluster. Table 2 summarizes the sociodemographic and cardiovascular risk factors across the 3 clusters. The mean ± SD age of the sample was 59 ± 6.07 y and 37% were women. The proportion of higher education decreased from cluster 1 to cluster 3, while the proportion of current smokers and diabetics increased from cluster 1 to cluster 3. The mean values of BMI and triglycerides and the median values of hs-CRP and IL-6 progressively increased from cluster 1 to cluster 3. In contrast, the opposite was found for HDL cholesterol and NT-proBNP.

Survival Description and Cox Regression Results

After a median follow-up of 8.32 y (interquartile range, 8.00 to 10.05 y), 128 incident nonfatal CHD events were ascertained. The unadjusted cumulative hazard functions for CHD gradually increased from cluster 1 to cluster 3 (Fig. 2). Table 3 summarizes the incidence rates and crude and adjusted HR estimates for clusters 2 and 3 as compared with cluster 1. After adjusting for sociodemographic factors, CVD risk factors, IL-6, and NT-proBNP, the risk of CHD increased gradually from cluster 2 (HR, 1.45; 95% CI, 0.98 to 2.15) to cluster 3 (HR, 2.47; 95% CI, 1.34 to 4.57; $P < 0.05$ for trend). As sensitivity analysis (Appendix Table 3), associations between oral health clusters and incident CHD retained their significance in complete case analysis (n = 4,486 participants and n = 118 nonfatal CHD events).

Discussion

The clustering approach of oral clinical conditions recorded during routine dental examination among 5,294 adults participating in a community-based prospective study identified 3 ordered groups. The majority of the participants had optimal oral health and preserved masticatory capacity (cluster 1); a quarter had moderate oral health and moderately impaired masticatory capacity (cluster 2); and a small subset had poor oral health and severely impaired masticatory capacity (cluster 3). CVD risk factors and circulating markers of chronic inflammation were gradually distributed across the 3 clusters. Furthermore, the risk of CHD increased from cluster 1 to cluster 3. In particular, participants with poor oral health and severely impaired masticatory capacity (cluster 3) had twice the CHD risk than those with optimal oral health and preserved masticatory capacity (cluster 1).

So far, clustering approaches have been scarcely used to investigate oral conditions. Previous cluster analyses were conducted on oral health attitude and behaviors (Komabayashi et al. 2006; Austregésilo et al. 2019) and the potential combination of periodontal clinical characteristics and corresponding oral microbial profiles (Boutin et al. 2017). To our best knowledge, the NHANES (National Health and Nutrition Examination Survey) is the sole community-based study that correlates clusters of oral health with systemic conditions such as CVD risk factors. In the subsample with a full-mouth periodontal examination (n = 1,022), 5 clusters depicting the severity of periodontitis were identified, and more severe periodontitis was associated with type 2 diabetes and low socioeconomic factors in cross-sectional analysis (Ghassib et al. 2021). Thus, our report is the first longitudinal study to investigate the association between clusters of oral conditions and hard clinical endpoints, here incident CHD events.

Two-thirds of the participants from cluster 3 had severely impaired masticatory capacity. Accordingly, participants from this cluster had on average the highest number of missing teeth (the major driver of impaired masticatory capacity) and the least prosthetic replacement of missing teeth. Therefore, it is likely that severely impaired masticatory capacity is a major contributor to the significantly increased risk of incident CHD in participants from cluster 3 versus cluster 1, and a nutrition pathway is likely to support this association. Indeed, fewer teeth (the main driver of impaired masticatory capacity) are associated with low dietary quality, micronutrients, and fiber and lower consumption of fruits, vegetables, and nuts (Zhu and

Table 1. Distribution of Overall Oral Health Conditions and across Oral Health Clusters.

	Total	Cluster 1	Cluster 2	Cluster 3	*P* Value for Trend[a]
Participants	5,294	3,688 (69.66)	1,356 (25.61)	250 (4.72)	
Healthy teeth	16.25 ± 6.50	17.65 ± 6.16	13.58 ± 6.06	10.10 ± 5.48	<.05
Filled teeth	4.97 ± 3.58	5.49 ± 3.66	4.02 ± 3.13	2.39 ± 2.39	<.05
Fixed prosthodontic units	5.35 ± 5.17	5.24 ± 4.88	6.09 ± 5.91	2.92 ± 4.14	—
Missing teeth	3.88 ± 3.41	2.37 ± 1.50	6.01 ± 1.31	14.61 ± 5.56	<.05
Decayed teeth	1,094 (20.66)	655 (17.76)	340 (25.07)	99 (39.60)	<.05
Dental plaque	161 (3.04)	102 (2.77)	41 (3.02)	18 (7.20)	<.05
Gingival inflammation	494 (9.33)	325 (8.81)	131 (9.66)	38 (15.20)	<.05
<5 FMUs	374 (7.06)	3 (0.08)	212 (15.63)	159 (63.60)	<.05

Values are presented as mean ± SD or *n* (%). Cluster 1, participants with optimal oral health and preserved masticatory capacity; cluster 2, participants with moderate oral health and moderately impaired masticatory capacity; cluster 3, those with poor oral health and severely impaired masticatory capacity.
FMU, functional masticatory unit.
[a]*P* value for trend: linear regression (mean trend) and chi-square trend (proportion trend). Dash (—) denotes a lack of trend test assumption.

Table 2. Distribution of Overall Baseline Sample Characteristics and across Oral Health Clusters.

	Total	Cluster 1	Cluster 2	Cluster 3	*P* Value for Trend[a]
Participants	5,294	3,688 (69.66)	1,356 (25.61)	250 (4.72)	
Age, y	58.98 ± 6.06	58.66 ± 5.96	59.79 ± 6.26	59.20 ± 6.04	.17
Women	1,964 (37.10)	1,309 (35.49)	573 (42.26)	82 (32.80)	.39
Higher education	2,073 (39.16)	1,598 (43.33)	437 (32.23)	38 (15.20)	<.05
EPICES score	18.47 ± 18.46	18.37 ± 18.46	18.43 ± 18.29	20.23 ± 19.39	.29
Current smoker	815 (15.39)	471 (12.77)	270 (19.91)	74 (29.60)	<.05
Hypertension	1,978 (37.36)	1,385 (37.55)	510 (37.61)	83 (33.20)	.16
Type 2 diabetes	246 (4.65)	146 (3.96)	77 (5.68)	23 (9.20)	<.05
BMI	25.28 ± 3.83	25.16 ± 3.68	25.41 ± 4.08	26.21 ± 4.45	<.05
LDL cholesterol, mg/dL	143.02 ± 32.45	142.80 ± 31.80	143.15 ± 33.19	145.61 ± 37.45	.26
HDL cholesterol, mg/dL	58.12 ± 15.39	58.40 ± 15.34	58.1 ± 15.67	53.95 ± 14.04	<.05
Triglycerides, mg/dL	103.86 ± 63.22	101.73 ± 62.75	106.49 ± 59.86	120.97 ± 82.11	<.05
Lipid-lowering medication	660 (12.49)	446 (12.11)	184 (13.58)	30 (12.10)	.40
hs-CRP, mg/L	1.30 (0.65 to 2.76)	1.26 (0.63 to 2.63)	1.37 (0.68 to 2.96)	2.01 (0.98 to 4.67)	<.05
IL-6, pg/mL	0.62 (0.46 to 0.84)	0.60 (0.45 to 0.81)	0.63 (0.47 to 0.87)	0.79 (0.57 to 1.14)	<.05
Nt-proBNP, pg/mL	207.69 (102.23 to 411.63)	205.58 (103.44 to 403.66)	219.96 (99.61 to 439.17)	183.73 (100.21 to 375.49)	.40

Values are presented as mean ± SD, *n* (%), or median (interquartile range [0.25 to 0.75]). Cluster 1, participants with optimal oral health and preserved masticatory capacity; cluster 2, participants with moderate oral health and moderately impaired masticatory capacity; cluster 3, those with poor oral health and severely impaired masticatory capacity.
BMI, body mass index; EPICES, Evaluation of Deprivation and Inequalities in Health Examination Centres (social deprivation measure); HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]*P* value for trend: linear regression (mean trend), Jonckheere-Terpstra (median trend), and chi-square test (proportion trend).

Table 3. Hazard Ratios Associated with Oral Health Clusters for Incident Coronary Heart Disease Events.

	Total	Cluster 1	Cluster 2	Cluster 3	*P* Value for Trend[a]
CHD events	128/4,954	74/3,688	41/1,356	13/250	
PY	41.40×10^3	29.63×10^3	10.32×10^3	1.46×10^3	
Rate[b] (95% CI) per 1,000 PY	3.09 (2.60 to 3.68)	2.50 (1.99 to 3.14)	3.97 (2.93 to 5.40)	8.93 (5.18 to 15.38)	<.05
Model, HR (95% CI)					
Crude (unadjusted)	—	1	1.59 (1.09 to 2.34)	3.42 (1.90 to 6.17)	<.05
Adjusted[c]	—	1	1.45 (0.98 to 2.15)	2.47 (1.34 to 4.57)	<.05

Cluster 1, participants with optimal oral health and preserved masticatory capacity; cluster 2, participants with moderate oral health and moderately impaired masticatory capacity; cluster 3, those with poor oral health and severely impaired masticatory capacity.
CHD, coronary heart disease; EPICES, Evaluation of Deprivation and Inequalities in Health Examination Centres (social deprivation measure); HR, hazard ratio; PY, person-years.
[a]*P* value for trend: the trend test for the survivor functions (the log-rank test for trend) and proportional hazard regression trend.
[b]Rate: events/person-time.
[c]Adjusted for age, sex, smoking, body mass index, education, EPICES score, hypertension, type 2 diabetes, low- and high-density lipoprotein cholesterol, triglycerides, lipid-lowering medication, and NT-proBNP and IL-6 serum levels.

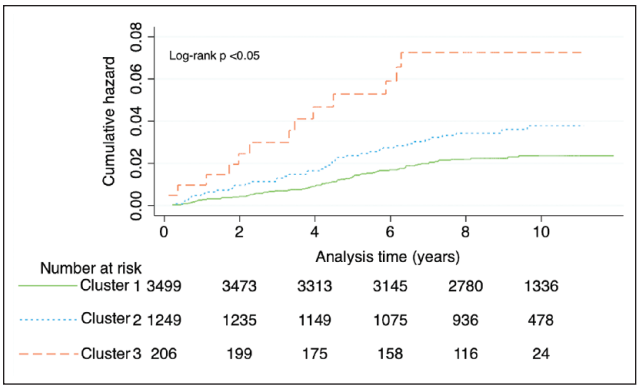

Figure 2. Cumulative hazards of incident coronary heart disease by oral health clusters. Nelson-Aalen plot shows the unadjusted cumulative hazards for coronary heart disease according to the 3 clusters of oral health indicators. The log-rank tests the trend in survival function among the 3 clusters. The number of individuals at risk is reported for 2-y intervals.

Hollis 2014; Logan et al. 2020). In addition, severe tooth loss has been associated with obesity and metabolic syndrome (Nascimento et al. 2016; Iwasaki et al. 2019). These metabolic complications may contribute to atherosclerosis development and CHD onset. Additional mechanisms supporting the association between cluster 3 and incident CHD might be those relating periodontal diseases with atherosclerosis, such as low-grade chronic inflammation (Haynes and Stanford 2003), systemic oxidative stress, and endothelium dysfunction (Masi et al. 2018; Pietropaoli et al. 2020). In the present study, however, the association between cluster 3 and CHD remained significant even after adjusting for inflammatory factors and conditions, such as type 2 diabetes and IL-6 serum level, or confounders, such as smoking and BMI, which were more prevalent in cluster 3 than cluster 1.

Prior evidence supports a diet-dependent increase in production of TMA/TMAO (trimethylamine/trimethylamine N-oxide) resulting from gut microbiome dysbiosis, attributed to increased choline, l-carnitine, and betaine intake. The increased production of TMAO has been associated with atherosclerosis, endothelial dysfunction, increased foam cell formation, increased thrombosis via platelet activation, and disruption of cholesterol metabolism, which contribute to CHD occurrence (Pietiäinen et al. 2018; Simó and García-Cañas 2020). The association between cluster 3 and incident CHD may also be related to oral-gut microbiome dysbiosis resulting from the bacterial proliferation characterizing dental plaque formation and eventual dental decay (Fåk et al. 2015; Koren et al. 2011).

Although a causal link cannot be demonstrated in the current analysis, the following may have public health implications for CHD prevention: 1) the high burden of oral diseases in the population, 2) the gradient of CHD risk across the clusters of oral health, 3) the magnitude of the association between participants with poor oral health and severely impaired masticatory capacity and incident CHD (i.e., 2-fold increased risk of incident CHD), and 4) that such an association was independent of sociodemographic and major CVD risk factors. In particular, preventing the onset of poor oral health behaviors and conditions that contribute to tooth loss, which increases the risk of impaired masticatory capacity, may be an additional component of the preventive strategy for CHD in the community (De Oliveira et al. 2010). A recent observational study suggests that regular toothbrushing and professional cleaning were associated with a decreased CVD risk, especially when started early before an irreversible condition such as tooth loss (Park et al. 2019). These findings support oral health promotion in the population and closer transdisciplinary collaboration between primary care and cardiometabolic physicians and oral health professionals.

The present study has several methodological strengths. Given the longitudinal design of the data set, we were able to investigate the temporality of the association between oral health conditions and incident CHD events. Furthermore, with 5,294 participants, this is the largest study examining the associations of clusters of oral conditions with incident CHD events.

We acknowledge the following study limitations. The participants were mostly of European ancestry and aged 50 to 75 y at baseline, so the results may not apply to other ethnic or age groups. The study focused on CHD events and did not consider other CVD phenotypes. Cluster 3 had a relatively small sample size and few CHD events. The potential change in oral health status during follow-up and its impact on the outcome were not measured. Dichotomization of oral health indicators ignores the spectrum of severity so that associations between the clusters and incident CHD events might even be stronger. More complex oral indices could have been used, but we selected oral indicators routinely recorded in any dental practice.

To summarize, the present hierarchical cluster analysis of routinely collected oral conditions during dental examination uncovered a cluster of adults >50 y old with poor oral health and severely impaired masticatory capacity who present twice the risk or more of incident CHD than those with optimal oral health and preserved masticatory capacity. The findings support oral health promotion in the population and more transdisciplinary collaboration among primary care physicians, cardiometabolic specialists, and dental and oral health professionals. Furthermore, from a research standpoint, it opens a new translational outlook. Future analyses should 1) extend the present analyses to other populations with different characteristics and 2) include longitudinal studies with repeated clinical oral examinations to evaluate the association between change in oral conditions and CVDs.

Author Contributions

O. Deraz, performed the data statistical analysis and contributed to the interpretation of the results, drafted the manuscript; H. Rangé, E. Chatzopoulou, T. Van Sloten, W. Bougouin, contributed to data interpretation of the results, critically revised the manuscript; P. Boutouyrie, contributed to conception, design, and data acquisition, critically revised the manuscript; A. Asselin, contributed to the data statistical analysis methodology, critically revised the

manuscript; C. Guibout, contributed to conception and design, critically revised the manuscript; M. Andrieu, B. Vedié, F. Thomas, N. Danchin, contributed to data acquisition, critically revised the manuscript; X. Jouven, contributed to conception, design, data acquisition, and interpretation of the results, critically revised the manuscript; P. Bouchard, contributed to data acquisition and interpretation of the results, drafted and critically revised the manuscript; J.P. Empana, contributed to conception, design, data acquisition, and interpretation of the results, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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