

Combinations of chronic conditions, functional limitations and geriatric syndromes associated with periodontal disease

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ABSTRACT

Objective To identify complex multimorbid conditions, including chronic conditions, functional limitations and geriatric syndromes, associated with the presence and severity of periodontal disease (PD), after accounting for a series of demographic and behavioural characteristics.

Design This cross-sectional study used secondary data from a nationally representative sample, classification and regression tree analysis and random forest identified combinations of specific conditions constituting complex multimorbidity associated with the presence and severity of PD.

Setting US National Health and Nutritional Examination Survey (2013–2014).

Participants Individuals 60 years of age or older who completed a periodontal examination.

Results Among 937 participants aged 60 and over, the prevalence of PD was 72.6%. PD was associated with sociodemographic factors and limitations in instrumental activities of daily living. Male sex and non-white race were the two most critical predictors of stage III/IV PD. Other important factors included age, education level and the federal poverty level.

Conclusions Rather than chronic conditions or geriatric syndromes, PD was associated with sociodemographic factors and functional limitations. Accounting for the co-occurrence of sociodemographic and functional limitations will help recognise older adults who are at an increased vulnerability to the severity of PD.

INTRODUCTION

Periodontal disease (PD), which is initiated by plaque biofilm dysbiosis, results in chronic detractor in the periodontium.¹ According to the recent consensus report, PD is a long-life condition, even following successful periodontal treatment.² The prevalence of PD varies based by severity. Mild PD affects about half of the global population, and severe PD affects 11.2%.³ In addition, oral diseases, including PD, contribute the most years lost to disability from among more than three hundred diseases and injuries.⁴ The association between a variety of systemic conditions

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Is there an association between complex multimorbid conditions and periodontal disease (PD)?

WHAT THIS STUDY ADDS

⇒ Our findings showed that PD was associated with sociodemographic factors and limitations in instrumental activities of daily living.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Healthcare providers should target those with complex multimorbidity by screening them for PD and referring them for periodontal care. The development of integrated multidisciplinary approaches between the medical and periodontal fields will aid in the care of people suffering from complex multimorbidity.

and PD has been confirmed by several studies.^{5–8} Several risk factors and indicators are shared between PD and several systemic conditions, including cardiovascular disease, obesity, rheumatoid arthritis, prostate cancer, stroke, cognitive impairment and hypertension.⁵ Suggested mechanisms include bacteraemia through the epithelial lining of periodontal pockets and elevation of systemic inflammatory cytokines.⁶

Complex multimorbidity (MM), defined as not only the co-occurrence of chronic conditions, but also functional limitations and/or geriatric syndromes, occurs in about 26% of middle-aged and older adults.⁹ Functional limitations and geriatric syndromes are particularly relevant to older people, especially because their presence likely indicates a decline in their ability to care for themselves (eg, inadequate oral hygiene) and/or a shift in the priority of oral care (eg, lack of adherence with the recommended frequency of maintenance visits for PD). Due to the added burden of and/or shifts in prioritisation of



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care for functional limitations and geriatric syndromes, the presence of these conditions may be associated with inadequate PD care and increased PD severity.

Given the common co-occurrence of PD and chronic conditions, and the common co-occurrence of chronic conditions with functional limitations and geriatric syndromes, we hypothesise that PD is also common among people with complex MM. In addition, we hypothesise that among people with PD, there are combinations of conditions constituting complex MM that are most strongly associated with severe PD.

To the best of our knowledge, no previous studies have identified complex MM to be associated with PD or its severity. Identifying these highest-risk groups will help healthcare providers to take a more proactive role in managing the presence and severity of PD by screening people with complex MM for PD and referring them for periodontal care as needed.

In this study, we aimed to identify combinations of conditions constituting complex MM that are associated with the presence and severity of the PD among people 60 years of age or older, after accounting for a series of demographic and behavioural characteristics.

METHODS

Data source and study population

A cross-sectional study using data from a US representative sample of people from the 2013–2014 National Health and Nutritional Examination Survey (NHANES), the most recent years with data on PD using full-mouth periodontal examination protocol, was conducted. NHANES consists of data collected through interviews and examinations performed by trained medical personnel. Periodontal examinations are performed in mobile clinics. If necessary, however, transportation to and from the mobile centre is provided. This study included participants from NHANES 2013–2014 who were 60 years of age or older. We restrict our criteria to include participants who were at least 60 years of age because data for some conditions constituting complex MM, especially functional limitations, and geriatric syndromes, are available only for participants in the older age group. In addition, due to the inability to perform periodontal examinations, edentulous people are not included in the NHANES 2013–2014.

Variables of interest

PD was classified into stages I, II, III/IV, and participants with no PD groups based on the value of clinical attachment loss (CAL) on two non-adjacent teeth.¹⁰ If CAL was 1–2 mm, the case was diagnosed as stage I PD. For stage II PD and stage III/IV PD, CAL was 3–4 mm and >5 mm, respectively. Complex MM measures included:

1. Self-reported chronic conditions indicating whether a physician ever told the individual that he or she had: hypertension, diabetes, arthritis, coronary heart disease, overweight, stroke, hyperlipidaemia, asthma,

chronic obstructive pulmonary disease, emphysema, chronic bronchitis, cancer, liver condition, kidney dysfunction, thyroid problems and psoriasis.

2. Functional limitations included limitations in leisure and social activities, general physical activities, lower extremity mobility, activities of daily living and/or instrumental activities of daily living (IADLs).
3. Geriatric syndromes included cognitive impairment, measured by digital symbol score; depressive symptoms, based on Patient Health Questionnaire; urinary incontinence; visual impairment; hearing impairment; fracture and osteoporosis.

Other covariates of interest included age, sex, race/ethnicity, education, the federal poverty level (FPL), marital status, smoking status, alcohol use, vigorous recreational activities, body mass index, insurance status and whether insurance provides coverage for dental procedures. Age was categorised in five groups (60–64, 65–69, 70–74, 75–79, >80). Race/ethnicity included three groups: white, black and other. Years of education were classified in three categories (high school or below, some college or AA degree and college graduate or above). Income was measured based on the FPL (<200%, 200%–400% and >400%). Marital status (married, divorced and other), insurance status (Medicare, Private insurance and other) and smoking status (current, former and none) had three categories. Body mass index included two groups (non-obese (<30 kg/m²) and obese (>30 kg/m²)). We also included alcohol use (yes, no), vigorous recreational activities (yes, no) and whether insurance provides coverage for dental procedures.

Statistical analysis

In addition to descriptive analysis, we used conditional inference regression tree (CTree)¹¹ and random forest¹² methods to identify which combinations of conditions constituting complex MM are associated with the presence and severity of PD.

CTree is a machine learning method that continuously splits the data into two partitions based on the values of the predictor variables, the result of which is a model that resembles a tree. The ends of the tree are known as terminal nodes and each study subject falls in one and only one terminal node.¹¹ A maximum tree depth of five splits and a p value of 0.2 were used as stopping criteria. We started by partitioning the data into training and test datasets. We used the training dataset to build the CTree model and validated the dataset to test the accuracy of the CTree model. We used random forest to identify the top predictors of PD. Random forest creates many classification trees through bootstrap sampling and aggregates the results.¹² Three thousand trees were created for each random forest model, and three candidate variables for splitting were randomly sampled at each node split. CTree and random forest models were compared regarding the most important predictors for the presence and severity of PD. We used R V.3.6.2 and the ‘partykit’ (CTree), ‘randomForest’ (random forest) packages.

Table 1 Demographic characteristics of the study population

Demographic characteristics	No PD	Stage I PD	Stage II PD	Stage III/IV PD	Total (PD+no PD)	Total PD
No of subjects	257	125	396	159	937	680
Age categories						
(60–65)	60 (22.8)	43 (16.3)	112 (42.6)	48 (18.3)	263	203 (77.2)
(65–70)	55 (22.4)	38 (15.4)	98 (39.8)	55 (22.4)	246	191 (77.6)
(70–75)	59 (30.9)	24 (12.6)	87 (45.5)	21 (11.0)	191	132 (69.1)
(75–80)	36 (35.0)	*	43 (41.7)	16 (15.5)	103	67 (65.0)
(80–81)	47 (35.1)	12 (9.0)	56 (41.8)	19 (14.1)	134	87 (64.9)
Sex						
Male	106 (24.6)	36 (8.3)	173 (40.0)	117 (27.1)	432	326 (75.5)
Female	151 (29.9)	89 (17.6)	223 (44.2)	42 (8.3)	505	354 (70.1)
Race/ethnicity						
White	150 (28.8)	80 (15.3)	241 (46.3)	50 (9.6)	521	371 (71.2)
Black	56 (29.5)	14 (7.4)	62 (32.6)	58 (30.5)	190	134 (70.5)
Other	51 (22.6)	31 (13.7)	93 (41.1)	51 (22.6)	226	175 (77.4)
Marital status						
Married	148 (26.2)	89 (15.8)	227 (40.3)	100 (17.7)	564	416 (73.8)
Divorced	45 (28.8)	16 (10.3)	67 (43.0)	28 (17.9)	156	111 (71.2)
Never married	64 (29.5)	20 (9.2)	102 (47.0)	31 (14.3)	217	153 (70.5)
Education						
High school graduate or below	128 (33.8)	38 (10.0)	123 (32.5)	90 (23.7)	379	251 (66.2)
Some college or associates degree	75 (25.6)	43 (14.7)	136 (46.4)	39 (13.3)	293	218 (74.4)
College graduate or above	54 (20.4)	44 (16.6)	137 (51.7)	30 (11.3)	265	211 (79.6)
Federal poverty level						
<200%	116 (32.2)	28 (7.8)	136 (37.8)	80 (22.2)	360	244 (67.8)
200%–400%	78 (27.8)	37 (13.2)	118 (42.0)	48 (17.0)	281	203 (72.2)
>400%	63 (21.3)	60 (20.3)	142 (48.0)	31 (10.4)	296	233 (78.7)
Smoking status						
No	115 (24.4)	74 (15.7)	227 (48.2)	55 (11.7)	471	356 (75.6)
Former	99 (27.7)	46 (12.9)	140 (39.2)	72 (20.2)	357	258 (72.3)
Current	43 (39.4)	5 (4.6)	29 (26.6)	32 (29.4)	109	66 (60.6)
Alcohol use						
Yes	173 (26.2)	90 (13.6)	269 (40.8)	128 (19.4)	660	487 (73.8)
No	84 (30.3)	35 (12.7)	127 (45.8)	31 (11.2)	277	193 (69.7)
Body mass index						
Non-obese <30	88 (27.6)	42 (13.1)	133 (41.7)	56 (17.6)	319	231 (72.4)
Obese >30	169 (27.3)	83 (13.4)	263 (42.6)	103 (16.7)	618	449 (72.7)
Vigorous exercise						
No	21 (17.5)	20 (16.7)	66 (55.0)	13 (10.8)	120	99 (82.5)
Yes	236 (28.9)	105 (12.8)	330 (40.4)	146 (17.9)	817	581 (71.1)
Insurance						
Other	46 (25.6)	19 (10.5)	68 (37.8)	47 (26.1)	180	134 (74.4)
Medicare	156 (32.2)	59 (12.2)	202 (41.8)	67 (13.8)	484	328 (67.8)
Private	55 (20.1)	47 (17.2)	126 (46.2)	45 (16.5)	273	218 (79.9)
Insurance cover the dental procedure						
No	251 (27.6)	121 (13.3)	388 (42.7)	149 (16.4)	909	658 (72.4)

Continued

Table 1 Continued

Demographic characteristics	No PD	Stage I PD	Stage II PD	Stage III/IV PD	Total (PD+no PD)	Total PD
Yes	6 (21.4)	4 (14.3)	8 (28.6)	10 (35.7)	28	22 (78.6)

*Cells with counts <11 were masked.
PD, periodontal disease.

RESULTS

Descriptive statistics

The demographic characteristics of the study population are presented in [table 1](#). Among 937 participants, 73% had PD. In those with PD, 18.4% were identified with stage I PD, 58.2% with stage II PD and 23.4% with stage III/IV PD. A higher percentage of participants with PD was observed among those who were 60–75 years old, with a higher level of education and income (FPL $\geq 200\%$), non-current smokers, those without vigorous physical activity and those who were not with Medicare insurance. In the stage III/IV PD group, there were more men, of a non-white race, with a lower level of education (high school or below), income (FPL <200%), current smokers and those with types of insurance other than Medicare.

[Table 2](#) shows that having arthritis or asthma or being overweight were the most common chronic conditions across all PD groups. Urinary incontinence was the most common conditions under geriatric syndromes. Even so, its frequency in our study population was low. Functional limitations in leisure and social activities and lower extremity mobility were the most common functional limitations.

Ctree analyses

The Ctree analysis for the presence and severity of PD using conditions constituting complex MM and sociodemographic variables is shown in [figure 1](#). Male participants and those with a non-white race had the highest prevalence of stage III/IV PD at 40% (nodes 1, 2 and 6). Conversely, the lowest prevalence of stage III/IV PD (less than 10%) was observed among female participants, who were less than 75 years of age and had income (FPL $\geq 200\%$), (nodes 1, 7, 8 and 12), and was observed among female participants who were more than 74 years of age (nodes 1, 7 and 13).

The highest percentage of no PD observed among female participants who were younger than 75 years of age, FPL <200%, and with limitations in IADLs (nodes 1, 7, 8, 9 and 10), leading to a prevalence of 60% among respondents with these combinations of sociodemographic and functional limitations. Although the number of participants with combinations of sociodemographic and limitations in IADLs was small (n=23) compared with those without limitations in IADLs (n=103), they had a very high proportion of stage II PD.

Random forest analyses

In [figure 2](#), random forest, using conditions constituting complex MM and sociodemographic variables, ranks the most important variables for the presence and severity of PD: age, education level, race, gender, smoking status and the FPL. Many of these variables appear in the Ctree, validating our tree model and verifying their significant influence on PD's presence and severity.

DISCUSSION

We identified conditions constituting complex MM associated with the presence and severity of PD using machine learning approach in a nationally representative sample of people who were 60 years of age or older. Accounting for conditions constituting complex MM in our Ctree model, we showed that sociodemographic factors and limitations in IADLs were better predictors for the presence and severity of PD than chronic conditions or geriatric syndromes. Participant's sex, age, race, education and income levels were the most important sociodemographic variables for the severity of PD. The prevalence of PD in our study was relatively high, according to the 2017 case definition of PD. When compared with the prior criteria based on a combination of CAL values and/or probing depth values, the alone use of CAL values can partially explain the higher prevalence of PD. In addition, because all teeth were examined in the NHANES 2013–2014, the full-mouth periodontal examination approach is more likely to accurately assess and classify PD.¹³ The elderly, on the other hand, have a lower prevalence of PD because they are more likely to have fewer existing teeth and, as a result, better periodontal status. In addition, the 2013–2014 NHANES excludes edentate people who may have already lost their teeth due to PD, representing a biased sample of a dentate subgroup of older people.

Among individuals 60 years of age or older, hypertension, hyperlipidaemia, arthritis, functional limitations in general physical activities and urinary incontinence were the most prevalent conditions, regardless of their periodontal status. Interestingly, these common conditions represent our expanded definition of complex MM, including functional limitations and geriatric syndromes beyond chronic conditions. Although those chronic conditions and geriatric syndromes failed to show in our tree, limitations in IADLs variables in addition to sociodemographic factors emerged as strongly associated with the severity of PD. This is evidenced by the fact that they

Table 2 Description of the study population by conditions constituting complex multimorbidity (MM)

Conditions constituting MM	No PD	Stage I PD	Stage II PD	Stage III/IV PD	Total (PD+no PD)	Total PD
No of subjects	257	125	396	159	937	680
Chronic conditions						
Hypertension	181 (31.1)	80 (13.7)	225 (38.7)	96 (16.5)	582	401 (68.9)
Hyperlipidaemia	162 (29.1)	84 (15.1)	230 (41.3)	81 (14.5)	557	395 (70.9)
Diabetes	71 (30.3)	30 (12.8)	88 (37.7)	45 (19.2)	234	163 (69.7)
Arthritis	112 (25.5)	67 (15.2)	198 (45.0)	63 (14.3)	440	328 (74.5)
Coronary heart disease	37 (44.1)	*	27 (32.1)	11 (13.1)	84	47 (56.0)
Overweight	91 (25.9)	54 (15.3)	149 (42.3)	58 (16.5)	352	261 (74.1)
Stroke	17 (36.2)	*	15 (31.9)	*	47	30 (63.8)
Asthma	30 (24.6)	22 (18.0)	58 (47.5)	12 (9.9)	122	92 (75.4)
Chronic obstructive pulmonary disease	19 (36.5)	*	20 (38.5)	11 (21.2)	52	33 (63.5)
Emphysema	*	*	*	*	21	13 (61.9)
Bronchitis	17 (27.9)	*	32 (52.5)	*	61	44 (72.1)
Cancer	59 (27.3)	24 (11.1)	102 (47.2)	31 (14.4)	216	157 (72.7)
Liver	11 (30.6)	*	17 (47.2)	*	36	25 (69.4)
Thyroid	53 (30.6)	33 (19.1)	75 (43.4)	12 (6.9)	173	120 (69.4)
Psoriasis	*	*	13 (48.1)	*	27	17 (63.0)
Kidney dysfunction	14 (45.2)	*	*	*	31	17 (54.8)
Functional limitations						
Activities of daily living	30 (31.3)	*	35 (36.5)	22 (22.9)	96	66 (68.8)
Instrumental activities of daily living	44 (33.6)	17 (13.0)	49 (37.4)	21 (16.0)	131	87 (66.4)
Leisure and social activities	22 (25.9)	12 (14.1)	34 (40.0)	17 (20.0)	85	63 (74.1)
Lower extremity mobility	61 (28.5)	24 (11.2)	94 (43.9)	35 (16.4)	214	153 (71.5)
General physical activities	145 (31.6)	56 (12.2)	186 (40.5)	72 (15.7)	459	314 (68.4)
Geriatric syndromes						
Cognitive impairment	56 (42.7)	*	34 (26.0)	32 (24.4)	131	75 (57.3)
Hearing impairment	32 (35.2)	*	40 (44.0)	13 (14.2)	91	59 (64.8)
Visual impairment	*	*	18 (40.9)	*	44	35 (79.5)
Urinary incontinence	84 (26.7)	41 (13.0)	144 (45.7)	46 (14.6)	315	231 (73.3)
Depression	19 (33.9)	*	21 (37.5)	*	56	37 (66.1)
Osteoporosis	41 (32.8)	21 (16.8)	56 (44.8)	*	125	84 (67.2)
Fractures	31 (31.6)	13 (13.3)	43 (43.9)	11 (11.2)	98	67 (68.4)
*Cells with counts <11 were masked. PD, periodontal disease.						

are the splitting variables in the CTree and top-ranked factors in random forest analysis, highlighting the importance of sociodemographic factors and functional limitations variables in predicting PD severity. On the other hand, among those without PD, coronary heart disease, kidney dysfunction and cognitive impairment were the most common conditions constituting MM. The use of self-reported data may underestimate the true prevalence of these conditions if these conditions have not yet been diagnosed, and/or the participant is unable to recall.

Limitations in IADLs measure the participants' difficulties in doing such chores around the house, preparing meals and managing finances. Participants with combinations of sociodemographic factors and limitations of IADLs

had a higher prevalence of no PD in the CTree than those who did not have IADLs. This may be explained by the low number of participants with IADLs (n=23) compared with those without IADLs (n=104). Although the prevalence of limitations in IADLs was 14% among the study population (n=131), 66.4% of those people had PD. Older people with IADL limitations are more likely to decline their ability to practice adequate oral hygiene and do not comply with regular periodontal maintenance visits, leading to PD. In addition, they may prioritise their general health over their oral health, given that older people are more likely to have conditions constituting complex MM. Therefore, functional limitations seem to play a more significant role in the severity of PD alongside sociodemographic factors.

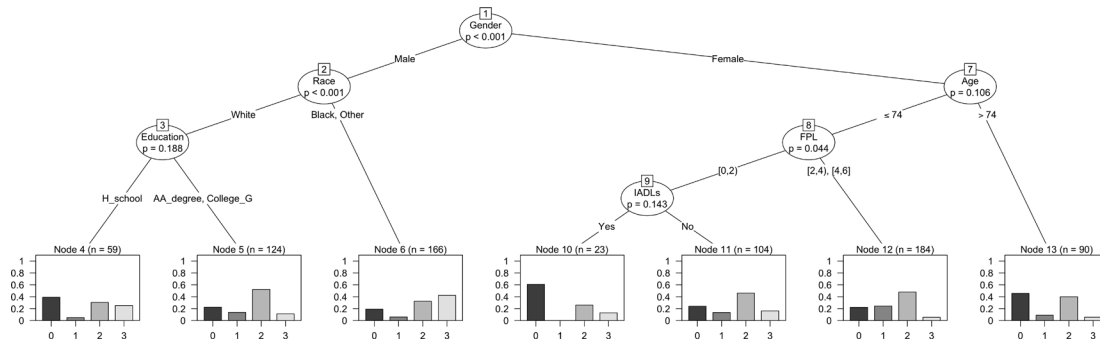


Figure 1 Conditional inference regression tree analysis to predict the presence and severity of PD. 0, no PD; 1, stage I PD; 2, stage II PD; 3, stage III/IV PD; AA_degree, Some college or associates degree; College_G, College graduate or above; FPL, federal poverty level; H_school, High school graduate or below; IADLs, instrumental activities of daily living.

Several research and clinical implications for these findings can apply in the periodontal field. Regarding research implications, these findings indicate the importance of accounting for functional limitations in addition to the sociodemographic factors when assessing PD. Older people are more likely to have functional limitations beyond chronic conditions and geriatric syndromes; therefore, they may be associated with higher severity of PD. No previous studies have identified complex MM associated with PD or its severity to the best of our knowledge. Instead, research in this area had solely assessed the relationship between PD and chronic conditions, which may explain the conflicting findings between studies that evaluated the PD using single or co-occurring chronic

conditions. Indeed, the recent findings indicate the need to redirect our focus when studying PD to include functional limitations variables, rather than only chronic conditions or geriatric syndromes.

In clinical practice, identifying people with the most common combinations of conditions constituting complex MM associated with the presence and severity of PD will help healthcare providers target those by screening people with complex MM for PD and referring them for periodontal care. In addition, our findings argue for the development of integrated multidisciplinary approaches between medical and periodontal filed in the care of people with complex MM, specifically among older adults who are more likely to have conditions composing complex MM. Moreover, applying personalised periodontal medicine is crucial in managing potential etiological factors among the most vulnerable people to the development or severity of PD. Furthermore, rather than focusing on conditions constituting complex MM, clinicians should pay more attention to sociodemographic and behavioural characteristics, as they were the top-ranked variables for PD in the variable importance plot.

To our knowledge, this is the first study to identify conditions composing complex MM that are associated with the presence and severity of PD. This study expands our prior work¹³ to incorporate geriatric syndromes and functional limitations beyond chronic conditions to evaluate its association with PD. Second, the use of innovative machine learning methods, CTree and random forest, is also a significant strength in this study. Both CTree and random forest using automatic variable selection to identify interactions and non-linear relationships. The ability of CTree to capture the complex relationship allows us to identify specific combinations of conditions composing complex MM that are highly associated with the presence and severity of PD without any prior assumptions by producing a tree that is easy to interpret. Random forest uses a bootstrap aggregation method to rank the importance of several variables simultaneously. The availability of comprehensive data among a nationally representative sample of the US older population that includes functional limitations, geriatric syndrome and chronic conditions is another strength of this study that further

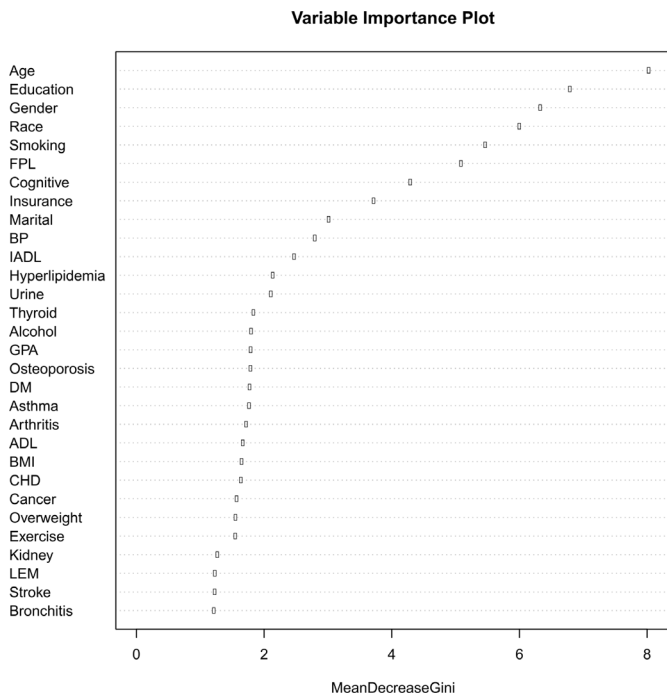


Figure 2 Random forest plot ranking the factors that most influence the distribution of PD. ADL, activities of daily living; BMI, body mass index groups; BP, blood pressure (hypertension); CHD, coronary heart disease; DM, diabetes; FPL, federal poverty level; GPA, general physical activities; IADL, Instrumental activities of daily living; LEM, lower extremity mobility.

investigates the potential etiologies associated with developing PD.

This study has several limitations. First, our model failed to recognise that chronic conditions or geriatric syndromes were stronger predictors for PD. A large sample size may identify additional predictors for the presence and severity of PD. Second, CTree and random forest identified several variables for the PD; however, CTree produces only a single tree, whereas random forest is a bootstrap aggregation method that produces multiple trees without identifying the most common combinations of conditions that affect PD. Third, the cross-sectional design of our study does not allow us to assess the progression of PD as complex MM conditions arise or worsen, or even to assert the causal direction of associations. Fourth, all conditions constituting complex MM are self-reported data. Fifth, because other factors that may affect probing depth accuracy, such as gingival inflammation and the presence of local factors on the tooth surface, are not included in the public dataset, we did not include periodontitis-associated CAL that could occur in mid-buccal or mid-lingual surfaces in combination with a pocket depth of 4mm or greater. Sixth, we were unable to determine whether participants received periodontal treatment to have clinical gingival health or gingivitis on reduced periodontium due to the nature of the NHANES dataset. Seventh, due to the small number of Asian and Hispanic/non-Hispanic ethnicities, we included them in the 'other' category. We had three racial/ethnic groups: white, black and other. Lastly, we note that people with PD who had dental insurance are less likely to benefit from it, because unlike dental caries, the treatment of PD is usually not covered by dental plans. In addition, the number of people with dental insurance coverage was very low in the present study. Therefore, future research focusing on the role of dental insurance plans that provide coverage for PD treatment would be beneficial.

CONCLUSIONS

Sociodemographic factors and limitations in IADLs were stronger predictors for PD than chronic conditions and geriatric syndromes. Male sex and non-white race, age, low education level and low FPL were the most critical sociodemographic factors that predict PD. Accounting for the co-occurrence for demographics and conditions constituting complex MM will be more informative than only chronic conditions for identifying vulnerable people to the development of PD.

Contributors HMA and SMK contributed to conception, design, data acquisition, analysis and interpretation, drafted and critically revised the manuscript; HMA is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish; KS, NFB and NKS contributed to interpretation, critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Patient consent for publication Not applicable.

Ethics approval The Institutional Review Board at Case Western Reserve University considered that our study is not human subjects research (# 2021-0469).

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Data availability statement No data are available.

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