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High cotinine levels as an associated factor with frailty status in older adults: evidence from the NHANES study

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Abstract

Introduction Smoking has been recognized as a contributing factor to frailty in older adults. Nevertheless, it remains uncertain whether the degree of smoking has a discernible impact on frailty among older smokers. This cross-sectional study was conducted to investigate the correlation between serum cotinine levels, a biomarker reflecting tobacco exposure, and the presence of frailty within a nationally representative cohort of older adults.

Method A total of 1626 individuals aged ≥ 60 who identified as smokers were included in the analysis. Participants were selected based on self-reported current smoking status. According to the Fried Phenotype, frailty is assessed through five dimensions: unintentional weight loss, slow walking speed, weakness, self-reported exhaustion, and low physical activity. Participants with three or more of these conditions were categorized as frailty, those with at least one but less than three as pre-frailty, and those with none as robust. Multinomial logistic regression models were employed to explore the relationship between serum cotinine level quartiles, with the lowest quartile as the reference group, and the various frailty statuses, with robustness as the reference category. These models were adjusted for covariates, including age, sex, race/ethnicity, alcohol drinking, daily protein intake, systolic blood pressure, serum albumin level, depressive symptoms, and cognitive function. The data used for this analysis were sourced from the National Health and Nutrition Examination Survey for the years 2011 to 2014.

Results The median age of the participants was 69.0 years. The majority were male (62.2%) and non-Hispanic White (49.0%). The distribution of frailty statuses among the participants revealed that the highest proportion had pre-frailty (50.7%), followed by robustness (41.1%), and frailty (8.2%). Multinomial logistic regression showed that participants in the 4th quartile of serum cotinine level exhibited a higher probability of pre-frailty versus robustness (Odds ratio [OR] 1.599, 95% confidence interval [CI] 1.017, 2.513, $P=0.042$). Participants in the 3rd quartile of serum cotinine level had higher odds of frailty versus robustness (OR 2.403, 95% CI 1.125, 5.134, $P=0.024$). Moreover, participants whose serum cotinine levels were higher than the literature cutoffs (≥ 15 ng/ml) were more likely to be pre-frail (Odds ratio [OR] 1.478, 95% confidence interval [CI] 1.017, 2.150, $P=0.035$) or frail (Odds ratio [OR] 2.141, 95% confidence interval [CI] 1.054, 4.351, $P=0.041$).

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Conclusions A higher serum cotinine level is linked to an elevated probability of pre-frailty and frailty among older smokers. Initiatives geared towards assisting older smokers in reducing or quitting their smoking habits might possibly play a crucial role in preventing pre-frailty and frailty.

Keywords Cotinine, Frailty, Older adults, NHANES, Smoking, The fried phenotype, Pre-frailty

Introduction

In the US, about 11.2% of older adults aged 55 and above were smokers in 2018 [1]. Although smoking in older adults is less common than in the younger population [2], it poses a significant public health concern as older adults are less likely to try to quit smoking [3], and most countries throughout the world are experiencing a sharp rise in the population of older adults [4]. Smoking is associated with many adverse health outcomes in older adults, including cognitive impairment [5, 6], frailty [7], depression [8], falls or fall injuries, functional impairment, and all-cause mortality [9].

Frailty is a prominent geriatric syndrome featured by long-term, cumulative deterioration in a person's functions in multiple physiological systems and increased the person's susceptibility to external stressors [10]. In one meta-analysis involving more than 120,000 older adults from 28 countries, the incidence of frailty and prefrailty was estimated as 43.4 and 150.6 new cases per 1000 person-years, respectively [11]. Frailty is usually described as a stage from healthy aging to disability [12], and negatively affects older adults' physical health, mental health, and social engagement [13]. Pre-frailty is a potentially reversible state that predisposes a person to frailty and usually precedes the development of frailty [14].

Many studies have investigated the relationship between smoking habits and frailty in older adults and found mixed results [15]. Some studies only adjusted for a limited number of confounding factors. More importantly, most studies used participants' self-reported data for measuring smoking and thus are subject to recall bias. To our knowledge, few studies have used biomarkers to measure older adults' smoking. Serum cotinine levels directly reflect recent exposure to nicotine in tobacco smoke, which offers a more objective, quantifiable, and biological measure compared to self-reported smoking status. Many studies have indicated that the threshold values of serum cotinine to distinguish between smokers and non-smokers range from 3 to 40 ng/ml, with the optimal cotinine cutoff values ranging from 10 to 20 ng/ml (14 ng/ml [16], 10–20 ng/ml [17], and 10 ng/ml [18, 19]). In this study, with the National Health and Nutrition Examination Study (NHANES) 2011 to 2014 [20], we sought to examine the association between serum cotinine level and frailty in older smokers. The findings of this research will provide implications for developing clinical practices and policies that prevent frailty in older adults.

Methods

The parent study

The NHANES is an ongoing, cross-sectional survey of civilian, non-institutionalized U.S. population conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention [21]. The NHANES adopted a complex, multistage probability strategy. Thus, participants from diverse sociodemographic regions were recruited every two years in a cycle [22]. The sociodemographic, health, and nutritional status of the participants were assessed using in-person interviews and health exams. For this analysis, to boost sample size, the NHANES 2011–2012 (n=9338) and 2013–2014 (n=9813) were merged. The inclusion criteria were people who (1) were ≥60 (n=3472), (2) were smokers (n=1736), and (3) did not have missing information on serum cotinine level and frailty (n=1626). Finally, the study population comprised 1626 older smokers aged 60 and above. The Appendix showed the comparison of the included and excluded participants.

Ethical considerations

The NHANES was approved by the National Center for Health Statistics Research Ethics Review Board.

Measures

Serum cotinine level

The primary metabolite of nicotine, cotinine, is the most common biomarker of smoking (half-life between 15 and 20 h). Both active and passive smoking can be identified using cotinine levels in the blood or urine [23]. In the NHANES, participants' serum samples were collected as part of the physical examinations, aliquoted, kept at -20 °C, and were analyzed. The level of serum cotinine was clarified utilizing the isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometric (ID HPLC-APCI MS/MS) method. With repeated analyses of a 0.2 ml spiked serum sample, the lower detection limit (LLOD) of measuring serum cotinine using this method was 0.015 ng/mL. Detailed methodology has been published in another place [24].

Standard quality control and assurance procedures were implemented by Division of Laboratory Sciences of the National Center for Environmental Health [25]. In our study, the participants' serum cotinine level was categorized into four groups based on quartiles (≤0.01, 0.01–0.05, 0.05–89.38, and >89.38 ng/ml), with the lowest

quartile group serving as the reference. This is consistent with prior NHANES studies [5]. In addition, considering the optimal cutoffs in the literature ranging from 10 to 20 ng/ml [16–19], the participants' serum cotinine level was also categorized into two groups by the median of optimal cotinine cutoff ranges at 15 ng/ml.

Frailty status (pre-frailty, frailty, and robustness)

Based on the Fried Phenotype, the five frailty dimensions included (1) unintentional weight loss, (2) slow walking speed, (3) weakness, (4) self-reported exhaustion, and (5) low physical activity [26]. If the participant had three or more of the above conditions, he/she was categorized as being frail. If the participants had at least one but less than three of the above conditions, he/she was categorized as being pre-frail. If the participants had none of the above conditions, he/she was robust.

1) Unintentional weight loss. Participants' responses to the three following questions determined whether they had unintentional weight loss: (a) "How much do you weigh without clothes or shoes?" (b) "How much did you weigh a year ago?" and (c) "was the change between your current weight and weight a year ago intentional?" Body mass index less than or equal to 22.5 kg/m^2 or at least 5% unintentional weight loss over the previous year were both considered to be indicators of low body weight for height, consistent with existing studies [27, 28].
2) Slow walking speed. While the NHANES did not contain direct information about walking speed, we used a similar question, "by yourself and without using any special equipment, how much difficulty do you have walking for a quarter of a mile?". If participants responded, "with some difficulty," "great difficulty," or "unable to do", they would be categorized as having slow walking [29].
3) Weakness. For this question, "by yourself and without using any special equipment, how much difficulty do you have lifting or carrying something as heavy as 10 pounds?" participants who responded, "with some difficulty," "much difficulty," or "unable to do" were defined as having a weakness [30–36].
4) Self-reported exhaustion. For this question, "by yourself and without using any special equipment, how much difficulty do you have walking from one room to another on the same level?" to assess their walking speed. Participants who responded "with some difficulty," "with significant difficulty," or "unable to do" were defined as being exhausted [30–36].
5) Low physical activity. For this item, we used participants' reported minutes of vigorous and moderately intensive exercise for work, going to and from locations, and recreation. The amount of oxygen consumed when seated at rest was calculated as metabolic equivalent (MET) minutes [37]. One MET minute is determined by multiplying the number of minutes spent sitting at rest by 3.5 ml of oxygen per kilogram of body weight. If a participant's weekly MET minutes were less than 600, they were classified as having low physical activity [7, 38, 39].

The details about how the questions were asked in the NHANES were published elsewhere [21].

Covariates

To minimize the confounding between serum cotinine level and frailty status, we reviewed the literature [6, 7] and included age (years), sex (male or female), race/ethnicity (Mexican Americans, other Hispanics, non-Hispanic White, or non-Hispanic Black), alcohol drinking (0-1drink/day, 2 drinks/day, 3 or more drinks/day), daily protein intake (g/day), systolic blood pressure (mmHg), serum albumin level (g/dl), depressive symptoms, and cognitive function in the analysis. The Patient Health Questionnaire (PHQ-9) total score (range from 0 to 27) measured depressive symptoms [40]. Cognitive function was measured using the Consortium to Establish a Registry for Alzheimer's disease Word Learning subtest (CERAD-WL) immediate recall tests (range from 0 to 30) and delayed recall tests (range from 0 to 10). This scale has demonstrated reliability and validity for use in the general population [41]. The detailed methodology has been published elsewhere [21].

Statistical analysis

For continuous data with a normal distribution, means and standard deviations (SD) were used. For continuous data not following a normal distribution, medians and interquartile range (IQR) were used. For categorical data, frequency and percentages were used. Comparison according to serum cotinine quartiles was performed by the Kruskal-Wallis test for continuous variables and $\chi 2$ test for categorical variables. Multinomial logistic regression models were constructed to investigate the relationship between serum cotinine level and frailty status (pre-frailty, frailty, or robustness, reference: robustness), adjusting covariates of age, sex, race/ethnicity, alcohol drinking, daily protein intake, systolic blood pressure, serum albumin level, depressive symptoms, and cognitive function. A 2-tailed P-value < 0.05 was regarded as statistical significance. All analyses were performed using SPSS 25.0.

Results

The characteristics of the participants were shown in Table 1. The median age of the participants in the study was 69.0 years. The majority were male (62.2%) and non-Hispanic White (49.0%). The median serum cotinine level was 0.05 (0.01–89.38) ng/ml. Participants with higher serum cotinine levels were slightly younger, less likely to be non-Hispanic whites, more likely to be drinkers, and had lower body mass index.

Multinomial logistic regression (Table 2) showed that compared with participants in the 1st quartile (the lowest) of serum cotinine level, those in the 4th quartile (the highest) of serum cotinine level had increased probability of pre-frailty versus robustness (odds ratio [OR] 1.599, 95% confidence interval [CI] 1.017, 2.513, $P=0.042$). Compared with participants in the 1st quartile (the lowest) of serum cotinine level, those in the 3rd quartile of serum cotinine level had increased probability of frailty versus robustness (OR 2.403, 95% CI 1.125, 5.134, $P=0.024$). No significance was showed in pre-frailty or frailty for the 2nd quartile, compared with the 1st quartile.

According to the optimal literature cutoffs (15 ng/ml), the serum cotinine level was divided into two groups. Multinomial logistic regression (Table 3) showed that compared with participants in the low serum cotinine group (<15 ng/ml), those in the high serum cotinine group (≥15 ng/ml) had increased probability of pre-frailty (odds ratio [OR] 1.478, 95% confidence interval [CI] 1.017, 2.150, $P=0.035$) and frailty (odds ratio [OR] 2.141, 95% confidence interval [CI] 1.054, 4.351, $P=0.041$) versus robustness.

Table 1 Characteristics of the participants by quartile of serum cotinine level (ng/ml) ($n=1626$)

Variables	Quartile 1 ≤ 0.01 ($n=461$)	Quartile 2 0.01 < cotinine ≤ 0.05 ($n=393$)	Quartile 3 0.05 < cotinine ≤ 89.38 ($n=366$)	Quartile 4 > 89.38 ($n=406$)	Total ($n=1626$)	*P*-value
Age, years	72.0(66.0, 79.0)	69.0(64.0, 77.0)	68.0(63.0, 76.0)	65.0(62.0, 71.0)	69.0(64.0, 76.0)	*< 0.001*
Sex, n (%)						*0.389*
Male	274(59.4%)	242(61.6%)	238(65.0%)	257(63.3%)	1011(62.2%)	
Female	187(40.6%)	151(38.4%)	128(35.0%)	149(36.7%)	615(37.8%)	
Race/ethnicity, n (%)						*< 0.001*
Mexican Americans	40(8.7%)	34(8.7%)	42(11.5%)	33(8.1%)	149(9.2%)	
Other Hispanics	35(7.6%)	39(9.9%)	35(9.6%)	37(9.1%)	146(9.0%)	
Non-Hispanic Whites	299(64.9%)	184(46.8%)	147(40.2%)	167(41.1%)	797(49.0%)	
Non-Hispanic Blacks	56(12.1%)	93(23.7%)	113(30.9%)	142(35.0%)	404(24.8%)	
Other	31(6.7%)	43(10.9%)	29(7.9%)	27(6.7%)	130(8.0%)	
Body mass index, n (%)						*< 0.001*
< 22.5 kg/m^2	34(7.5%)	24(6.3%)	36(10.1%)	89(22.1%)	183(11.5%)	
22.5–24.9 kg/m^2	71(15.7%)	58(15.1%)	51(14.4%)	83(20.6%)	263(16.5%)	
≥ 25.0 kg/m^2	347(76.8%)	301(78.6%)	268(75.5%)	230(57.2%)	1146(72.0%)	
Alcoholic drinks/day, n (%)						*< 0.001*
0–1 drink	160(57.6%)	109(52.7%)	75(36.9%)	77(32.1%)	421(45.4%)	
2 drinks	76(27.3%)	52(25.1%)	64(31.5%)	68(28.3%)	260(28.0%)	
3 or more drinks	42(15.1%)	46(22.2%)	64(31.5%)	95(39.6%)	247(26.6%)	
Depressive symptoms	2.0(0.0, 4.0)	1.0(0.0, 4.0)	1.0(0.0, 6.0)	2.0(0.0, 6.0)	2.0(0.0, 5.0)	*0.029*
Systolic blood pressure, mmHg	129.0(118.0, 141.0)	130.0(119.0, 143.0)	131.0(119.0, 147.0)	132.0(119.0, 146.0)	131.0(119.0, 144.0)	*0.191*
Serum albumin, g/dl	4.2(4.0, 4.4)	4.2(4.0, 4.4)	4.2(3.9, 4.4)	4.2(4.0, 4.4)	4.2(4.0, 4.4)	*< 0.001*
Daily protein intake, g/day	71.6 (52.7, 91.6)	67.4 (47.5, 92.8)	73.5 (51.6, 94.8)	63.7 (45.4, 92.6)	69(49.7, 92.9)	*0.089*
CERAD W-L immediate recall	19 (17, 22)	19 (16, 22)	18 (15, 21)	19 (16, 22)	19(16, 22)	*0.020*
CERAD W-L delayed recall	6 (5, 8)	6 (4, 7)	6 (4, 7)	6 (5, 7)	6(4, 7)	*0.002*
Frailty, n (%)						*0.003*
Robust	150(40.8%)	147(48.8%)	78(34.5%)	73(37.4%)	448(41.1%)	
Pre-frail	192(52.2%)	135(44.9%)	118(52.2%)	108(55.4%)	553(50.7%)	
Frail	26(7.1%)	19 (6.3%)	30(13.3%)	14(7.2%)	89(8.2%)	
Serum Cotinine level, ng/mL	0.01(0.01, 0.01)	0.03(0.02, 0.04)	0.29(0.11, 5.36)	257.00(174.75, 363.00)	0.05(0.01, 89.38)	-

Data was presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Comparison according to serum cotinine quartiles was performed by Kruskal-Wallis test for continuous variables, χ2 test for categorical variables. CERAD W-L, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest (CERAD-WL)

Table 2 The independent associations of serum cotinine level quartile (reference: ≤0.01 ng/ml) with pre-frailty and frailty ($n=1626$)

		Serum cotinine level, ng/ml			
		Quartile 1 ≤ 0.01	**Quartile 2 0.01 < cotinine ≤ 0.05**	**Quartile 3 0.05 < cotinine ≤ 89.38**	**Quartile 4 > 89.38**
Pre-Frailty Versus Robust	OR (95% CI)	Reference	0.870(0.604, 1.252)	1.515(0.999, 2.296)	**1.599(1.017, 2.513)**
	P-value	-	*0.453*	*0.050*	***0.042***
Frailty Versus Robust	OR (95% CI)	Reference	0.752(0.339, 1.666)	**2.403(1.125, 5.134)**	2.333(0.977, 5.569)
	P-value	-	*0.482*	***0.024***	*0.056*

Bolded values mean statistical significance ($P<0.05$). OR (95% CI) were based on multinomial logistic regression models adjusting for age, sex, race/ethnicity, alcohol drinking, daily protein intake, systolic blood pressure, serum albumin level, depressive symptoms, and cognitive function

Table 3 The independent associations of serum cotinine level by the optimal literature cutoffs (15 ng/ml) with pre-frailty and frailty ($n=1626$)

		Low serum cotinine group (< 15 ng/ml)	**High serum cotinine group (≥ 15 ng/ml)**
Pre-Frailty Versus Robust	OR (95% CI)	Reference	**1.478(1.017, 2.150)**
	P-value	-	***0.035***
Frailty Versus Robust	OR (95% CI)	Reference	**2.141(1.054, 4.351)**
	P-value	-	***0.041***

Bolded values mean statistical significance ($P<0.05$). OR (95% CI) were based on multinomial logistic regression models adjusting for age, sex, race/ethnicity, alcohol drinking, daily protein intake, systolic blood pressure, serum albumin level, depressive symptoms, and cognitive function

Discussion

In this study, we examined the associations between serum cotinine levels and frailty status among older NHANES participants who are current smokers at the time of the survey. We found that compared to participants in the 1st quartile, participants in the 4th quartile (the highest) of serum cotinine level had elevated pre-frailty probability, and participants in the 3rd quartile of serum cotinine level had an increased probability of frailty. Compared to participants in the low group of serum cotinine level according to literature cutoffs, participants in the high group had elevated probability of pre-frailty and frailty. The study implies that there is an association between smoking activity and frailty. Further, smoking cessation in older smoking adults might possibly be helpful in reducing their frailty.

Previous research has explored the correlation between self-reported smoking status and frailty among older adults. Some studies demonstrated significant associations, while others did not [15]. This inconsistency could be attributed to potential recall bias in self-reported smoking status, which may result in inaccuracies in exposure assessments. Serum cotinine level has emerged as a promising biomarker, offering a dependable indication of recent nicotine exposure from tobacco smoke [16–19]. Nonetheless, only a limited number of studies have employed this biomarker to assess its connection with frailty. Earlier research suggested that the threshold values of serum cotinine to distinguish between smokers and non-smokers range from 3 to 40 ng/ml, and the optimal cutoff values range 10–20 ng/ml.

In our study, since only the participants' serum cotinine levels in the 3rd and 4th quartiles (>0.05 ng/ml) can reach such cut-off values, we inferred that at least half of the participants might not be active smokers (smoke every day). As our findings indicated that no statistical significance was showed in pre-frailty or frailty for the 2nd quartile compared to the 1st quartile, the study implied that active smokers were more likely to be frail or pre-frail compared to other smokers. Furthermore, participants whose serum cotinine levels were higher than the previous literature cutoffs were more likely to be pre-frail or frail. Therefore, our study confirmed previous research showing that active smoking is detrimental to physical status, particularly frailty status, in older adult [15].

The mechanisms of the relationship between cotinine and frailty have been studied extensively. Studies have shown that active smoking can result in increased protein degradation and reduced protein synthesis, leading to muscle wasting [42]. Furthermore, smoking causes impaired skeletal muscle oxygen delivery to the mitochondria, leading to reduced ability of the muscle to maintain a giver force or power output (muscle fatigue resistance) [43]. This further leads to smoking-related sarcopenia [44], decreased grip strength [45], weight loss [46, 47], and lowered exercise capacity and physical activity in older adults [48]. In addition to age-related decline in muscle mass and physical activity, smoking can further accelerate this process [49].

This study has many strengths. To the best of our knowledge, few studies investigated the relation between smoking utilizing serum cotinine level and frailty exclusively among a large sample of older adults, current smokers. We found that half of the current smokers may not be active smokers, and the dose-dependent relationship between serum cotinine and frailty only existed in active smokers. Therefore, our study shows that active smoking increases the probability of frailty in older adults. Our conclusions can be potentially generalized to other populations with different socioeconomic statuses or races/ethnicities, even if our sample size is representative and relatively large. Moreover, to reduce residual

confounding, we adjusted for covariates related to sociodemographics, lifestyle, physical health, and mental health in our regression models.

This study has several limitations. First, this cross-sectional study did not allow us to assess the temporal relationship between active smoking and frailty. Due to its short half-life (15–20 h), serum cotinine only assesses a person's recent exposure to tobacco and could not reflect their long-term exposure, even though the serum cotinine level can somewhat distinguish heavy, active, and non-active smokers among current smokers. Additionally, ethnic, mental health, and physical health differences existed between the participants who were included and those who were omitted due to missing data and being current smokers. Selection bias may, therefore exist. Future research is anticipated to utilize longitudinal designs to investigate the temporal relation between the level of serum cotinine or other tobacco exposure biomarkers with a longer half-life, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and the frailty status in older smokers, particularly the population from non-western countries.

This study has the following clinical implications: we observed an independent association between serum cotinine level, a biomarker of recent tobacco exposure, and frailty status in active smoking older adults. When assessing the frailty risk for older patients, clinicians should carefully inquire about patients' smoking status since active smokers can carry more risk. Given the unfavourable effects of active smoking on frailty in older adults, policymakers should constantly advocate for smoking-free policies and inform the public about the hazards of active smoking through social media and other educational approaches. Doctors and health instructors should encourage older active smokers to enroll in community smoking cessation programs.

In conclusion, increased serum cotinine level is independently associated with frailty status in actively smoking older adults. Smoking cessation in older active smokers might possibly help reduce their frailty.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05482-4.

Supplementary Material 1

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Author contributions
Song Ge, Li Xu, Xuechun Lin, and Yi Liu drafted the initial manuscript, designed the study, and searched for literature. Tian Zhou conducted statistical analysis. Xuechun Lin revised the manuscript. All authors critically revised and approved the manuscript.

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Data availability
The data are openly available on the NHANES website. https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The NHANES was approved by the National Center for Health Statistics Research Ethics Review Board. All participants provided written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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