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Smoking impairs cognitive function through the mediating effect of periodontitis in older adults

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Abstract

Objectives Evidence has shown that both smoking and periodontitis were linked to cognitive impairment. This study examines whether periodontitis mediates the effects of smoking status on cognitive function in older adults.

Methods Using data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014, the study included 1728 older participants who have data on smoking, serum cotinine, periodontal examination, and cognitive function. Mediation analysis was performed to test whether extent of periodontitis mediated associations between smoking status and cognitive function, adjusted for sociodemographic and basic health factors.

Results Compared to never-smokers, daily smokers exhibited significantly worse global cognitive function, with periodontitis mediating this effect (effect= -0.16; 95% CI= -0.29, -0.05). Similarly, periodontitis mediated the association between serum cotinine levels and cognitive function in the total sample (effect= -0.02; 95% CI= -0.03, -0.00).

Conclusions Periodontitis significantly mediates the impact of smoking on cognitive function. The findings highlight the potential roles of maintaining oral health and smoking cessation in mitigating cognitive decline.

Keywords Periodontitis, Smoking, Cognitive function, NHANES, Mediation

Introduction

Global aging population is leading to an increase in the prevalence of cognitive impairment and dementia, straining public health systems [1]. Cognitive function refers to a broad range of mental processes, including memory, attention, language, and executive function. Cognitive impairment includes several processes such as memory loss, reduced attention, and slowed thinking, which have adverse impacts on individuals' life quality and well-being [2]. U.S. data reports from 2023 Alzheimer's disease (AD) Facts and Figures indicated that about 6.7 million Americans aged 65 and older have AD, which is expected to reach 13.8 million by 2060 [3]. The blood biomarkers for dementia indicate the presence of axonal damage, glial activation, and Aβ pathology [4]. Empirical studies have

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identified smoking as an important and modifiable factor linked to dementia's onset [5, 6]. The Lancet Commission 2020 report on dementia also highlighted that smoking raises the risk of dementia by 5% in later life [7]. Studies across various countries, including the U.S [8], Europe [9], and Korea [10], have consistently confirmed that smoking accelerates cognitive impairment in non-demented older individuals. As there will be a rapid rise in the older population in the following decades [11], an increasing number of older smokers may experience cognitive impairment in the future, bringing burden on individuals' family and social healthcare system. Therefore, it is of clinical importance to understand the mechanisms underlying the association between smoking and cognitive impairment.

Periodontitis has emerged as a significant health condition especially among older adults worldwide [12, 13]. In recent years, there has been growing evidence on the relationship between periodontitis and cognitive impairment or dementia [14–16]. Periodontitis is defined as a chronic inflammatory disease affecting the tissues surrounding. It is characterized by loss of attachment and the destruction of the alveolar bone, leading to tooth loss if left untreated [17]. However, it is not merely an oral disease but is increasingly recognized for its systemic impact on overall health [18, 19]. It is proposed that periodontitis may lead to systemic chronic inflammation, which may increase blood-brain barrier permeability and lead to neuroinflammation [20]. Moreover, oral pathogens associated with periodontitis can enter the bloodstream and potentially reach the brain, contributing to neuroinflammation and cognitive impairment [20, 21]. Periodontal inflammation can disrupt the immune system, which may have negative effect on cognitive function [22]. Our resent works show that the dysregulation of innate immunity protein IFITM3 significantly contributes to the pathogenesis of AD [23, 24]. Furthermore, growing evidence indicates that drugs beneficial to periodontitis are also beneficial for AD [25, 26]. These mechanisms highlight the potential role of periodontitis in the development of cognitive decline, particularly in older adults who are more susceptible to both periodontitis and cognitive impairment.

The relationship between smoking and periodontitis is well-established. Smoking is a known risk factor for periodontitis, as it can exacerbate oral health conditions and contribute to the development and progression of the disease [27, 28]. Empirical study supports that smokers were more prone to periodontitis compared to non-smokers, and their oral condition tended to be more severe and deteriorate more rapidly [27]. Study on rats revealed that cigarette smoke aggravated periapical periodontitis by elevating the levels of pro-inflammatory cytokines [29]. Importantly, it seems that the adverse impacts of smoking on periodontal tissues can be reversed after smoking cessation [30]. The reversibility of smoking's effects on periodontal health underscores the clinical significance of intervening on this factor.

Given the relationship between smoking and periodontitis, and the potential for periodontitis to lead to cognitive decline, it is plausible that periodontitis may be one of the complex mechanisms through which smoking affects cognitive function. However, no studies yet investigate the mediating role of periodontitis in the association between smoking and cognitive function. Therefore, the present study aimed to examine the association between smoking and cognitive function and to test whether the extent of periodontitis mediates the association in older populations. Supplementary Figure S1 showed the hypothesized mediation model.

Methods

Data source

Data for the present study were extracted from the 2011–2014 cycles of the National Health and Nutrition Examination Survey (NHANES). NHANES was a nationally representative cross-sectional survey of community-dwelling individuals in the United States, conducted by the Centers for Disease Control and Prevention (CDC). Each cycle of NHANES used a stratified, multistage probability sampling design to select participants. Written informed consent was obtained from all participants. Detailed descriptions of the survey design were available on the website of the CDC [31].

This research merged 2011–2014 NHANES data on smoking, periodontal examination, cognitive function, participant demographics, and physical examination. In the raw data, there was a total of 19,931 participants, and our analysis was limited to 2934 participants aged 60 years and over who had data on cognitive function. Among them, 979 participants with missing data on clinical attachment loss were excluded. Further, 90 participants with missing serum cotinine and 165 participants with missing demographics and health-related data were excluded. In most variables, the proportion of missing values does not exceed 5%, with the exception of PIR (7.6%). Finally, a total of 1728 participants were included in the study. Supplementary Figure S2 depicts the sample selection flow chart. Given the data are de-identified and publicly, available institutional review board approval was not required for this study.

Classification of smoking status

Smoking status was defined using the two questions: "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?" Participants who answered "no" in the former were classified as "never-smokers". Among those answered "yes",

participants who further answered "Every day", "Some days", and "Not at all" in the latter question were classified as "daily smokers", "occasional smokers", and "previous smokers". This classification of smoking status has been used previously in other studies [32]. The operational definitions of smoking status and other variables described below are summarized in Supplementary Table S1 and Supplementary Figure S3. In addition, serum cotinine concentration was also used to measure the extent of exposure to tobacco smoke. The cotinine concentration was right-skewed, so the data was ln-transformed before the regression and mediation analyses.

Periodontitis

Participants with at least one remaining tooth, were eligible for a full-mouth periodontal examination. All examiners were trained and calibrated with reference examiners before the beginning of the survey to assure the consistency between examiners [33]. Gingival recession and pocket depth were measured at 6 sites/tooth (including wisdom teeth), using a colour-coded periodontal probe (HuFriedy). Clinical attachment loss (CAL; the difference between gingival recession and pocket depth) at each site was subsequently calculated from the measurements. For this study, the proportion of sites per subject with CAL ≥ 3 mm was used as an extent measure of periodontitis, which is a recommended measure for epidemiology study [34, 35].

To address potential limitations associated with relying on a single measure, we also used the EFP/AAP (European Federation of Periodontology/ American Academy of Periodontology) 2018 classification to define periodontitis severity. The EFP/AAP criteria classify periodontitis severity based on a combination of CAL and probing pocket depth (PPD) measurements [36]. Specifically, a CAL of 1–2 mm was defined as Stage I, of 3–4 mm as Stage II, and of ≥ 5 mm as Stages III-IV. In addition, patients in Stage I or II were reclassified as Stage III-IV if the maximum PPD was ≥ 6 mm. The number of occluding pairs of teeth was not considered in this study, due to the lack of relevant data. This classification of periodontitis was treated as continuous variable and applied in sensitivity analysis to validate the robustness of results.

Cognitive function

We defined global and domain-specific cognitive function using a series of cognitive function tests in NHANES 2011–2014. Cognitive function tests included the following separate tests: the word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-WL), the Animal Fluency test (AFT), and the Digit Symbol Substitution Test (DSST).

The CERAD-WL consisted of three consecutive immediate recall tests (IRT) and a delayed word recall test (DRT) [37]. The IRT assessed the ability to recall newly learned verbal information, while the DRT assessed delayed memory on this information. Specifically, in IRT, participants were instructed to read aloud 10 words and recall as many words as possible immediately after their presentation. The number of words correctly recalled was the score of each trial. The DRT was performed after two other cognitive tests (AFT and DSST), where participants had to recall all 10 words (approximately 8–10 min from the start of word learning trials).

The AFT assessed verbal fluency, which can sensitively discriminate those with normal cognitive function and those who have mild or more severe cognitive impairment, such as Alzheimer's disease [38]. Participants were instructed to name aloud as many animals as possible in 1 min. The number of named animals was obtained as the score of AFT.

The DSST, as a performance module from the Wechsler Adult Intelligence Scale (WAIS III) was a highly sensitive test that primarily assesses attention, processing speed, and working memory [39]. This test was conducted using a paper form that has a key at the top containing nine numbers paired with symbols. Participants had two 2 min to copy the matching symbol in boxes that adjoin the numbers. The number of correct matches represented the score of the DSST.

The global cognitive function was calculated using the sum of standardized scores of four cognitive tests, as described previously [40, 41].

Covariates

The analyses adjusted for potential confounders likely associated with GGT and telomere length. Information on demographic data was collected by questionnaires. From these data, we examined age (continuous), gender (male, female), race (Mexican American or other Hispanic, non-Hispanic white, non-Hispanic black, others/ multiracial), education level (< 9th grade, 9-12th grade, high school/GED, some college/AA degree, and College graduate & higher), and family income-to-poverty ratio (PIR; ≤ 1.3, 1.3 ~ 3.5, > 3.5). Furthermore, health factors including body mass index (BMI; ≤25 kg/m^2, 25–30 kg/m^2, > 30 kg/m^2), alcohol use (yes, no), diabetes (yes, no), and hypertension (yes, no) were extracted. The alcohol use was defined based on the question "Had at least 12 alcohol drinks/1 year?" Participants will be considered hypertensive if it was diagnosed by a physician or average measured blood pressure ≥ 140/90 mmHg. Participants were considered diabetic if they answered "yes" or "borderline" to the question "Doctor told you have diabetes".

Statistical analysis

Analyses were performed R Statistical language (version 4.3.1; [42]) including the use of following packages: haven

[43], tidyverse [44], and gtsummary [45]. In descriptive analyses, we assessed means of demographic characteristics and physical examination among the total sample and then stratified by smoking status. Categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean and standard error of mean. To test whether demographic characteristics differed by smoking status, one-way ANOVA (for continuous variables) and chi-square tests (for categorical variables) were conducted.

Multivariate linear regression models were then conducted to investigate the associations between smoking status and cognitive function, and between periodontitis and cognitive function. Model 1 was a crude model and Model 2 was adjusted for socio-demographic factors including sex, age, race/ethnicity, education, marital status, and PIR. Model 3 was further adjusted for health factors including BMI, alcohol use, diabetes, and hypertension.

Then, mediation analyses assessed (using the Model 4 of PROCESS macro in SPSS; [46]) whether periodontitis might serve as a mediator explaining the link between smoking status and cognitive functioning. For smoking status, 3 dummy variables were constructed (previous smoker, occasional smoker, and daily smoker), and the reference category is never-smoker. Moreover, a separate model periodontitis mediating the link between serum cotinine and cognitive functioning was also tested. As recommended by Hayes [46], we used bootstrapping method (5000 bootstrapping samples) with 95% bias-corrected confidence intervals (CIs) to detect the significance of the effects. The mediating effect was considered significant when the 95% CI did not include zero.

Finally, to test the stability of our results, we repeated the mediation analysis using periodontitis severity defined by the EFP/AAP 2018 classification as the mediator. Additionally, we repeated our analysis using a full sample ($n = 1983$) with missing values in demographic and health-related variables imputed by multiple imputation by chained equations (MICE). This approach was employed to avoid potential bias caused by excluding samples with missing values and to test the robustness of our results.

Results

Baseline characteristics of the study population

A total of 1728 participants from the 2011–2014 NHANES data were eligible for analysis. The sociodemographic characteristics, health factors, and cognitive function of the participants based on smoking status are described in Table 1.

Most participants were never-smokers ($n = 897$), accounting for 51.9% of total sample. Occasional smokers ($n = 638$) comprised 37.0% of the total sample, while daily smokers ($n = 164$) comprised 9.4% of the total sample. Only 1.7% of participants were previous smokers ($n = 29$). More females were never-smokers (61.9%), while more male were daily smokers (62.2%). Never-smokers were older than daily smokers (68.8 years vs. 65.0 years, Bonferroni $P < 0.001$). More never-smokers had obesity than daily smokers (BMI ≥ 30 kg/m^2, 36.7% vs. 24.4%). The prevalences of diabetes and hypertension were not significantly different across participants of four smoking statuses. Furthermore, the severity of periodontitis of daily smokers was higher than never-smokers (0.56 vs. 0.24, Bonferroni $P < 0.001$). For cognitive function, never-smokers had better performance in DSST than daily smokers (48.49 vs. 45.09, Bonferroni $P = 0.012$).

Association between smoking and cognitive function

Table 2 presents the results of multivariate linear regression models of the associations of smoking status and cotinine concentration with cognitive function tests. Using the "never-smokers" as reference class, in model 1, occasional smokers and daily smokers were both significantly associated with IRT (Occasional smokers: B=-0.11, 95% CI=-0.21, -0.01; daily smokers: B=-0.22, 95% CI=-0.38, -0.06). For DSST and global cognitive function, daily smokers was also significant (DSST: B=-0.26, 95% CI=-0.42, -0.09; Global cognitive function: B=-0.67, 95% CI=-1.18, -0.16). In model 2 and full adjusted model 3, the associations between daily smokers and IRT, DSST, and global cognitive function remains significant, while the association between occasional smokers and IRT was no longer significant. When cotinine served as independent variable, in unadjusted model, the level of cotinine was significantly associated with IRT (B=-0.02, 95% CI=-0.03, -0.003), AFT (B=-0.02, 95% CI=-0.03, -0.002), DSST (B=-0.04, 95% CI=-0.05, -0.03), and global cognitive function (B=-0.09, 95% CI=-0.13, -0.04). In model 2 and model 3, only the associations of cotinine with DSST and global cognitive function remained significant.

Association between periodontitis and cognitive function

Multivariate linear regression models tested the association between periodontitis and cognitive function (Supplementary Table S2). In crude model 1, periodontitis was associated with all cognitive tests and global cognitive function. In model 2 and full adjusted model 3, only the association of periodontitis with DSST (Model 3: B=-0.38, 95% CI=-0.52, -0.25) and global cognitive function (Model 3: B=-0.78, 95% CI=-1.23, -0.32) remained significant. When the indicator of periodontitis was classified into quartiles, the associations between periodontitis severity quartiles and cognitive function scores were visualized in Fig. 1, which consistently showed a negative association between periodontitis and cognitive function.

Table 1 Basic characteristics of participants by smoking status in NHANES 2011–2014

	Total (*N* = 1728)	Never-smokers (*N* = 897)	Previous smokers (*N* = 29)	Occasional smokers (*N* = 638)	Daily smokers (*N* = 164)	*P*-value
Age	68.66 (0.16)	68.80 (0.22)	66.59 (1.10)	69.5 (0.26)	65.02 (0.36)	< 0.001
Sex						< 0.001
Female	860 (49.8%)	555 (61.9%)	13 (44.8%)	230 (36.1%)	62 (37.8%)	
Male	868 (50.2%)	342 (38.1%)	16 (55.2%)	408 (63.9%)	102 (62.2%)	
Race/ethnicity						< 0.001
Mexican American	161 (9.3%)	80 (8.9%)	4 (13.8%)	62 (9.7%)	15 (9.1%)	
Other Hispanic	180 (10.4%)	96 (10.7%)	3 (10.3%)	68 (10.7%)	13 (7.9%)	
Non-Hispanic White	836 (48.4%)	432 (48.2%)	8 (27.6%)	333 (52.2%)	63 (38.4%)	
Non-Hispanic Black	381 (22.0%)	180 (20.1%)	12 (41.4%)	128 (20.1%)	61 (37.2%)	
Other/multiracial	170 (9.8%)	109 (12.2%)	2 (6.9%)	47 (7.4%)	12 (7.3%)	
Education levels						< 0.001
< 9th grade	160 (9.3%)	75 (8.4%)	4 (13.8%)	65 (10.2%)	16 (9.8%)	
9-12th Grade	197 (11.4%)	96 (10.7%)	4 (13.8%)	68 (10.7%)	29 (17.7%)	
High School/GED	395 (22.9%)	189 (21.1%)	6 (20.7%)	155 (24.3%)	45 (27.4%)	
Some College or AA degree	522 (30.2%)	260 (29.0%)	12 (41.4%)	196 (30.7%)	54 (32.9%)	
College graduate & higher	454 (26.3%)	277 (30.9%)	3 (10.3%)	154 (24.1%)	20 (12.2%)	
BMI						< 0.001
< 25 kg/m2	462 (26.7%)	239 (26.6%)	11 (37.9%)	146 (22.9%)	66 (40.2%)	
≥ 30 kg/m2	634 (36.7%)	332 (37.0%)	7 (24.1%)	255 (40.0%)	40 (24.4%)	
25 ~ 30 kg/m2	632 (36.6%)	326 (36.3%)	11 (37.9%)	237 (37.1%)	58 (35.4%)	
PIR						< 0.001
> 3.5	607 (35.1%)	328 (36.6%)	4 (13.8%)	239 (37.5%)	36 (22.0%)	
≤ 1.3	439 (25.4%)	222 (24.7%)	6 (20.7%)	147 (23.0%)	64 (39.0%)	
1.3 ~ 3.5	682 (39.5%)	347 (38.7%)	19 (65.5%)	252 (39.5%)	64 (39.0%)	
Marital status						0.03
Married/living with partner	1044 (60.4%)	545 (60.8%)	15 (51.7%)	403 (63.2%)	81 (49.4%)	
Widowed/divorced/separated	579 (33.5%)	294 (32.8%)	13 (44.8%)	204 (32.0%)	68 (41.5%)	
never married	105 (6.1%)	58 (6.5%)	1 (3.4%)	31 (4.9%)	15 (9.1%)	
Alcohol use						< 0.001
no	527 (30.5%)	407 (45.4%)	3 (10.3%)	94 (14.7%)	23 (14.0%)	
yes	1201 (69.5%)	490 (54.6%)	26 (89.7%)	544 (85.3%)	141 (86.0%)	
Diabetes						0.151
no	1272 (73.6%)	675 (75.3%)	18 (62.1%)	455 (71.3%)	124 (75.6%)	
yes	456 (26.4%)	222 (24.7%)	11 (37.9%)	183 (28.7%)	40 (24.4%)	
Hypertension						0.955
no	535 (31.0%)	283 (31.5%)	9 (31.0%)	194 (30.4%)	49 (29.9%)	
yes	1193 (69.0%)	614 (68.5%)	20 (69.0%)	444 (69.6%)	115 (70.1%)	
Periodontitis	0.31 (0.29)	0.24 (0.25)	0.51 (0.31)	0.33 (0.29)	0.56 (0.32)	< 0.001
Cognitive tests						
IRT	19.38 (0.11)	19.66 (0.16)	20 (0.7)	19.14 (0.17)	18.65 (0.34)	0.019
DRT	6.18 (0.06)	6.3 (0.08)	6.28 (0.51)	6.07 (0.09)	5.97 (0.16)	0.139
AF	17.11 (0.13)	17.12 (0.19)	16.86 (0.81)	17.16 (0.21)	16.87 (0.42)	0.932
DSST	48.49 (0.41)	49.5 (0.56)	45.31 (2.91)	48.1 (0.68)	45.09 (1.28)	0.01
Serum Cotinine, μg/L	36.44 (2.69)	6.67 (1.84)	127.2 (19.98)	14.1 (3.15)	270.06 (12.69)	< 0.001

Continuous variables were presented as mean and standard error. Categorical variables were presented as cases (n) and percentage (%). Abbreviation: PIR, the ratio of family income to poverty; BMI, body mass index; IRT, immediate recall test; DRT, delayed recall test; AFT, animal fluency test; DSST, digital symbol substitution test

Mediation analysis

Table 3 presents the mediating effects of periodontitis in the associations between smoking status and global cognitive function, and between cotinine and global cognitive function. Using "Never-smokers" as reference, relative mediation analysis showed the significant mediating effects of periodontitis were significant for previous smokers (indirect effect=-0.13, 95% CI=-0.26, -0.03), occasional smokers (indirect effect=-0.03, 95% CI=-0.07, -0.01), daily smokers (indirect effect=-0.16, 95% CI=-0.29,

Table 2 Associations between serum cotinine, smoking status, and cognitive function tests

	Cognitive function test β (95% CI)				
	IRT	**DRT**	**AFT**	**DSST**	**Global cognitive function**
Smoking status					
Never-smokers (reference)					
Previous smokers					
Model 1	0.072 (-0.292, 0.437)	-0.011 (-0.376, 0.354)	-0.048 (-0.418, 0.322)	-0.244 (-0.606, 0.118)	-0.23 (-1.367, 0.906)
Model 2	0.155 (-0.175, 0.485)	0.077 (-0.257, 0.411)	0.043 (-0.291, 0.377)	-0.012 (-0.276, 0.251)	0.262 (-0.647, 1.172)
Model 3	0.139 (-0.194, 0.471)	0.101 (-0.235, 0.437)	0.018 (-0.318, 0.353)	-0.064 (-0.328, 0.199)	0.193 (-0.718, 1.104)
Occasional smokers					
Model 1	-0.113 (-0.213, -0.013)*	-0.101 (-0.201, -0.001)*	0.007 (-0.094, 0.109)	-0.081 (-0.181, 0.018)	-0.288 (-0.600, 0.024)
Model 2	0.037 (-0.056, 0.131)	0.054 (-0.041, 0.148)	0.019 (-0.076, 0.113)	0.06 (-0.015, 0.135)	0.17 (-0.087, 0.427)
Model 3	0.026 (-0.071, 0.123)	0.048 (-0.050, 0.146)	-0.007 (-0.105, 0.091)	0.019 (-0.058, 0.096)	0.086 (-0.180, 0.351)
Daily smokers					
Model 1	-0.22 (-0.384, -0.056)**	-0.143 (-0.307, 0.021)	-0.046 (-0.213, 0.120)	-0.257 (-0.420, -0.094)*	-0.666 (-1.178, -0.155)*
Model 2	-0.19 (-0.344, -0.036)*	-0.125 (-0.281, 0.030)	-0.049 (-0.204, 0.107)	-0.13 (-0.253, -0.007)*	-0.494 (-0.918, -0.070)*
Model 3	-0.207 (-0.365, -0.049)*	-0.117 (-0.276, 0.043)	-0.075 (-0.234, 0.084)	-0.179 (-0.304, -0.054)**	-0.577 (-1.010, -0.145)**
Serum Cotinine					
Model 1	-0.016 (-0.030, -0.002)*	-0.013 (-0.027, 0.001)	-0.016 (-0.030, -0.002)*	-0.04 (-0.054, -0.026)***	-0.085 (-0.129, -0.042)***
Model 2	-0.013 (-0.026, 0.001)	-0.011 (-0.025, 0.003)	-0.008 (-0.022, 0.005)	-0.019 (-0.030, -0.008)***	-0.052 (-0.089, -0.014)**
Model 3	-0.014 (-0.028, 0.000)	-0.011 (-0.025, 0.003)	-0.011 (-0.025, 0.004)	-0.023 (-0.034, -0.012)***	-0.059 (-0.097, -0.020)**

Model 1 was unadjusted. Models 2 were adjusted for sex, age, race/ethnicity, education, marital status, PIR. Models 3 were adjusted for sex, age, race/ethnicity, education, marital status, PIR, BMI, alcohol use, diabetes, and hypertension. Abbreviation: IRT, immediate recall test; DRT, delayed recall test; AFT, animal fluency test; DSST, digital symbol substitution test; PIR, the ratio of family income to poverty; BMI, body mass index. *$P<0.05$; **$P<0.01$; ***$P<0.001$

-0.05). That is, compared with never-smokers, smokers were more likely to impair global cognitive function by having periodontitis. Notably, the total effects and direct effects for previous smokers and occasional smokers were not significant, while the total effect for daily smokers were significant (c=-0.59, 95% CI=-1.02, -0.16). The relative mediating effects for daily smokers accounted for 27% of the total effect. In addition, the mediating effect of periodontitis in the association between cotinine and global cognitive function was also significant (indirect effect=-0.02, 95% CI=-0.03, -0.00), accounting for 25% of the total effect (Fig. 2).

Sensitivity analysis

To address the potential limitation of relying solely on CAL as the measure of periodontitis and to test the robustness of our results, we performed a sensitivity analysis by defining periodontitis severity using the EFP/AAP criteria. The identified severity was as follows: Stage I ($n=53$), Stage II ($n=690$), and Stage III-IV ($n=984$). Detailed demographic characteristics grouped by severity are presented in Supplementary Table S3. Mediation analysis was then conducted using the periodontitis severity as a mediator. The results were largely consistent with formal analysis in terms of significance and direction (Supplementary Table S4), while the proportion of mediating effect was slightly decreased.

In another sensitivity analysis, we used multiple imputation by chained equations (MICE) to impute missing values in demographic and health-related variables and included all 1983 participants. The mediation analysis was repeated with the imputed data, and the results were also consistent with the main analysis in direction and significance. The indirect effect of periodontitis on the association between smoking status and global cognitive function remained significant, with a slightly higher proportion of mediation in the total effect for daily smokers (40%). These results are presented in Supplementary Table S5. Overall, the above sensitivity analyses confirmed the stability and robustness of our results.

Discussion

In this study, we found that both self-reported smoking and high serum cotinine levels were associated with poor cognitive function in community-dwelling older population in the US. Moreover, we identified the mediating effect of periodontitis in the association between smoking and cognitive impairment.

Firstly, we classified four types of self-reported smoking status: never-smokers, previous smokers, occasional smokers, and daily smokers. The level of serum cotinine,

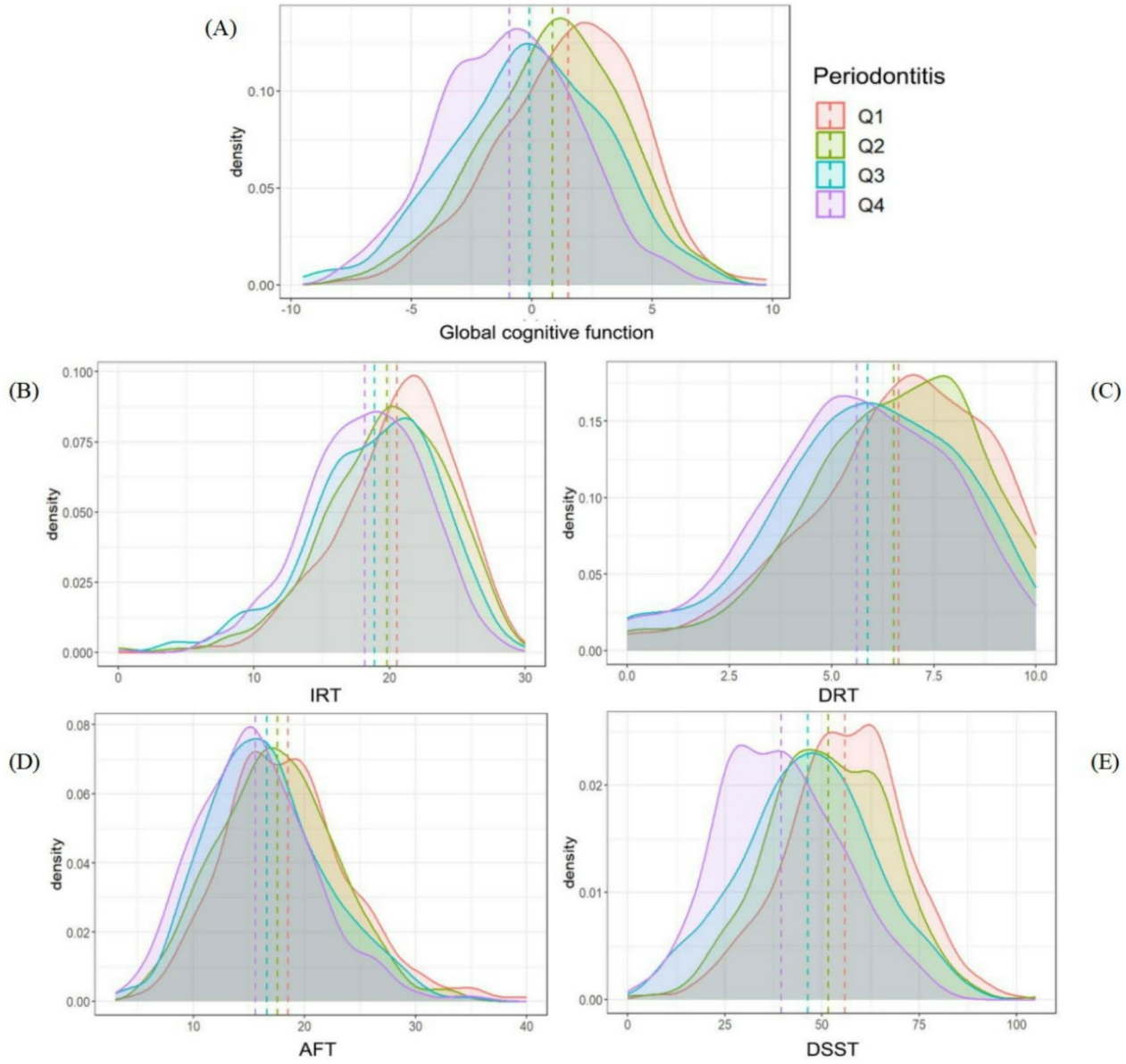

Fig. 1 Distribution of cognitive function scores by quartiles of periodontitis severity. (**A**) global cognitive function; (**B**) IRT; (**C**) DRT; (**D**) AFT; (**E**) DSST. Vertical dotted lines represent the mean value of each cognitive test scores. Q, quartile; IRT, immediate recall test; DRT, delayed recall test; AFT, animal fluency test; DSST, digital symbol substitution test

a metabolite of nicotine, was also used as an indicator of tobacco exposure [47]. We found the serum cotinine level generally aligned well with the self-reported smoking status, as daily smokers had the highest cotinine level while never-smokers had the lowest. However, previous smokers unexpectedly had a higher level of cotinine than occasional smokers. This may be due to the small sample size of previous smokers and the result of social desirably bias [48]. For instance, the smokers tend to report smoking cessation in order to conform to a socially desirable manner or avoid potential criticism [49]. Adjusting for sociodemographic and health factors, we found daily smokers had poorer performance in the IRT and DSST, indicating the impairment in shorter memory and working memory [50, 51]. In addition, we also found increased cotinine level was associated with poor score in DSST, which was similar to the results of smoking status. This evidence together supported the potential association between smoking and cognitive impairment. In line with our results, previous studies found that cognitive impairment was associated with rising cotinine levels, adjusting for factors like diabetes, hypertension, body mass index, and alcohol consumption [52]. Evidence from prior studies showed that active smoking people had worse

Table 3 Periodontitis as mediator in the associations between smoking status and global cognitive function

	a Estimate (95%CI)	b Estimate (95%CI)	Direct effect (c') Estimate (95% CI)	Indirect effect (a*b) Estimate (95% CI)	Total effect	Proportion Mediated
Smoking status						
Never-smokers (reference)						
Previous smokers	0.19 (0.1, 0.28)***	-0.69 (-1.16, -0.21)***	0.31 (-0.61, 1.22)	**-0.13 (-0.26, -0.03)**	0.18 (-0.73, 1.09)	NA
Occasional smokers	0.05 (0.02, 0.07)***	-0.69 (-1.16, -0.21)***	0.12 (-0.15, 0.38)	**-0.03 (-0.07, -0.01)**	0.09 (-0.18, 0.35)	NA
Daily smokers	0.24 (0.20, 0.28)***	-0.69 (-1.16, -0.21)***	-0.43 (-0.87, 0.02)	**-0.16 (-0.29, -0.05)**	-0.59 (-1.02, -0.16)**	27%
Serum Cotinine	0.02 (0.02,0.03)***	-0.64 (-1.11,-0.16)**	-0.04 (-0.084,-0.00)*	**-0.02 (-0.03,-0.00)**	-0.06 (-0.10,-0.02)**	25%

Adjusted for sex, age, race/ethnicity, education, marital status, family income-to-poverty ratio, body mass index, drinking alcohol status, diabetes, and hypertension

*$P<0.05$; **$P<0.01$; ***$P<0.001$. The indirect effect estimates whose 95% confidential intervals do not include 0 are shown in bold, as the bootstrap method does not provide specific *p*-values for the indirect effects

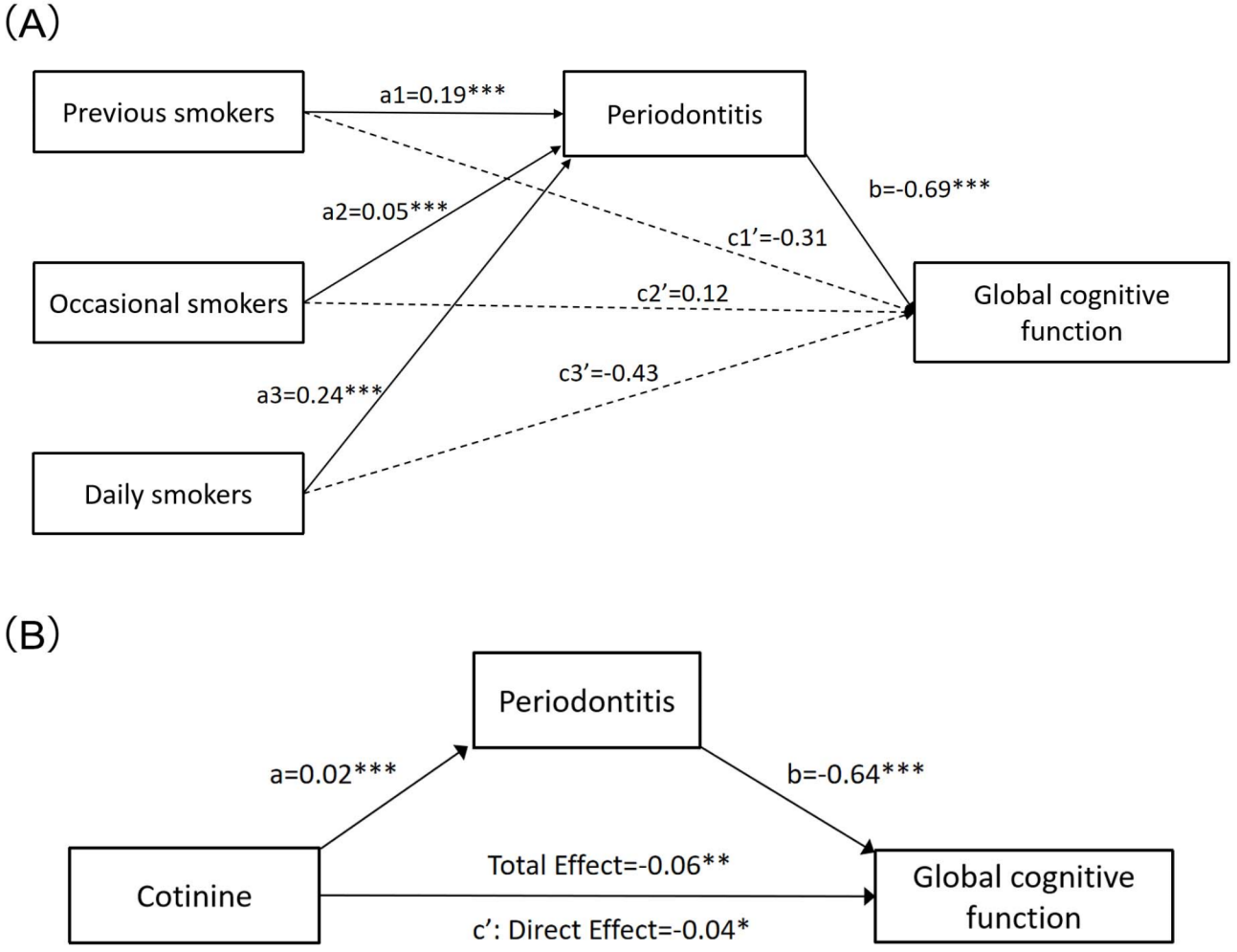

Fig. 2 The mediation models of periodontitis. (**A**) The relative mediation model where periodontitis mediates the relation between smoking status and global cognitive function, using "never-smokers" as reference class. (**B**) The mediation model where periodontitis mediates the relation between serum cotinine and global cognitive function. All coefficient shown are unstandardized. *$P<0.05$, ** $P<0.01$, *** $P<0.00$

performance than never-smokers in executive functions, processing speed, and general intellectual abilities [53–55], which was consistent with our results that daily smoker had worst cognitive function.

Our study further found that the smoking status was associated with the extent of periodontitis. Daily smokers and previous smokers had relatively high levels of periodontitis. This result was consistent with previous evidence on the association between smoking and periodontitis. For instance, another NHANES study using data from 1988 to 1994 found that current smokers were 4 times more likely to have periodontitis than never-smokers [56]. As several key chemicals in tobacco smoke are toxic and carcinogenic [57], smoking may induce a chronic inflammatory state and reduce insulin sensitivity, which accelerate microvascular diseases and cause periodontitis [58].

In recent years, the association between periodontitis and dementia has been proposed [59, 60]. In this line, our study found that the severity of periodontitis was associated with cognitive impairment, especially in the aspects of working memory and processing speed. A 5-year cohort study on Japanese older adults reported that periodontitis defined by either EWP (the European Workshop in Periodontology Group C) or CDC/AAP (the American Academy of Periodontology/Centers for Disease Control and Prevention) definition is significantly associated with cognitive impairment, which is consistent with our results [61]. A meta-analysis including 46 studies supported that periodontitis was associated with the risk of both cognitive disorder and dementia [62]. The links between oral health and cognitive function can be complex and may involve in diverse factors such as microbiological and immunological mechanisms [63]. Na et al. found a unique microbial composition(various Prevotella spp. and several anaerobic bacteria) in the gum areas of periodontitis individuals with Alzheimer's disease, indicating a potential role of periodontal pathogens in the oral-cognitive links [64]. Periodontitis can trigger systemic inflammation, which may further induce cognitive impairment [65]. Studies on mice indicated that periodontitis can impair neurons and glia by inducing neuroinflammatory responses in brain [66].

Finally, our findings suggested that periodontitis mediates the association between smoking status and cognitive function. Compared with never-smokers, daily smokers were more likely to have more severe periodontitis, which may lead to cognitive impairment. The indirect effect explained 27% of the total effect of being daily smokers on cognitive impairment. Notably, while the total effects of occasional smokers and previous smokers on cognitive function were not found, the indirect effects through periodontitis were also significant. These differences among smoking status may be explained by the distinct exposure to tobacco. Smoking can impair the immune response, leading to a higher susceptibility to bacterial infections and more severe periodontal inflammation [67]. As daily smokers may be more frequently and constantly exposed to tobacco smoke, they had significantly different composition of oral microbiome from non-current smokers [68], which make them more susceptible to periodontitis and its systemic effects. This can contribute to the elevated risk of cognitive impairment through several mechanism discussed above. Besides, when cotinine concentration was served as the predictor, the indirect effect explained 25% of the total effect, which is consistent with the results of daily smokers model. It should be noted that while some values of coefficient may appear small, this might be due to the fact that the coefficients presented are not standardized and are thus affected by the units and scaling of the variables. However, these results still suggest that smoking may have a negative impact on cognitive function, and periodontitis mediates this effect to some extent. If periodontitis can be managed or prevented, it may help reduce the cognitive decline associated with smoking. From a public health perspective, even small effects can be meaningful, as they highlight the potential for interventions targeting smoking cessation and oral health to mitigate cognitive decline. In clinical practice, this emphasizes the importance of considering oral health in the management of smokers to potentially reduce the risk of cognitive impairment.

Despite the findings, the study had some limitations. First, the present study was unable to determine the causal relationship between smoking, periodontitis, and cognitive impairment due to the cross-sectional nature of the data. Longitudinal study with a long term is needed to further confirm the mediating role of periodontitis in the association between smoking and cognitive impairment. Second, smoking status was based on self-reported data, which may be subject to recall bias or social desirability bias.The "previous smokers" category had relatively small sample size, which may limit the statistical power to detect significant associations in this group. Therefore, interpretation on the results of this group should be cautious and future study are needed to investigate these associations within a larger sample size of previous smokers. Besides, the data in NHANES is from nationally representative population in the United States, so care should be taken when extending the results to other populations. Finally, despite we have incorporated the EFP/AAP criteria to address potential limitations related to the definition of periodontitis severity, our primary measure of periodontitis was solely relying on the proportion of sites with CAL ≥ 3 mm. In addition, due to the tooth loss in older population, which is common and often a consequence of periodontitis [69], the accuracy

of periodontitis assessment may be affected. Specifically, tooth loss can reduce the number of measurement sites available for periodontal examination, potentially leading to an underestimation of periodontitis severity. Moreover, the presence of missing teeth may disrupt the occlusal relationship, further complicating the assessment of periodontal health. These factors highlight that our measure, while useful, may not fully capture the complex nature of periodontitis in an older population with prevalent tooth loss, as periodontitis is one of causes lead to increased tooth loss.

Conclusions

In this large cross-sectional study, we observed significant associations of smoking status and cotinine concentration with cognitive impairment in older adults in the United States, with periodontitis playing a major mediating role in the associations. Our findings highlight that smokers, especially daily smokers, may be susceptible to periodontitis-induced cognitive impairment. Therefore, the present study may be of clinical significance for monitoring smokers' oral health, as it may guide strategies for the prevention of cognitive impairment. While our study did not directly examine the role of smoking cessation, these results also imply that quitting smoking may potentially bring benefits in mitigating the risk of periodontitis and cognitive decline among older adults.

Supplementary Information

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Supplementary Material 1

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Author contributions

WS and YW supervised the project. XL, ZJ, SX, JL, YA, JG, SW, HX, SP, YZ, WS, and YW performed the experiments and analyzed the data. XL and ZJ wrote the manuscript. WS and YW revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analyzed during the current study are available in the NHANES repository, https://www.cdc.gov/nchs/nhanes/.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Helsinki declaration and its later amendments or comparable ethical standards. All information from the NHANES is available and free for public, so the agreement of the medical ethics committee board was not necessary. The studies involving human participants were approved by the National Center for Health Statistics Research Ethics Review Board, and informed consent was obtained from all participants in this study.

Consent for publication

This study did not require institutional board approval or participant consent, as all NHANES data were de-identified.

Competing interests

The authors declare no competing interests.

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