TITLE: Clustering by periodontitis-associated factors -- a novel application to NHANES data

AUTHORS: Iya H. Ghassib DDS, [*] Feras A. Batarseh PhD, [†] Hom-Lay Wang DDS MS PhD, [*] Wenche S. Borgnakke DDS MPH PhD[*]

[*]University of Michigan, School of Dentistry, Department of Periodontics and Oral Medicine, Ann Arbor, Michigan, USA

[†]George Mason University, College of Science, Fairfax, Virginia, USA

ORCIDs & E-MAIL ADDRESSES:

Iya Ghassib: 0000-0002-0067-377X; ighassib@umich.edu

Feras A. Batarseh: 0000-0002-6062-2747X; fbatarse@gmu.edu

Hom-Lay Wang: 0000-0003-4238-1799; homlay@umich.edu

Wenche S. Borgnakke: 0000-0003-3593-093X; wsb@umich.edu

AUTHORS' CONTRIBUTIONS:

Iya Ghassib: conception; study design; data-extraction, preparation, analysis and interpretation; drafted and critically revised the manuscript. Feras A. Batarseh: conception; study design, data extraction, preparation, analysis, and interpretation; and critically reviewed the manuscript. Hom-Lay Wang: conception, drafted and critically reviewed the manuscript. Wenche S. Borgnakke: design, contributed to data interpretation; drafted and critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

CORRESPONDING AUTHOR:

Iya Ghassib DDS

Department of Periodontics and Oral Medicine

School of Dentistry

University of Michigan

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1011 North University Avenue

Ann Arbor, MI 48109-1078, USA

ighassib@umich.edu

Tel.: (734) 604-7060

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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SHORT RUNNING TITLE: Clustering by periodontitis-associated factors

ONE SENTENCE SUMMARY: Data mining and cluster analysis can aid in identifying population subgroups at high risk for periodontitis and thus may guide public health preventive, interventional initiatives and improve precision clinical management of periodontitis.

KEYWORDS: cluster analysis, chronic periodontitis, dental health surveys, knowledge discovery, patient reported outcome measures

ABSTRACT

Background: Unsupervised clustering is a method used to identify heterogeneity among groups and homogeneity within a group of patients. Without a prespecified outcome entry, the resulting model deciphers patterns that may not be disclosed using traditional methods. This is the first time such

clustering analysis is applied in identifying unique subgroups at high risk for periodontitis in NHANES 2009-2014 datasets using over 500 variables.

Materials and methods: Questionnaire, examination, and laboratory data (33 tables) for 1,000+ variables were merged from 14,072 respondents who underwent clinical periodontal examination. Participants with ≥6 teeth and available data for all selected categories were included (N=1,222). Data wrangling produced 519 variables. k-means/modes clustering (k=2:14) was deployed. The optimal k-value was determined through the elbow method, formula=$\sum (x_i^2) - ((\sum x_i)^2 / n)$. The 5-cluster model showing the highest variability (63.08%) was selected. The 2012 CDC/AAP and 2018 EFP/AAP periodontitis case definitions were applied.

Results: Cluster 1 (n=249) showed the highest prevalence of severe periodontitis (43%); 39% self-reported "fair" general health; 55% had household income <$35,000/year; and 48% were current smokers. **Cluster 2** (n=154) had 1 participant with periodontitis. **Cluster 3** (n=242) represented the greatest prevalence of moderate periodontitis (53%). In **Cluster 4** (n=35) only 1 participant had no periodontitis. **Cluster 5** (n=542) was the systemically healthiest with 77% having no/mild periodontitis.

Conclusion: Clustering of NHANES demographic, systemic health, and socioeconomic data effectively identifies characteristics that are statistically significantly related to periodontitis status and hence detects subpopulations at high risk for periodontitis without costly clinical examinations.

INTRODUCTION

Chronic periodontitis, a microbe-initiated and host-mediated inflammatory disease includes periodontal attachment loss in susceptible individuals.[1] The disease is estimated to affect 42.2% of the dentate US population aged 30 – 79 years[2] with about 75% of seniors affected.[3] Severe periodontitis is the sixth most prevalent chronic disease in the world[4] affecting 11% of adults.[2,4] Periodontitis is a major cause of tooth loss and is linked with multiple health determinants, such as medical conditions (hypertension, atherosclerosis, diabetes mellitus (DM), obesity, other inflammatory diseases), physiological, dental, dietary, behavioral, socioeconomic, and environmental factors,[5-10] some of which are reciprocal.[6,11,12] Because periodontitis can be prevented, treated, or managed, it is imperative to identify high-risk population groups for prevention, improved clinical management, and administration of public health interventions.[13,14]

Decreasing the proportion of adults with moderate to severe periodontitis remains an objective of Healthy People 2030.[15] The National Health and Nutrition Examination Surveys (NHANES) conducted by the National Center for Oral Health Statistics (NCHS) of Centers for Disease Control and Prevention (CDC) collect data for population based-surveillance of health and disease among nationally representative population samples in the US. For the first time, the protocols for the three 2-year cycles 2009-2010, 2011-2012, and 2013-2014 – hereafter collectively referred to as "NHANES 2009-2014" -- included a full-mouth periodontal examination (FMPE) at 6 sites around all non-third molar teeth[2] as well as survey items for self-report of periodontitis. Both the periodontal probing depth (PPD) and the distance from the periodontal margin to the cemento-enamel junction (CEJ) were recorded in millimeters. The resulting dataset was selected for our study because NHANES protocols have not included clinical assessment of periodontal health since 2014.

Therefore, this publically accessible repository is valuable for exploring factors potentially intertwined with periodontitis. Data mining is applied to extract 'useful' knowledge from large datasets. This process allows for deciphering meaning through data processing and analysis.[16,17]

The objective of this study was to explore the feasibility of applying data-driven approaches to identify unique subgroups with periodontitis by investigating 500 + variables in the NHANES 2009-2014 dataset related to periodontal clinical parameters and self-reported periodontitis, in the presence of health-related and socioeconomic factors. Income, education, age, sex, and poverty have previously been investigated and were found to be implicated with the prevalence of periodontitis.[30,31] Therefore, it is imperative to assess periodontitis in that context.

Cluster analysis was used to reveal class similarities, while maximizing heterogeneity among groups. In healthcare, clustering can help identify participants and groups most in need of targeted interventions.[18,19] This approach can serve to supplement 'clinical judgement' by taking into perspective several variables commonly collected for recording in medical charts, but routinely limited to individual interpretation by the medical provider, which invariably could result in biased interpretation depending on provider factors. In contrast, a more automated and consistent way of handling such data could result in individualizing risk assessment and subsequent potential intervention. The "k-means" clustering is a method that uses vector quantization for grouping elements. It is an unsupervised algorithm that creates inferences from big datasets using only input variables without referring to pre-defined outcomes. The "k-modes" is an extension of k-means that instead of vectors and distances uses dissimilarities to cluster (or group) observations. There is no prior knowledge of the resulting groups; and therefore, k-means/k-modes enable grouping of

observations by periodontitis categories, based on all aforementioned variables into distinct categories.

MATERIAL AND METHODS

Data collection: NHANES

NHANES was conducted in agreement with the Helsinki Declaration of 1975[20] as most recently revised in 2013.[21] NHANES are cross-sectional in design, based on multi-stage stratification and clustering of the US civilian, non-institutionalized population. The CDC's National Center for Health Statistics Ethics Review Board approved the oral health data collection protocols, and all survey participants provided written informed consent.[22] Mobile examination centers that contained space for clinical examinations, sampling of body fluids, blood pressure measurement, and interviews were used.

Data extraction, inclusion and exclusion criteria

This report follows strengthening the reporting of observational studies in epidemiology (STROBE) guidelines[23].

The data analyzed are publically available, so no approval from any institutional review board was needed.

Each participant's barcode corresponded to a unique "Sequence ID." Participants eligible for clinical periodontal examination *included* those who 1) underwent medical history screening, 2) were 30-79 years old, 3) had natural teeth, 4) were not in need of prophylactic antibiotics, and 5) provided informed consent for the oral examination. Examiners were calibrated dental hygienists (2009 - 2010) or dentists (2011-2014). Clinical measurements were performed as described in Methods S1A in online JOP. A total number of 14,072 IDs were marked as records (2009 – 2014).
Thirty-three tables were selected from NHANES 2009-2014 ~~l~~aboratory, questionnaire, and clinical data related to subjects' behavior, systemic condition(s), demographic, socioeconomic status~~es~~, and oral health, based on previously identified periodontitis risk-factors.[1,5] Variables pertaining to periodontal health status, cardiovascular status, smoking, DM, obesity, arthritis and habits were selected. Data on demographic and socioeconomic status were collected. For systemic conditions, clinical, self -reported as well as laboratory data were used for a more comprehensive overall evaluation.

Participants whose data were *excluded* were those who 1) had <6 natural teeth (to ensure adequate representation of dentition) or 2) had data missing in any of the 33 merged data tables, including periodontal examination data. The selection process for inclusion in our study is presented in Figure 1.

Application of periodontitis case definitions

Clinical attachment loss (CAL) was calculated as the difference between PPD and CEJ. The 2012 CDC/American Academy of Periodontology (AAP) periodontitis case definitions were applied to categorize participants with no, mild, moderate, or severe periodontitis,[24] respectively (Methods S1B in online JOP). Categorization into the group with severe periodontitis required ≥2 interproximal sites with CAL ≥6 mm (not on same tooth) and ≥1 interproximal site with PPD ≥5mm.[24]

Moreover, the European Federation of Periodontology (EFP)/AAP 2018 periodontitis classifications were applied to the best of our ability, given the availability of relevant data.[1] The disease stage was assigned to each participant based on CAL at 6 sites/tooth to differentiate Stage I [1-2mm], II [3-4mm], and III/IV [≥5mm]; PPD in Stage I [≤4mm], Stage II [≤5mm], and Stage III and IV [≥6mm]). Participants could not be classified as either Stage III or Stage IV because the reason behind tooth loss was not included in the NHANES dataset. No radiographic images, or information regarding factors pertaining to local periodontitis complexity were available in this dataset. Consequently, an attempt to apply the 2018 EFP/AAP case definitions was made with major limitations, such as staging severity being assessed based on only interproximal CAL.

For grading, only data on the grade modifiers DM ("glycated hemoglobin $A1_c$" and "DM diagnosis") and smoking ("daily smokers") were available. Methods S1B and Table S1 in online JOP provide a detailed overview of which data necessary for correct allocation of the EFP/AAP classification are available.

Data analysis

The selected data tables were merged for analysis (see Methods S1A in online JOP). Columns with a majority of "null"/undefined values were not included in training the model. Out of 1,000+ variables, 519 were included in the cluster analysis. As mentioned, k-modes, a variation of k-means, was used for clustering, whereby participants are grouped into a specified number (k) of clusters.[25] Off-the-

shelf R libraries were used for clustering. The elbow method simulated k-means clustering for values from 2 to 14 (k= 2:14). For each k, a score was computed using the total within-cluster simple matching distance, namely the sum of squared estimate of errors (SSE) via the following formula:

$$SSE = \sum_{n=1}^{n} (x_i^2) - \sum_{n=1}^{n} (x_i)^2 \Big/ n,$$

where xi is the i'th (sample) value of variable x and n the number of observations (participants), to interpret how well different k-values and their corresponding models fit the data. These results were plotted in an elbow diagram (see Figure S1 in online JOP). The selected number of clusters (k=5) yielded a small SSE. SSE tends to decrease toward 0 as k increases. The value of the sum of squares error is zero (SSE=0) when k=number of data points in the dataset where each data point is its own cluster. The goal was to select a small value of k that still had a low SSE. The model learns patterns in the dataset and allocates each participant to exactly one cluster. Due to the high number of variables, visual assessment of heterogeneity of clusters in 3 dimensions (x-, y-, z-axes) was a challenge (see Figure S2 in online JOP). Validation of the model relied on inter-class variability (63.08%) and post-scoring analysis. Based on oral variables included in clustering, principal component analysis (PCA) was conducted to reduce the dimensions, accounting only for the greatest variance/variability.

The unsupervised method of clustering was executed prior to any determination of values,' thresholds, and application of either periodontal classification. For included variables (500+) and analysis of clusters' outcome, cutoff values used for demographic and socioeconomic factors were those originally used in the NHANES dataset and medical thresholds were defined based on standard national health values, such as those determined by the American Diabetes Association for ($HbA1_c$).[26]

In an attempt to further assess the identified outcome systemic factors related to periodontal health, multi-variance analysis was conducted using obesity, smoking, and DM as examples. These variables were: 1) body mass index (BMI), 2) smoking, 3) systolic and diastolic blood pressure (SBP and DBP), 4) pre-DM/DM, and 5) elevated cholesterol levels.

Different forms of bias were mitigated. Confirmation bias, for example, was dealt with by assigning equal weights to all variables entered into the model. Other forms of bias are discussed later.

Model validity evaluation

To further evaluate the model, we conducted a complete second execution of clustering, including re-training and re-scoring. The second run used a subset of the variables: age, sex, income, and education, as well as smoker/non-smoker, number of cigarettes smoked daily, and $HbA1_c$ level, along with clinical periodontal data; that is, variables that are agreed upon in the literature as correlated to periodontitis. As an outcome, Cluster 1 was distinct from other clusters, as it had no severe, moderate, or mild periodontitis. However, other clusters from the same perspective were not clearly distinct (i.e., their inter-cluster values were high resulting in an overlap between the clusters; or clusters included a small number of participants). Such outcomes mean that variables passed to the model are not sufficient for it to identify unique patterns in all clusters. This was not a surprise because it is known that unsupervised models require big data, namely more than included in this second re-run. Accordingly, the first execution was deemed more successful because it is more reasonable and includes all variables.

RESULTS

From the initially identified 14,072 participants with periodontal data, a total of 1,222 were included in our analyses (Fig. 1). All had participated in the 2013-2014 cycle.

Allocation to the 5 clusters

The 1,222 included participants were allocated by the model to exactly 1 of 5 clusters, resulting in the following cluster sizes: **Cluster 1** (n=249), **Cluster 2** (n=154), **Cluster 3** (n=242), **Cluster 4** (n=35), and **Cluster 5** (n=542).

Categories of periodontitis in the 5 clusters

The model resulted in grouping participants with the greatest proportion of no periodontitis in **Cluster 2**, mild periodontitis in **Cluster 5**, moderate periodontitis in **Cluster 3** followed by **Cluster 4,** and severe periodontitis in **Cluster 1** (Table 1). The proportion with total or any (mild, moderate, or severe) periodontitis in **Cluster1** was 65.0%, namely 6.0% mild, 16 .1% moderate, and 43% severe periodontitis, leaving about one-third (34.9%) with no periodontitis. The corresponding results in **Cluster 5** were 78.7% with total periodontitis (55.5% mild, 20.9% moderate, and 2.3% severe),

leaving about one-fifth (21.3%) with no periodontitis. In reference to all other included variables, Figure 2 (A, B) and Figure S3 (A, B, C) in online JOP display the top influential variables, arranged in order of magnitude per cluster.

Demographic and socioeconomic factors

The non-Hispanic Caucasian race/ethnic group prevailed in all clusters, followed by non-Hispanic blacks in **Clusters 1, 2,** and **3.** The sex distribution was about even, except in **Cluster 4** in which males constituted more than 70 % (71.42%) (see Table S2 in online JOP). In **Clusters 1** through **4**, more than 40% reported annual family income of <35,000 US dollars (USD). Only in **Cluster 5**, the majority of participants earned between USD 35,000 and USD 99,999. Two-thirds of **Cluster 1** had attained high school or less education *versus* half in **Cluster 5**. The most prevalent age group in all clusters was 50-69 years, most explicitly in **Cluster 1** (71.08%), where age 50-69 years was the eighth most influential variable (Fig. 2A).

Periodontal status, oral health, and recommendation of care

Cluster 1 followed by **Cluster 4** contained the greatest proportions of participants with severe periodontitis; shown in Table 2. In accordance with EFP/AAP case definitions, this group also showed the greatest prevalence of Stage IV periodontitis (52%) (Figure 3). In **Cluster 1**, 109 of identified smokers had periodontitis and were classified within good, fair, and poor general self-reported general health. A large subset of the same group (80 participants) had several decayed teeth. This group also had the greatest proportion of grade C risk modifiers (17%), based on the number of cigarettes smoked daily and the $HbA1_c$ level. One participant in **Cluster 2** had periodontitis (45-year-old female, multiple sites with CAL $\geq$4 mm, anti-hypertensive medication, and smoked >10 cigarettes a day), and 93% had Stage I periodontitis.

More than half (53%) of **Cluster 3** had moderate periodontitis and 75% responded "Yes" to the question "Do you think you might have gum disease?" In **Clusters 3** and **4**, 98% had some form of periodontitis, i.e., total periodontitis. Additionally, **Cluster 4** had the greatest proportion of Stage III periodontitis (83%) followed by **Cluster 3** (58%). Finally, 77% of **Cluster 5** had only no or mild periodontitis. Three-quarters (76%) of these subjects had Stage II periodontitis.

Risk modifiers were included in grading. Participants were categorized by either DM together with number of cigarettes or DM exclusively, depending on data availability. Only 2.6% of all participants

could not be graded by either factor. Of 985 subjects considered as Grade A, 461 subjects were determined by both modifiers and 524 only by diabetes variables.

Furthermore, a total of 85% of participants in **Cluster 4** were thought to have oral hygiene issues, followed by 65% in **Cluster 3** and 45% in **Cluster 1**. Interestingly, while over 40% in **Clusters 3** and **4** had decayed teeth, 82% in **Cluster 5** had none. Additionally, **Cluster 4** contained the greatest proportion (46%) advised to see a dentist either immediately due to acute injuries or within 2 weeks of examination due to "chronic pain, gum issues, or for counseling."

The scatterplot in Figure 4 represents the 5-cluster model derived by the PCA based on dental and care recommendation variables. It shows homogeneity and heterogeneity among individuals in the same cluster and between clusters.

Chronic conditions

DM, coronary heart disease, rheumatoid arthritis (RA), and hypercholesterolemia were among the most alternating conditions among clusters. Of all included participants, 13% had DM ($HbA1_c \geq 6.5\%$). Among those with DM, elevated fasting blood glucose level (>100 mg/dl) was found in >65% of **Clusters 1** and **4.** Nearly 1 in 10 **(**8.6%) of those suffering from DM had $HbA1_c$ levels of >7%, i.e., uncontrolled DM. The greatest proportions of them (15%) were found in **Clusters 1** and **4**. Moreover, 40% of **Cluster 1** had pre-DM defined as $HbA1_c$ between 5.7% and 6.4% (Fig. 2 Panel A; Table S3 in online JOP). Interestingly, participants in **Clusters 2** and **3** showed similar proportions of pre-DM according to $HbA1_c$ but not to the 2-hr glucose test or fasting blood glucose level (see Table S3 in online JOP).

Regarding participants' cardiovascular health status, the majority in **Cluster 1** took anti-hypertensive medications and >60% had been told they had elevated blood pressure. Having been told of having coronary heart disease represented about 10% in all groups and did not play a significant role in characterizing clusters.

Most participants who had smoked ≥100 cigarettes in their lifetime were grouped into **Cluster 1**. "Active smoker" shown by >10 mg/dL cotinine in urine samples accounted for >50% in **Clusters 1** and **3**. Current daily smokers constituted 38% of **Cluster 1**, the greatest prevalence among all clusters. The variable "smoked ≥100 cigarettes in your lifetime" was largely representing past smokers in **Cluster 2**, shown by cotinine levels <1 mg/dL, reflecting the lack of active and environmental smoke exposure.

More than 80% in **Cluster 5** fell within normal range of laboratory testing for cotinine, and 85% stated there were no smokers in the household. Low-density lipoprotein (LDL) levels were highest in **Cluster 4**. **Clusters 1** and **4** featured the greatest proportions of individuals with elevated (>2.2 mmol/L) triglyceride levels, contributing to their poorer overall health status. Finally, one-third of **Cluster 1** members had been told they had RA.

Other health conditions and habits

In **Cluster 1,** 39% assessed their general health as "fair," 23% had DM, almost half (48%) had elevated cotinine levels and 33% had elevated LDL levels. **Clusters 3** and **4** showed the greatest proportions rating their overall health condition "fair." **Cluster 5** included the healthiest members with 30% regarding their health "very good" (Fig. 2 Panel B, see Table S3 in online JOP).

Obesity (BMI $\geq$ 30 kg/m^2) was significant to grouping participants and obese individuals constituted 35% of all clusters. Additionally, **Cluster 4** had the greatest proportion of overweight people (25$\leq$BMI<30 kg/m^2) with more than half (54%) affected. Multi-variate analysis showed the greatest F-values for BMI and cotinine, meaning their values were highly variable and contributed strongly to the process of clustering (see Table S4 in online JOP).

DISCUSSION

Taking into account that our 5 clusters only include data from 1,222 of the participants in the 2013-2014 NHANES cycle, our results regarding the prevalence of periodontitis defined by the CDC/AAP classifications,[2] obesity,[27] and DM are in line with the respective CDC findings.[28] Results from glucose tolerance tests and the $HbA1_c$ levels enabled detection of undiagnosed pre-DM as well as DM. This finding could support advocating for action on identifying pre-DM and early detection of disease in the dental care setting, especially for people who do not undergo routine medical health checkup,[29,30] but do visit a dental office.

Likewise, we confirm previous findings that show an inverse relationship between prevalence of periodontitis and socioeconomic status assessed by education attainment and family income.[31-34] This is evident in **Cluster 1**, in which the majority of individuals had family income >USD 35,000 and high school level of education *versus* **Cluster 5** where 40% had college education and one-third had annual family income >USD 100,000.

We applied the CDC/AAP periodontitis case definitions because they were designed specifically for population surveillance.[24] When attempting to translate these case definitions[24] to the 2018 EFP/AAP classification,[1] moderate and severe periodontitis defined by the former are most likely of stage III or IV. Our data show an overall prevalence of severe periodontitis of 15%, most prominent in **Cluster 1** that contains the greatest proportion of smokers. Since the majority were current smokers, had severe periodontitis, and had $HbA1_c$ levels $\geq$7%, they would potentially exhibit rapid progression and hence be classified as Grade C.[1] Age groups >60 years (n=329) showed a prevalence of 22.4% *versus* only 0.1% severe periodontitis cases among those 30 – 50 years old (n=410). Previously, 65+ year-old adults were estimated to have a 7-fold increased risk of periodontitis compared to younger groups.[3,37,38] While **Cluster 4** showed the second largest group of severe periodontitis; it is likely due to oral hygiene issues as reported by dental examiners.

Despite some overlap in demographic, socioeconomic, and systemic conditions (e.g., obesity, pre-DM), **Cluster 3** showed the greatest proportion with moderate periodontitis, while **Cluster 2** had almost none with any periodontitis. This difference is likely due to oral hygiene issues, prevalent DM, and current smoking in **Cluster 3**.

Strengths

Because this study is the first of its kind, there are no prior studies to which we can compare our results. Unsupervised learning models are increasingly popular in precision medicine. For example, this approach can help identify homogenous groups and result in deciphering stronger associations between periodontitis and underlying risk factors.[39] We applied k-means clustering as such a model that groups participants into distinct categories based on periodontal variables with no pre-determined outcomes assigned. We showed that cluster models indeed can help identify population groups at high risk for periodontitis and hope that this common disease thereby can be better prevented, identified, treated, or managed.

To the best of our knowledge, this is the first comprehensive model built via exploring a large, nationally representative database with 1,000+ original variables to group periodontally examined participants.

Our comprehensive dataset was extracted from the NHANES data collected on many periodontitis-related factors that were identified *a priori* according to their known influence on pathogenesis and progression of periodontitis.[6] The NHANES 2009-2014 dataset is the world's largest reference to periodontitis prevalence. This is due to the extensive number of participants aged 30-79 years and to the application of the gold standard periodontal examination with probing at 6 sites around all non-third molar teeth for both PPD and CEJ, ensuring that the prevalence of periodontitis can be

estimated by applying various periodontitis case definitions that include CAL and PPD, such as mean CAL and PPD as well as proportions with PPD and CAL above various thresholds.[2] These NHANES 2009-2014 data are the first to include measures from full-mouth periodontal clinical examinations, which should greatly improve the validity and reliability of estimates compared to data from earlier NHANES partial-mouth periodontal examination protocols that have underestimated the prevalence of periodontitis by up to 54%.[40]

Unlike some previous models, dental factors, i.e., caries, oral hygiene, and number of teeth, were included. The threshold of having a minimum of 6 natural teeth was selected to ensure inclusion of representative dentate participants due to having fewer teeth might indicate hopeless periodontitis or other severe situations.

Limitations

The cross-sectional study design of NHANES encompasses inherent limitations that prevent any conclusion regarding potential causality due to the simultaneous occurrence of the observed information.[41] Only the 2013-2014 NHANES 2-year cycle was included after merging data tables. While PPD and CEJ were recorded to assess the periodontal status, there was no assessment of the presence of dental plaque nor of bleeding on probing, which potentially could limit the identification of other disease phenotypes.[39] Additionally, application of the EFP/AAP classification was limited due to availability of relevant data in the NHANES dataset. Importantly, participants could not be classified distinctly into either Stage III or Stage IV, so these were merged into one category. Information on local complexity factors and radiographs are missing and thus, preventing accurate staging and grading. Only CAL could be regarded informative pertaining to severity. The CDC/AAP case definitions[24] define attachment loss of $\geq$3mm at $\geq$2 interproximal sites (not on the same tooth) as mild periodontitis. In the EFP/AAP classification, stage II indicates attachment loss of 3-4mm. Overlap could exist between Stage II (EFP/AAP) and mild periodontitis (CDC/AAP). Nonetheless, the aim of using both case definitions was to allow interpretation of the resulting clusters output in a familiar context in the field. However, comparing periodontitis prevalence determined by the two sets of case definitions might not adequately represent the results of clusters at this point. The use of CDC/AAP case definitions seem more justifiable to use with NHANES dataset as detailed in Supplementary Methods S1B in online JOP.

Furthermore, datasets from large population studies will not be complete, as some data inherently will be missing, due to participants' ineligibility or refusal to undergo certain exams, respond to

certain questionnaire items, or due to the inclusion/exclusion of certain measures from study protocols that are time-sensitive or vary by survey cycle. Self-reported data were not validated. Notably, while results from such large population studies may apply in the aggregate to groups, they may not be informative at an individual level.[39]

CONCLUSION

Clustering of NHANES data by integrating systemic health, demographic, and socioeconomic characteristics can effectively identify population group characteristics that are statistically significantly associated to periodontitis. Identification of such clusters can be enhanced by self-reported periodontitis measures *in lieu* of the extremely resource demanding clinical periodontal examination. Economical, non-intrusive clustering constitutes a low-cost alternative to identifying population groups at high risk for periodontitis, who could be targeted for preventive and therapeutic dental public health intervention.

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FIGURE LEGENDS

Fig. 1. Study participant selection from the three two-year National Health and Nutrition Examination Survey cycles 2009-2010, 2011-2012, and 2013-2014 ("NHANES 2009-2014").

Footnote: DM, diabetes; N/n, number; SQL, structured query language (a programming language).

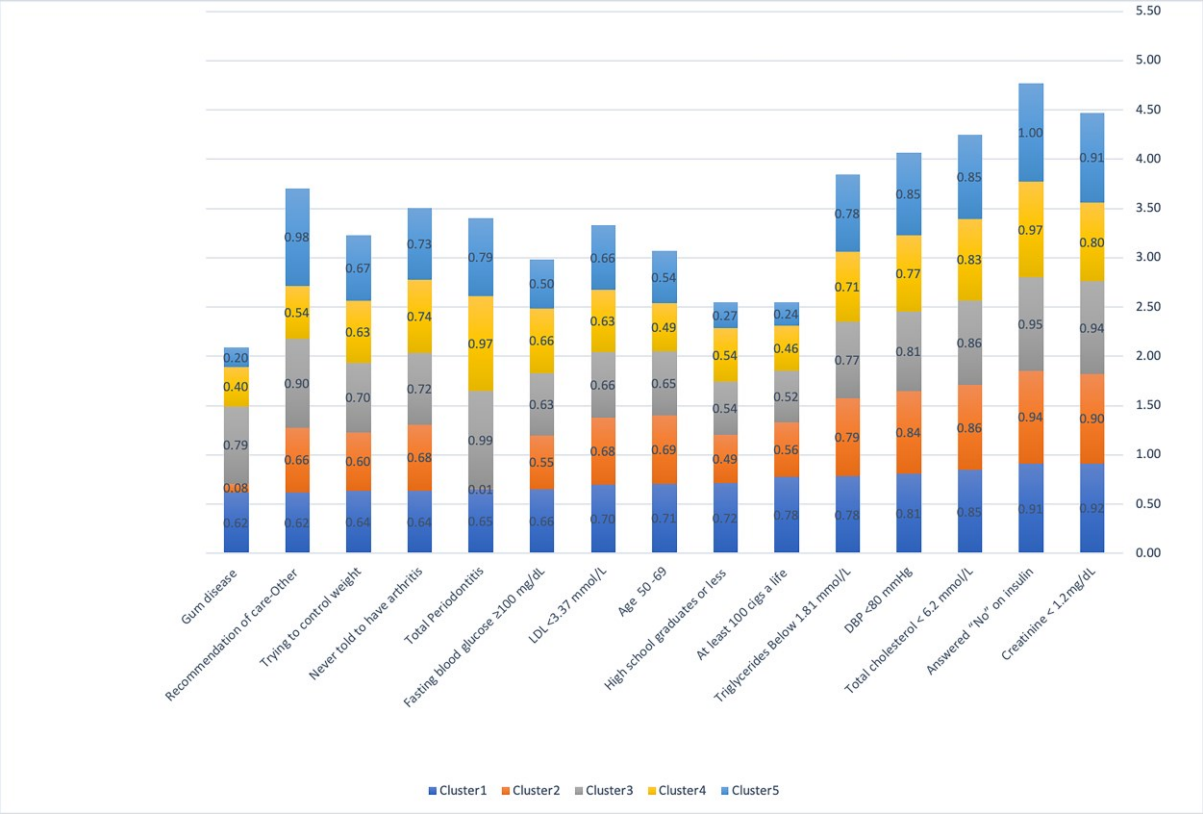


Fig. 2. Top variables describing A) **Cluster 1** (unhealthier) and B) **Cluster 5** (healthier), variables arranged in descending order of the greatest/right magnitude/influence to the lowest/left on grouping subjects within **Cluster 1** (dark blue) and **Cluster 5** (light blue), respectively. The 2012 CDC/AAP periodontitis case definitions are applied.[24] Please note, the corresponding graphs for **Clusters 2, 3**, and **4** are displayed in Supplementary Figure S3.

Footnote: AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention.

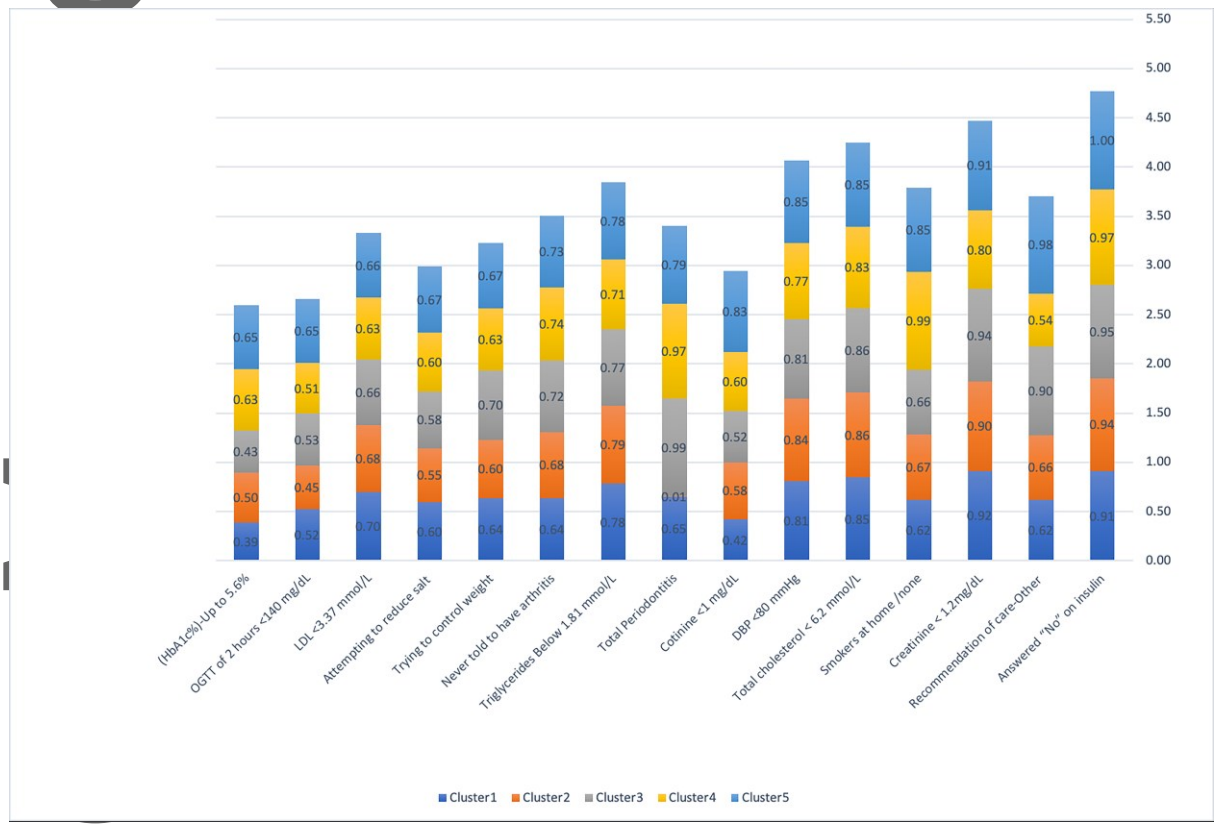


Fig. 3. Distribution by cluster of periodontitis prevalence according to the 2012 CDC/AAP case definitions for no, mild, moderate, and severe periodontitis[24] and Stages I, II, and III/ IV according to the 2018 EFP/AAP periodontitis classification.[1]

Footnote: AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention; EFP, European Federation of Periodontology.

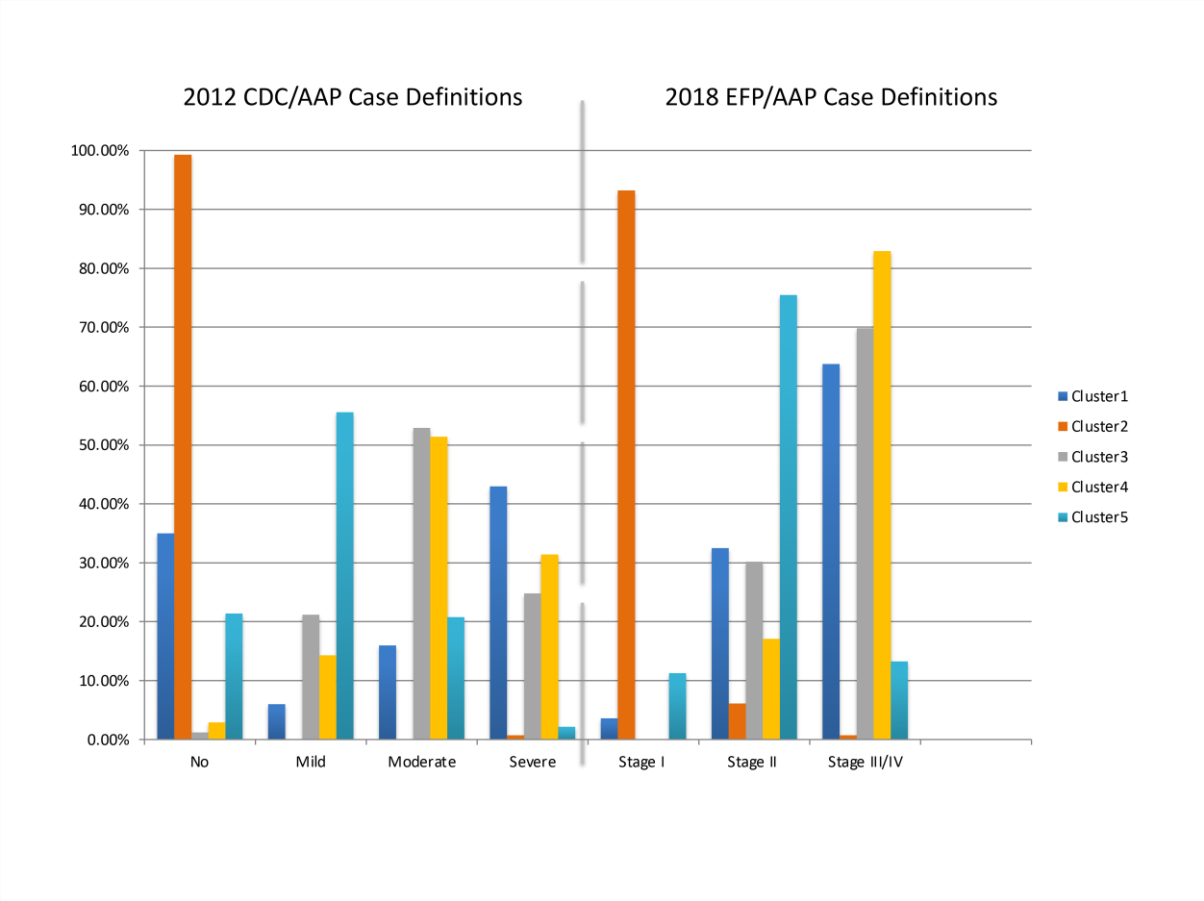
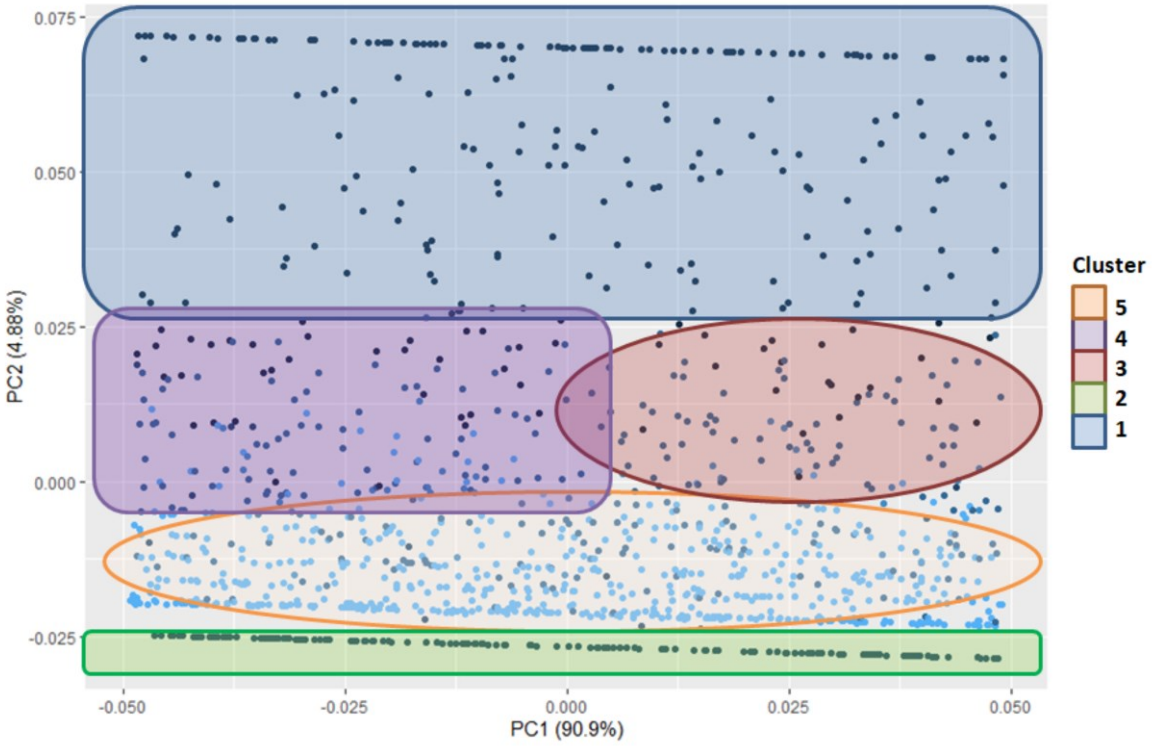


Fig. 4. Principal component analysis (PCA) scatterplot representation of the 5-cluster model based on periodontal health variables. The 2012 CDC/AAP periodontitis case definitions are applied.[24]

An R library (ggfortify) was used to consume the variables from the R engine and illustrate the clusters in a colored scheme. For example, the figure shows that **Cluster 1** (shaded blue) has the highest distribution among the components space. Participants in **Cluster 2** (green) are those most closely associated with each other. **Clusters 1** and **2** exhibit the furthest association in periodontal terms (most different). **Clusters 2** and **5** (orange) are the periodontally closest (most similar) with more than 99% having no periodontitis in **Cluster 2** and 77% having no or mild periodontitis in **Cluster 5. Clusters 3 and 4 are intermediary to cluster 1 and 5.**

Footnote: AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention.



Dear Iya: Please remember to change all these titles so they are identical to those in the corresponding files after your final decision on their wording.

SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLES

Table S1. Availability of data collected in the three 2-year NHANES waves that included a full-mouth periodontal examination required for application of the 2018 EFP/AAP periodontitis classification.[1]

Table S2. Distribution of demographic and socioeconomic characteristics by the 5 clusters – NHANES 2013-2014 (N= 1,222).

Table S3. Distribution of medical characteristics by the 5 clusters – NHANES 2013-2014 (N= 1,222).

Table S4. F-test two sample for variances of health outcomes and cluster labeling – NHANES 2013-2014 (N=1,222).

SUPPLEMENTARY FIGURES

Figure S1. Selecting the number of clusters (k) for further analysis.

Figure S2. k-means 5 clusters plot.

Footnote: [1]: **Cluster 1**, [2]: **Cluster 2**, [3]: **Cluster 3**, [4]: **Cluster 4**, [5]: **Cluster 5**.

Figure S3A, B & C. Variables ordered by their greatest value within **Clusters 2, 3,** and **4.**

Table1. Proportions of participants within the top influential variables sorted from the highest (green) to the lowest (red) value (Heatmap) displayed in descending order according to Cluster 1 – NHANES 2013-2014 (N=1,222).*

B) Diabetes related variables	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Do not take insulin	91.2%	94.2%	94.6%	97.1%	100.0%
Fasting blood glucose ≥100 mg/dL	65.5%	54.5%	63.2%	65.7%	49.6%
Answered "No" to DM	57.0%	50.0%	55.8%	60.0%	53.5%
OGTT <140	52.2%	44.8%	52.5%	51.4%	64.9%
Close relatives with DM	43.0%	50.0%	44.2%	40.0%	46.7%
HbA1c - 5.7-6.4%	41.4%	33.8%	37.6%	20.0%	27.7%
HbA1c - ≤ 5.6%	39.4%	50.0%	43.0%	62.8%	64.5%
OGTT >200 mg/dL	32.5%	3.3%	5.4%	2.8%	4.6%
Officially diagnosed with DM	20.9%	20.1%	19.4%	17.1%	10.3%
On diabetic pills	14.1%	14.9%	15.7%	14.3%	8.1%
OGTT - 140-200 mg/dL	11.6%	14.9%	18.6%	20.0%	19.2%
HbA1c - >8%	10.0%	7.1%	5.8%	8.6%	2.6%
HbA1c - 6.5-7%	4.0%	7.8%	8.2%	2.9%	3.5%
On insulin	**8.8%**	**5.8%**	**5.4%**	**2.9%**	**0.0%**
Reported complications (exl. retinopathy)	**6.0%**	**3.9%**	**2.9%**	**5.7%**	**2.0%**
HbA1c -7.1-8%	**5.2%**	**1.30%**	**5.40%**	**5.70%**	**1.70%**

C) Demographics	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
High school graduates or less	71.8%	48.7%	53.7%	54.2%	26.6%
Age 50-69 years	71.1%	68.8%	65.3%	48.6%	53.5%
Annual family income $0-$34,999	55.4%	46.8%	45.9%	43.7%	22.9%
Male Sex	52.2%	44.8%	49.6%	71.4%	44.8%
Non-Hispanic white	35.3%	39.0%	34.3%	14.3%	48.0%
Annual income $35,000-$99,999	32.5%	37.1%	39.7%	36.3%	41.7%
Female Sex	27.8%	55.1%	50.4%	28.5%	55.2%
Non-Hispanic Black	27.3%	26.0%	28.1%	14.3%	11.8%

Age 30-49	26.9%	22.7%	28.5%	42.9%	42.1%
Some college degree	20.1%	30.5%	28.9%	34.3%	31.4%
Mexican American	13.6%	12.3%	15.7%	25.7%	11.3%
Other Hispanic	13.6%	8.4%	8.7%	14.3%	9.4%
Other-multiracial	10.2%	14.3%	13.2%	31.4%	19.6%
College or above	8.0%	20.8%	17.4%	11.5%	42.1%
Annual family income ≥$100,000	6.0%	11.6%	11.6%	11.4%	32.8%
Age 70 -79 years	2.0%	4.6%	5.4%	5.7%	4.1%

D) Periodontitis	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Total Periodontitis	65.0%	0.7%	98.8%	97.1%	78.7%
Severe Periodontitis	43.0%	0.7%	24.8%	31.4%	2.3%
No Periodontitis	34.9%	99.4%	1.2%	2.9%	21.3%
Moderate Periodontitis	16.1%	0.0%	52.9%	51.4%	20.9%
Mild Periodontitis	6.0%	0.0%	21.1%	14.3%	55.5%

E) Oral health and recommendation of care	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Gum disease	62.3%	8.4%	78.5%	40.0%	19.7%
Recommendation of care - other	62.3%	65.6%	89.7%	54.3%	98.2%
Decayed teeth	43.8%	20.1%	47.5%	45.7%	16.9%
Oral hygiene - Yes	53.4%	9.0%	64.5%	85.7%	21.4%
Do not floss	49.8%	53.0%	24.8%	57.2%	14.2%
Partial dentures or plates	30.1%	7.8%	9.9%	8.6%	0.4%
Flossing -(7days a week)	25.7%	22.1%	46.3%	25.7%	41.3%
Flossing -(1-4 days a week)	24.5%	24.9%	28.9%	17.1%	44.5%
Had treatment for gum disease	22.1%	22.7%	27.3%	22.9%	23.8%
Recommendation of care-immediate/urgent	21.3%	3.9%	10.3%	45.7%	1.8%
Told to have bone loss	18.8%	16.3%	20.3%	22.9%	9.2%

F) Habits

1) Smoking	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
At least 100 cigs a life	77.7%	55.8%	51.7%	45.7%	24.4%
Smokers at home - none	61.8%	66.8%	65.7%	99.0%	85.4%
Cotinine >102 mg/dL	48.2%	33.0%	43.4%	31.4%	12.5%
Cotinine <1 mg/dL	42.1%	58.0%	51.8%	60.0%	82.8%
Smokers at home	38.2%	33.2%	34.3%	1.0%	14.6%
Daily smokers	37.8%	25.3%	23.6%	28.6%	24.4%
Cotinine 10-101 mg/dL	7.4%	7.0%	2.8%	5.7%	3.3%
Cotinine 1-10 mg/dL	3.6%	2.0%	2.0%	2.9%	1.4%
2) Lifestyle	**Cluster1**	**Cluster2**	**Cluster3**	**Cluster4**	**Cluster5**
Trying to control weight	63.5%	59.7%	70.2%	62.9%	66.8%
Attempting to reduce fat	61.0%	53.2%	60.7%	60.0%	61.8%
Attempting to reduce salt	59.8%	54.5%	57.8%	60.0%	66.7%
Attempting to increase exercise	57.8%	55.2%	64.9%	48.6%	9.8%
3) Other	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**
Daily marijuana smokers	26.9%	13.0%	22.3%	17.1%	11.6%
Ever used meth/cocaine/heroin	21.3%	18.2%	18.6%	11.4%	11.8%
Answered "No" to meth/cocaine	15.2%	16.2%	4.4%	14.2%	6.5%

*The table is arranged in ascending order of **Cluster 1** and the total percentages per category add up to a 100%. For instance, the proportion with Total Periodontitis in **Cluster 1** is 65%, categorized as 43% severe, 16% moderate, 6% mild and 34.9% no periodontitis (totaling 100% of 65%).

HbA1c, glycated hemoglobin; OGTT, 2-hour glucose tolerance test; SPF, socio-position factors

Table 2. Self-reported periodontal disease, clinically determined oral health, and recommendation of dental care by clusters – NHANES 2013-2014 (N=1,222).

Charac-teristic	Cluster 1 (n, %)	Cluster 2 (n, %)	Cluster 3 (n, %)	Cluster 4 (n, %)	Cluster 5 (n, %)	Total n (%)
Total/All	249 (20.4%)	154 (12.6)	242 (19.8)	35 (2.9%)	542 (44.3%)	1,222 (100%)
Number of teeth present mean (±SE)	13.0 (±10.4)	19.0 (±10.2)	23.5 (±10.5)	26.0 (±10.3)	25.0 (±10.2)	20.6 (±10.3)
Think you have gum disease?						
Yes	101 (40.6%)	9 (5.9%)	167 (69.0%)	14 (40.0%)	107 (19.7%)	398 (32.6%)
No	0 (0%)	0 (0%)	0 (0%)	1 (2.9%)	0 (0%)	1 (0.1%)
NR	148 (59.4%)	145 (94.1%)	75 (31.0%)	20 (57.1%)	435 (80.3%)	823 (67.3%)
Ever been told you have lost bone around your teeth?						
Yes	47 (18.8%)	25 (16.3%)	49 (20.3%)	8 (22.9%)	50 (9.2%)	179 (14.6%)
No	201 (80.8%)	128 (83.1%)	190 (78.5%)	27 (77.1%)	488 (90.0%)	1,034 (84.6%)
N/R	1 (0.4%)	1 (0.6%)	3 (1.2%)	0 (0%)	4 (0.8%)	9 (0.8%)
Ever had treatment for gum disease?						
Yes	55 (22.1%)	35 (22.7%)	66 (27.3%)	8 (22.9%)	129 (23.8%)	293 (24.0%)
No	191 (76.7%)	117 (76.0%)	176 (72.7%)	27 (77.1%)	413 (76.2%)	924 (75.6%)
N/R	3 (1.2%)	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	5 (0.4%)
Oral Hygiene†						
Yes	133 (53.4%)	14 (9.0%)	156 (64.5%)	30 (85.7%)	116 (21.4%)	449 (36.7%)
No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
N/R	116 (46.6%)	140 (91.0%)	86 (35.5%)	5 (14.3%)	426 (78.6%)	773 (63.3%)
Flossing/using other devices						
7 days/ week	61 (24.5%)	38 (24.9%)	70 (28.9%)	6 (17.1%).	241 (44.5%)	416 (34.0%)
1-4 days	64 (25.7%)	34 (22.1%)	112 (46.3%)	9 (25.7%)	224 (41.3%)	443 (36.3%)
N/R	124 (49.8%)	82 (53.0%)	60 (24.8%)	20 (57.2%)	77 (14.2%)	363 (29.7%)

Charac-teristic	Cluster 1 (n, %)	Cluster 2 (n, %)	Cluster 3 (n, %)	Cluster 4 (n, %)	Cluster 5 (n, %)	Total n (%)
Decayed teeth						
Yes	109 (43.8%)	31 (20.1%)	115 (47.5%)	16 (45.7%)	92 (16.9%)	363 (29.7%)
No	140 (56.2%)	123 (79.9%)	127 (52.5%)	19 (54.3%)	448 (82.7%)	857 (70.1%)
N/R	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)	2 (0.2%)
Periodontitis category (CDC/AAP case definitions[24])						
No	87 (35.0%)	153 (99.3%)	3 (1.2%)	1 (2.9%)	116 (21.4%)	360 (30.0%)
Mild	15 (6.0%)	0 (0%)	51 (21.1%)	5 (14.3%)	301 (55.6%)	372 (30.4%)
Moderate	40 (16.0%)	0 (0%)	128 (52.9%)	18 (51.4%)	113 (20.8%)	299 (24.4%)
Severe	107 (43.0%)	1 (0.7%)	60 (24.8%)	11 (31.4%)	12 (2.2%)	191 (15.2%)
Total	162 (65.0%)	1 (0.7%)	239 (98.8%)	34 (97.1%)	426 (78.7%)	862 (70.0%)
Periodontitis category (EFP/AAP case definitions[1])						
Stage I	9 (3.6%)	145 (93.2%)	0 (0%)	0 (0%)	61 (11.3%)	213 (17.4%)
Stage II	81 (32.5%)	10 (6.1%)	73 (30.2%)	6 (17.1%)	409 (75.5%)	579 (47.4%)
Stages III/IV	159(63.8%)	1 (0.7%)	169 (69.8%)	29 (82.9%)	72 (13.3%)	430 (35.2%)
§Grade A	180 (72.3%)	123 (79.9%)	186 (76.9%)	28 (80.0%)	468 (86.3%)	985 (80.6%)
Grade B	22 (8.8%)	13 (8.4%)	16 (6.6%)	2 (5.7%)	30 (5.5%)	83 (6.8%)
Grade C	43 (17.3%)	11 (7.2%)	32 (13.2%)	5 (14.3%)	31 (5.7%)	122 (10.0%)
Not deter-mined	4 (1.6%)	7 (4.5%)	8 (3.3%)	0 (0%)	13 (2.5%)	32 (2.6%)
Recommendation for professional dental care						
See a dentist	53 (21.3%)	6 (3.9%)	25 (10.3%)	16 (45.7%)	10 (1.8%)	110 (9.0%)
Other‖	156 (62.7%)	101 (65.6%)	217 (89.7%)	19 (54.3%)	532 (98.2%)	1,025 (83.9%)
N/R	40 (16.0%)	47 (30.5%)	0 (0%)	0 (0%)	0 (0%)	87 (7.1%)

†Oral Hygiene refers to the examiner's assessment of "other" conditions designated in referral letters. Oral hygiene, gum

disease/problems are examples.

‡Clinical periodontitis status defined by CDC/AAP periodontitis case definitions (Eke et al. 2012) and 2018 EFP/AAP classification. In grading, the category under "not determined" refers to those considered with borderline diabetes and who have not received a diagnosis of diabetes but HbA1c% is between 6.5 and 6.9%.

§ Grading was assessed based on risk modifiers, namely, smoking and diabetes. For Grade A, 524 subjects were assessed by diabetes. For Grade B, 43 subjects were based on diabetes only. Those who were not categorized could not be allocated to a group due to lack of smoking and diabetes data due to missing values in the original NHANES dataset.

[l]Other recommendation of care included "See a dentist at your earliest convenience," and "Continue your regular routine care."

Footnote: AAP, American Academy of Periodontology; CDC, Centers for Disease Control and Prevention; EFP, European Federation of Periodontology; N/n, number; N/R, Not reported; SD, standard deviation; See a dentist, See a dentist immediately or within the next 2 weeks; total periodontitis, mild or moderate or severe (taken together).

The subgroups of Characteristics are categorized and displayed as described by CDC website in NHANES questionnaires and clinical examination