**Ecole Doctorale Pierre Louis de Sante Publique a Paris**
**Epidemiologie et Sciences de l’Information Biomedicale**

Directeur : Pierre-Yves Boëlle  
Responsable pour l’Université Paris Diderot : Matthieu Resche-Rigon  
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**PROPOSITION DE SUJET DE THESE**

**Sigle et Nom du Laboratoire:** PARCC (Paris Centre de Recherche Cardiovasculaire), INSERM U970  
**Nom de l’Equipe:** Integrative Epidemiology of Cardiovascular diseases  
**Directeur de thèse:** Jean-Philippe Empana  
**Adresse:** Hôpital Européen Georges-Pompidou  
56 rue Leblanc  
75015 PARIS, FRANCE  
**Titre de la thèse:** Oral Health and Multimorbidity  
**Co-encadrant éventuel:** Hélène Rangé  
**Equipe du co-encadrant:** U.F.R. d’odontologie, Université Paris Diderot

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**PRESENTATION DU SUJET**

1. **Le contexte scientifique du projet ; Scientific context of the project**

Oral diseases have been associated with chronic conditions such as CVD, type 2 diabetes, mortality and potentially Alzheimer’s disease\(^1\)(2)(3)(4). The link between oral health and systemic chronic diseases can be attributed in part to inflammatory mediators and cytokines in oral inflammatory pathologies such as periodontal disease\(^5\). Additionally, masticatory dysfunction affects general health through the degree of ability to chew food and adoption of poor nutritional value diet and eventual development of chronic conditions such as CVD\(^6\)(7)(8). There is a growing body of evidence linking oral health with incident CVD. However, most previous studies investigated one single oral health parameter, primarily periodontitis or tooth loss and one single disease outcome, mortality or CVD (single risk factor and disease outcome approach).

Multimorbidity is an emerging concept defined as the co-occurrence of multiple chronic condition. The definition varies in the literature depending on the number of concurrent conditions (commonly 2-3), in addition to the severity of disease and reduced physical or cognitive abilities\(^9\). It has been shown that up to 50% of the ageing population is multimorbid\(^9\)(10). So far, there is a gap in knowledge regarding the simultaneous evaluation of several oral health parameters with multimorbidity (multiple risk factor and disease outcome approach). From a statistical standpoint, clustering methods may represent a relevant approach to identify clusters of oral health parameters associated with multimorbidity.

Low-grade inflammation is thought to be one major pathway linking oral health and CVD, with lacking data in the general population. An additional pathway may include subclinical markers of cardiomyocytes damage such as troponin, although this issue has not been yet evaluated.

Use of risk assessment tools for cardiovascular events in the primary prevention setting is recommended by the guidelines and they rely on the so-called traditional risk factors such as age, sex, smoking, diabetes, blood pressure and cholesterol serum level. However, the potential usefulness and added value of oral health parameters for risk prediction beyond traditional risk factors has not been evaluated yet.

2. **Les questions posées ; The proposed questions**

1. Assessment of the relationship between oral and dental health and multimorbidity, cardiovascular disease and mortality.  
2. Evaluation of the mediating role of low-grade inflammation markers and subclinical cardiomyocyte damage in the relationships identified in objective 1.  
3. Quantify the added value of the best combination of oral health parameters for CVD risk prediction.

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3. Les sources de données qui seront utilisées ; Source of the data to be used

Paris Prospective Study 3 is an ongoing longitudinal cohort study promoted by INSERM that aims to investigate markers of sudden cardiac death and cardiovascular disease in healthy subjects. Recruitment took place in a preventive health centre (Centre d'Investigations Prévентives et Cliniques, IPC) which is subsidized by the French National Insurance System for Salaried Workers (Caisse Nationale de l'Assurance Maladie des Travailleurs Salaries). From June 2008 to May 2012, a total of 10 157 subjects (40% women) aged 50 to 75 agreed to participate in the study(11). Since then, participants are followed up every two years for 20 years. All the participants signed an informed consent and the study is registered in the WHO international trial registry (NCT00741728).

Dental exposure data

At study recruitment, the participants received a full-mouth clinical examination from one of five trained dental examiners from which 5 oral and dental parameters will be investigated. A simplified plaque index based on that developed by Silness and Loe was used and included the following ratings: low (plaque cannot be seen with the naked eye), moderate (limited quantity of plaque can be seen), and high amount (abundance of soft matter within the tooth and/or gingival margin). Similarly, the calculus index was rated: low (supragingival calculus covering no more than one-third of the tooth surface), moderate (supragingival calculus covering more than one-third but not more than two-thirds of the tooth surface and/or the presence of individual flecks of subgingival calculus around the cervical portion of the tooth), and high amount (supragingival calculus covering more than two-thirds of the tooth surface).

Gingival inflammation was evaluated using a simplified Modified Gingival Index (MGI) based on that described by Lobene et al. The degree of gingival inflammation was rated as low (absence of inflammation or mild inflammation), moderate (inflammation, including the preceding criteria, in all portions of the gingival marginal or papillary tissue), or high (erythema, edema or spontaneous bleeding. Masticatory ability was evaluated by the number of functional tooth units (FTUs) defined by pairs of natural or prosthetic opposing premolars and molars. Presence of a remaining root indicated for extraction was recorded by the dental examiners (at least 1 remaining root). The numbers of missing, carious and healthy teeth were also recorded.

Covariates

The participants received a detailed clinical examination and filled a series of questionnaires on socio-demographic factors, lifestyle and mental health. Body Mass Index (BMI) was calculated as [weight (kg)/height squared (m2)]. Glycaemia, total plasma cholesterol and triglycerides were measured under fasting conditions. Participants were invited to the health center with their most recent medications prescriptions/packages that were validated during a face to face interview with a physician.

Blood biomarkers:

Using the PPS3 biobank, high-sensitive CRP, high sensitive troponin I and Interleukin 6 have been measured at the baseline for all subjects employing state of the art highly sensitive techniques relevant to the general population.

Follow-up

Every two years, participants self-reported via questionnaires their health and hospitalizations for a series of chronic diseases. Reported hospitalizations of interest are subsequently validated using a standardized procedure by request of hospitalized records and physician contacts. SNDS data will be used as a complementary source (ongoing demand). So far, the 2, 4 and 6y follow-up has been closed and curated with retention rate between 84% and 92% depending on follow-up month. The 8y follow-up will end by September this year and the 10 year follow-up by 2022. As of January 2019, a total of 300 deaths occurred and 550 CVD events (coronary heart disease and stroke) have been already validated. For the current PhD, incident data up to 2020 will be used, corresponding to a range of follow-up between 8 to 10 years for each participant.
Multi-morbidity will be defined as having at least 2 incident chronic conditions which include hypertension, diabetes, depression, obesity, cardiovascular disease, cancer, cerebrovascular disorders (e.g. stroke) or neurodegenerative disease (e.g. dementia, Alzheimer’s)\(^{9,10}\).

4. **Les méthodes ; Methods**

   **Cox Proportional-Hazard regression**
   
   Data analyses will be performed using Stata version 15 and R version 3.5. The association of oral health markers with the outcomes will be assessed using Cox Proportional-Hazard regression models. Oral health parameters will be investigated separately and the most significant ones will be included in the same multivariate model.

   **Cluster analysis**
   
   Unsupervised descriptive analyses will be conducted to identify patterns of various dental exposures' aggregation. Factor analysis for mixed data algorithm is utilized in r studio package “FactoMineR” as a dimensionality reduction solution, the resulting dimensions/components are used as input for Hierarchical ascendant clustering via Ward's linkage and Euclidean distances. The clinical relevance of these clusters will be evaluated by quantifying their association with multimorbidity, CVD and mortality.

   **Mediation analysis**
   
   The mediating role of inflammatory biomarkers and cardiomyocytes markers will be first investigated by comparing the relative beta coefficient difference in the multivariable hazard ratios with and without adjustment for the biomarkers. Then, a formal mediation analysis will be carried out permitting to quantify direct and indirect effects of oral health parameters on outcomes using an extension of the Baron and Kenny method developed by Valeri L et al.\(^{12}\).

   **Risk prediction**
   
   The potential added value for CVD risk prediction of the most predictive oral and dental health parameters identified above will be evaluated. For this purpose, we will quantify whether the addition of these factors to a Framingham-like risk score containing traditional risk factors improves a) *calibration* (the concordance in the number of predicted and observed events), b) *discrimination* (the ability to dissociate future events from non-events) and c) reclassification (the % of correctly reclassified events towards higher risk categories and non-events towards lower risk categories between the model with and without oral and dental health parameters) by calculating the net reclassification index\(^{16}\). This approach will be carried out with oral and dental health parameters identified from the Cox analysis, and from those derived from the cluster analysis. A final approach will be carried out via machine learning techniques (e.g. deep neural network and random forest algorithms) aiming to reach the most predictive and informative risk prediction model.

   **Preliminary results**
   
   Preliminary analyses of separate associations between oral/ dental health parameters with all-cause mortality indicates that all studied parameters (caries, masticatory deficiency, gingivitis, remaining root, missing teeth and dental plaque) are significantly associated with the outcome after adjustment for age, sex and traditional risk factors, but only caries, having a remaining root and the combination of gingivitis and dental plaque remained associated with mortality after further adjustment for social deprivation index (EPICE), with hazards ratios ranging from 1.8 to 2.6.

5. **Puissance de l'étude/nombre de sujets ; Number of study subjects**
   
   The sample size of \(n = 10,157\) subjects has been calculated to obtain a minimum of 100 incident cases of sudden cardiac arrest over 10 years follow-up given an average incidence rate of 1 per 1000 person year.

6. **Le calendrier prévisionnel ; Project timeline**

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The baseline data including oral health parameters and covariates were curated and are ready for use. Clinical validation of the CVD events is available up to January 2019 with 550 events and 300 deaths.

- **Year 1:** assessment of the relationship between oral and dental health and multi-morbidity, cardiovascular disease and mortality.
- **M1-M6:** literature review and statistical analysis (Cox and Cluster Analysis);
- **M7-M12:** writing and submission of the paper

**Year 2:** mediation analysis and starting risk prediction modeling
- **M1-M3:** mediation analysis;
- **M4-M7:** writing of the manuscript on the mediating role of inflammatory and cardiomyocytes damage on the association between oral/dental parameters and outcomes
- **M8-M12:** risk prediction modeling and submission of 2nd paper

**Year 3:** risk prediction modeling and writing thesis
- **M1-M6:** finalizing risk prediction modeling, writing manuscript and submission of 3rd paper
- **M7-M12:** writing and submission

**7. Le thème de chacun des articles prévus. Une proposition de sujet de thèse doit comporter au moins deux articles originaux.**

1. Oral health parameters as predictors for multi-morbidity, cardiovascular events and mortality,
2. Mediation analysis of the inflammatory and cardiomyocytes damage markers for the associations between oral health parameters and multi-morbidity, cardiovascular events and mortality
3. Utility of machine learning techniques for cardiovascular event risk prediction models using oral health parameters in comparison to traditionally used risk models.

**The team:** the two teams have complementary expertise in CVD epidemiology and risk prediction (INSERM U970, PPS3 coordination) and oral health epidemiology (Pr. Bouchard’s team, Faculty of Odontology, University of Paris). The teams have been collaborating over the last 5 years using PPS3 data on the link between oral health and CVD, in particular the role of masticatory unit efficiency, together with the association between oral health and socio-economic factors at the individual and contextual levels.

**Bibliography**


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SPECIALITÉ DE LA THÈSE

- Santé publique - Epidémiologie
- Santé publique - Epidémiologie clinique
- Santé publique - Epidémiologie sociale
- Santé publique - Epidémiologie génétique
- Santé publique - Biostatistique
- Santé publique - Biomathématiques
- Santé publique - Biostatistique et Biomathématiques
- Santé publique - Informatique médicale
- Santé publique - Imagerie biomédicale
- Santé publique - Bioinformatique
- Santé publique - Recherches sur les services de santé
- Santé publique - Economie de la santé
- Santé publique - Science des données

AVIS FAVORABLE

SIGNATURE

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