RESEARCH ARTICLE

The association between tobacco smoke exposure and vitamin D levels among US general population, 2001–2014: temporal variation and inequalities in population susceptibility

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Abstract

Tobacco smoking is endocrine-disrupting and may interfere with vitamin D endocrine systems (VDES), but supporting evidence is limited and inconsistent. Also, there is a lack of evidence on whether the association between tobacco smoke exposure and VD levels exhibit temporal variation. Data from the National Health and Nutrition Examination Survey was used to evaluate the association between tobacco smoke exposure and VD levels among US general participants from 2001 to 2014. We examined the linear association between serum cotinine and 25(OH)D concentrations, as well as relationship between tobacco smoke exposure categories (active, passive, non-smoking) with VD status (deficiency, inadequacy, sufficiency, intoxication), and assessed whether specific gender, age (3–11, 12–19, 20–59, ≥ 60 years), ethnicity/race, or body mass index (BMI) groups were disproportionately impacted. During 2001–2004, a decrease in both serum cotinine and passive smoking prevalence was observed, with a stabilized active smoking rate. The estimates for the association between tobacco smoke exposure and suboptimal VD levels increased over the study period. Overall results indicated that serum cotinine was negatively associated with 25(OH)D in all participants. Tobacco smoke exposure, including both active and passive smoking exposure, was associated with increased risk of VD deficiency. Moreover, active smoking was additionally related to enhanced risk of VD inadequacy. These associations showed some age and gender differences, with consistent and stronger associations observed in female adults. In contrast, effects of tobacco smoke exposure on VD levels were mostly negative or non-significant among children and adolescents aged 3–19 years. The percentage of US general population with active smoking exposure stabilized over the 14-year period and was still high. Tobacco smoke exposure may disrupt vitamin D levels with an increasing temporal trend in the risk. Our results also provided initial evidence of smoking exposure on VD intoxication, which needs to be further verified. Convincing studies have linked tobacco use exposure, to dysfunctional VDES accompanied with declined serum levels of VD metabolites. However, evidence on the association between tobacco smoke exposure and VD status was rather limited and inconsistent, and there were no researches to date that estimated the temporal variation of the association as well as the effects of smoke exposure on VD intoxication. This study analyzed national survey data, to evaluate the temporal trends in effects of tobacco smoke exposure on VD levels over a decade, and to comprehensively assess the impacts of tobacco smoke exposure on VD levels across specific subgroups. The evidence suggests that the prevalence of active smoking exposure stabilized over the 14-year period and was still high. Moreover, tobacco smoke exposure may disrupt vitamin D levels among general population, with an increasing temporal trend and age-, gender-differences in risk.

Keywords Tobacco smoke · Cotinine · Vitamin D · Vitamin D deficiency · NHANES

Introduction

Evidence has affirmed the carcinogen, neurotoxic, and endocrine-disrupting roles of tobacco use exposure, including both active and passive smoking exposure, in the pathogenesis of a wide range of diseases (Mousavi et al. 2019). The principle component of tobacco products is nicotine.

The absorption of nicotine by human body from tobacco is mainly through inhalation via smoke and vaporization exposure; its other routes include oral mucosa absorption via chewing and sniffing, and also through skin absorption (Benowitz et al. 2009b). Once entering into the body, nicotine is absorbed immediately and rapidly reaches the bloodstream and the brain, leading to an extensive distribution to body tissues. About 70–80% of nicotine is metabolized into cotinine in humans (Benowitz and Jacob 1994).

Although substantial decline in smoking rates is expected through efforts in public consciousness, education, and public policy since 1964 in the USA (National Institute on Drug Abuse, 2020), studies have consistently indicated that the tobacco smoke exposure in the US general population is still high. For example, data accessed from the National Health and Nutrition Examination Survey (NHANES) for 1999–2004 revealed that 9% of adolescents aged 12–19 years and 30% of US adults aged 20 years or older were active smokers according to their serum cotinine values (Benowitz 2009a). Furthermore, it is worth noticing that smoking has become increasingly appealing to both smokers and non-smokers due to the emergence of electronic cigarettes (e-cigarettes) in the US market since 2007, together with increased flavor choices for both traditional and electronic cigarettes. Accordingly, the NHANES 2009–2010 data analysis showed that about 42% of the US children and adolescents of 3–17 years had serum cotinine concentrations reaching the secondhand smoke exposure levels, with 9% of the teenagers aged 13–17 years reaching the range of active smoking (Nwosu and Kum-Nji 2018; Chatham-Stephens (2014).

Vitamin D (VD) is a fat-soluble hormone and is well known for functions in maintaining bone health and skin barrier. Its nutrigenomic and epigenetic functions have also been demonstrated through links between VD insufficiency or deficiency with various diseases, including tumorigenesis metastasis (Mahamat-Saleh et al. 2020), autoimmune diseases (Sharief et al. 2011; Ahmed Mohamed et al. 2021), cardiometabolic disorders (Marquina et al. 2019; Pott-Junior et al. 2020), and even worse, coronavirus disease 2019 (COVID-19) risk and severity (Mitchell 2020; Pereira et al. 2020). Potential evidence also indicates that VD intoxication induces calcium and phosphorus dysregulation, causing damage to tissues and organs (Razzaque 2018). Although VD level was thought to be closely related to sun exposure and dietary intake, a few epidemiological studies have indicated the endocrine-disrupting role of tobacco smoke exposure, and linked it to dysfunctional Vitamin D endocrine systems (VDES) accompanied with declined serum levels of VD metabolites (Brot et al. 1999; Banihosseini et al. 2013; Manavi et al. 2015; Byun et al. 2017; Nwosu and Kum-Nji 2018). By estimating smoking status and VD levels among 510 healthy perimenopausal women aged 45–58 years,

Brot et al. (1999) reported that female smokers had significantly decreased levels of serum VD. A previous NHANES 2009–2010 analysis found that tobacco smoke exposure among 2263 US children (3–17 years) was independently associated with VD deficiency (Nwosu and Kum-Nji 2018). The NHANES 2001–2006 illustrated that serum cotinine of adults (18–70 years) was associated with lower VD concentration, with results varied by gender and ethnicity/race (Manavi et al. 2015). Contrastingly, a cohort study enrolling 54 mother-infant pairs in Iran concluded that maternal exposure to cigarette smoking during pregnancy showed insignificant influence on serum VD levels in mothers (Banihosseini et al. 2013). Moreover, a national cross-sectional study based on 2515 Korean adolescents aged 10–18 years during 2008–2011 also suggested no evidence of the relationship between cotinine-verified smoking and VD deficiency (Byun et al. 2017). However, the effects of tobacco smoke exposure on VD intoxication have not, to our knowledge, been evaluated. Also, because the emissions of tobacco have changed with different devices over time (Martuzevicius et al. 2019), the health impacts of tobacco smoke exposure might also display temporal variation. Nevertheless, few studies of tobacco smoke and VD levels have examined the temporal change in the association over time using a long-term analysis.

Thus, the association between tobacco smoke exposure and VD status are not consistent among previous human studies, the temporal trend and the complicated demographic characteristics that influence the relationship have not been sufficiently examined. More comprehensive investigations covering a broader range of people at extended period over time are needed. Therefore, this study was aimed to use NHANES data over the entire 14-year period (2001–2014) (1) to evaluate the associations between tobacco smoke and VD status, and to examine whether the relations were consistent or not among different cycles; (2) to estimate various demographic factors that influence the smoke-VD association, and to help discern the vulnerable subpopulations on which the public health interventions should be focused.

Methods

Study population

The National Health and Nutrition Examination Survey, or NHANES, is a nationally ongoing health survey conducted by the Centers for Disease Control and Prevention (CDC)/ National Center for Health Statistics (NCHS) since 1959 to monitor the health and nutritional status of the noninstitutionalized US residents (https://www.cdc.gov/nchs/nhanes). Representative participants of all ages were randomly selected through a statistical process using US census information, and were then personally contacted for a home

interview concerning sociodemographic characteristics, health history, and behavior. Meanwhile, a one-time specific health examination was completed based on their age, gender, and medication conditions, where biological samples were collected. The NCHS Research Ethics Review Board (ERB) approval and documented consent was obtained from all participants. NHANES released its data for public use in each 2-year cycle. Currently, serum cotinine was only available among participants aged ≥ 3 years; thus, we included a total of 49,338 participants aged ≥ 3 years who had available data on serum cotinine, vitamin D, and sociodemographic covariates (listed below) from seven surveys cycles (2001–2014) in the analysis.

Measurement of tobacco smoke exposure

Tobacco use smoke exposure for NHANES was assessed through the measurement of serum cotinine, a major metabolite of nicotine. Cotinine has been used as a highly specific and sensitive biomarker in quantifying short-term exposure of tobacco use due to its relatively long half-life (15–20 h; nicotine: 2 h), and wide detection in biological fluids, including blood, urine, saliva, hair, and nails (Benowitz 1996; Benowitz et al. 2009b; Akinkugbe et al. 2019).

In each survey cycle, about 90% of eligible participants (aged 3 years and older) had cotinine examined in serum in NHANES 2001–2014. Serum cotinine was measured by an isotope-dilution high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS) method. Detailed analytical methodology was available at NHANES website (https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/COT_H.htm). The lower limit of detection (LLOD in ng/mL) for serum cotinine in each 2-year cycle from 2001 to 2014 was 0.015 ng/mL. The results below the LLODs were replaced with the LLODs divided by the square root of two (LLOD/$\sqrt{2}$). The detection rates of cotinine are summarized in Table 1.

According to CDC, nonsmokers exposed to typical levels of passive/secondhand smoke (SHS) have serum cotinine levels of less than 1 ng/mL, with heavy exposure to SHS producing levels in the 1–10 ng/mL range. Active smokers are defined as levels higher than 10 ng/mL (https://www.cdc.gov/biomonitoring/Cotinine_BiomonitoringSummary.html).

Measurement of vitamin D

Serum 25-hydroxyvitamin D (25(OH)D) is the predominant circulating form of vitamin D, and is deemed as the most reliable index of vitamin D status. For NHANES 2001–2006, serum 25(OH)D concentrations were measured using the DiaSorin RIA kit. Due to observed method variation of DiaSorin assay, the CDC applied an ultra-high

performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method to detect 25(OH)D in serum for NHANES 2007–2014, and predicted LC–MS/MS equivalent quantity for NHANES 2001–2006. The detailed detecting methods and standardization were shown at the official site (https://wwwn.cdc.gov/nchs/nhanes/vitamind/analyticalnote.aspx?h=/Nchs/Nhanes/2003-2004/VID_C.htm&t=VID_C%20Doc).

US Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine (NASEM) defined the vitamin D status as: deficiency at serum 25(OH)D concentrations less than 30 nmol/L (12 ng/mL), inadequacy at 30 to 50 nmol/L (12–20 ng/mL), and sufficiency for bone and overall health at levels of 50 nmol/L (20 ng/mL) or more. We also defined the VD intoxication as 25(OH)D concentrations greater than 125 nmol/L (50 ng/mL) according to the FNB committee (https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/).

Sociodemographic and lifestyle factors

Potential confounding factors were considered according to previous researches (Juonala et al. 2019; Luo et al. 2020), including gender, age, ethnicity/race, ratio of family income to poverty (PIR), body mass index (BMI), tobacco products use, dietary vitamin D intakes, alcohol use, physical activity, kidney health, and NHANES cycle. Specifically, PIR represents the social economic status of the family (or individual), and is a ratio of family income to poverty guidelines specific to the survey year, family size, and geographic location. Of note, weight status categories for participants aged 3–19 years old was defined as four levels: underweight (BMI < 5th percentile), normal weight (5th ≤ BMI < 85th percentile), overweight (85th ≤ BMI < 95th percentile), and obese (BMI ≥ 95th percentile); for adults aged 20 years old and older, standard weight status categories associated with BMI ranges were underweight (< 18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥ 30 kg/m²). Given that there were few cases (1.7%) in the underweight category, we combined underweight and normal weight into one class in the regression analyses. In addition to the quantitative assessment of serum cotinine, questions regarding recent tobacco products use during the past 5 days were answered by eligible participants aged 12 years and older. From 2013–2014 survey cycle, e-cigarettes were also included as another form of tobacco. Specifically, participants were asked, "During the past 5 days, including today, did you smoke cigarettes, pipes, cigars, little cigars or cigarillos, water pipe, hookahs, or e-cigarettes?" Information on alcohol use was collected using question "Had at least 12 alcohol drinks per year?" (available from all participants aged 20 years and older in NHANES 2001–2010, aged 18 years and older in

Table 1 Population characteristics with serum cotinine and VD levels by survey cycle in NHANES 2001–2014[a]

	Overall (N=49,338)	2001–2002 (N=7017)	2003–2004 (N=7291)	2005–2006 (N=7343)	2007–2008 (N=6160)	2009–2010 (N=7434)	2011–2012 (N=6726)	2013–2014 (N=7367)
Age (year, mean (SD))	35.2 (23.1)	33.5 (22.1)	33.7 (23.7)	32.6 (22.5)	38.0 (23.8)	37.4 (23.2)	35.7 (22.9)	36.2 (23.1)
Age (%)								
3–11	8355 (16.9)	925 (13.2)	1213 (16.6)	1245 (17.0)	1111 (18.0)	1245 (16.7)	1263 (18.8)	1353 (18.4)
12–19	9857 (20.0)	1995 (28.4)	1934 (26.5)	1880 (25.6)	863 (14.0)	1065 (14.3)	989 (14.7)	1131 (15.4)
20–59	21,012 (42.6)	2857 (40.7)	2640 (36.2)	2942 (40.1)	2659 (43.2)	3464 (46.6)	3111 (46.3)	3339 (45.3)
>=60	10,114 (20.5)	1240 (17.7)	1504 (20.6)	1276 (17.4)	1527 (24.8)	1660 (22.3)	1363 (20.3)	1544 (21.0)
Ethnicity/Race (n, %)								
Hispanic	13,880 (28.1)	2085 (29.7)	2034 (27.9)	2076 (28.3)	1922 (31.2)	2297 (30.9)	1598 (23.8)	1868 (25.4)
Non-Hispanic Black	11,434 (23.2)	1616 (23.0)	1908 (26.2)	1934 (26.3)	1264 (20.5)	1348 (18.1)	1793 (26.7)	1571 (21.3)
Non-Hispanic White	20,257 (41.1)	3067 (43.7)	3039 (41.7)	2983 (40.6)	2718 (44.1)	3352 (45.1)	2256 (33.5)	2842 (38.6)
Other race	3767 (7.64)	249 (3.55)	310 (4.25)	350 (4.77)	256 (4.16)	437 (5.88)	1079 (16.0)	1086 (14.7)
BMI (kg/m² , mean (SD))	26.1 (7.40)	25.6 (6.74)	25.5 (6.95)	25.9 (7.44)	26.4 (7.44)	26.6 (7.60)	26.2 (7.62)	26.4 (7.87)
BMI category (n, %)								
Normal	19,012 (38.5)	2910 (41.5)	2990 (41.0)	2949 (40.2)	2214 (35.9)	2642 (35.5)	2584 (38.4)	2723 (37.0)
Obese	16,293 (33.0)	2033 (29.0)	2260 (31.0)	2405 (32.8)	2125 (34.5)	2625 (35.3)	2280 (33.9)	2565 (34.8)
Overweight	13,191 (26.7)	1948 (27.8)	1928 (26.4)	1866 (25.4)	1721 (27.9)	2042 (27.5)	1741 (25.9)	1945 (26.4)
Underweight	842 (1.71)	126 (1.80)	113 (1.55)	123 (1.68)	100 (1.62)	125 (1.68)	121 (1.80)	134 (1.82)
PIR (median (IQR))	1.89 (2.74)	2.12 (2.89)	1.84 (2.64)	2.09 (2.73)	1.92 (2.68)	1.78 (2.58)	1.70 (2.79)	1.79 (2.81)
Serum cotinine detection rate (n %)[b]	38,236 (77.5)	5425 (77.3)	6056 (83.1)	6063 (82.6)	5125 (83.2)	5708 (76.8)	4873 (72.5)	4986 (67.7)
Serum cotinine (ng/mL, median (IQR))	0.06 (1.13)	0.08 (1.31)	0.10 (1.44)	0.07 (1.10)	0.07 (1.51)	0.04 (1.00)	0.04 (0.60)	0.04 (0.90)
Cotinine exposure category (n, %)								
Active smokers (> 10 ng/mL)	9102 (18.45)	1286 (18.33)	1355 (18.58)	1326 (18.06)	1206 (19.58)	1428 (19.21)	1154 (17.16)	1347 (18.28)
Passive smokers (1–10 ng/mL)	3631 (7.36)	598 (8.52)	678 (9.30)	566 (7.71)	485 (7.87)	442 (5.95)	389 (5.78)	473 (6.42)
Nonsmokers (< 1 ng/mL)	36,605 (74.19)	5133 (73.15)	5258 (72.12)	5451 (74.23)	4469 (72.55)	5564 (74.84)	5183 (77.06)	5547 (75.30)
Tobacco/nicotine use (n, %)[c]								
Yes	8441 (20.6)	1259 (20.7)	1247 (20.5)	1251 (20.5)	1150 (22.8)	1300 (21.0)	1070 (19.6)	1164 (19.4)
No	29,696 (72.5)	4505 (73.9)	4415 (72.6)	4463 (73.2)	3619 (71.7)	4331 (70.0)	3914 (71.6)	4449 (74.0)
Missing	2846 (6.94)	328 (5.38)	416 (6.84)	384 (6.30)	280 (5.55)	558 (9.02)	479 (8.77)	401 (6.67)
Alcohol consumption (n, %)[d]								
Yes	20,805 (65.8)	2682 (65.5)	2674 (64.5)	2721 (64.5)	2797 (66.8)	3415 (66.6)	3131 (66.5)	3385 (65.7)
No	8502 (26.9)	1204 (29.4)	1181 (28.5)	1232 (29.2)	1161 (27.7)	1213 (23.7)	1121 (23.8)	1390 (27.0)
Missing	2321 (7.34)	211 (5.15)	289 (6.97)	265 (6.28)	228 (5.45)	496 (9.68)	456 (9.69)	376 (7.30)
Serum 25(OH)D (nmol/L, median (IQR))	59.2 (30.4)	56.3 (26.2)	58.1 (29.5)	56.8 (26.7)	61.8 (31.3)	62.1 (32.0)	60.7 (32.8)	61.7 (30.7)
VD status category (n, %)								
Deficiency (< 30 nmol/L; < 12 ng/mL)	3764 (7.63)	490 (6.98)	709 (9.72)	522 (7.11)	494 (8.02)	544 (7.32)	488 (7.26)	517 (7.02)
Inadequacy (30–50 nmol/L; 12–20 ng/mL)	12,718 (25.8)	2105 (30.0)	1860 (25.5)	2362 (32.2)	1425 (23.1)	1661 (22.3)	1682 (25.0)	1623 (22.0)
Adequacy (≥ 50 nmol/L; ≥ 20 ng/mL)	32,176 (65.2)	4388 (62.5)	4662 (63.9)	4421 (60.2)	4164 (67.6)	5096 (68.5)	4397 (65.4)	5048 (68.5)
Intoxication (> 125 nmol/L; > 50 ng/mL)	680 (1.38)	34 (0.48)	60 (0.82)	38 (0.52)	77 (1.25)	133 (1.79)	159 (2.36)	179 (2.43)
Oral contraceptives use (n, %)[e]								
Yes	10,590 (50.7)	1445 (45.7)	1393 (45.4)	1545 (49.3)	1402 (55.3)	1668 (53.3)	1455 (53.0)	1682 (53.9)
No	8361 (40.0)	1441 (45.6)	1410 (46.0)	1334 (42.5)	946 (37.3)	1092 (34.9)	982 (35.8)	1156 (37.1)
Missing	1937 (9.27)	273 (8.64)	262 (8.55)	257 (8.20)	185 (7.30)	372 (11.90)	308 (11.20)	280 (8.98)
Self-reported kidney health (n, %)[f]								
Healthy	841 (2.70)	97 (2.37)	106 (2.56)	108 (2.56)	120 (2.87)	112 (2.19)	145 (3.24)	153 (3.13)
Weak/fail	30,233 (97.1)	3988 (97.3)	4033 (97.3)	4098 (97.2)	4059 (97.0)	5005 (97.7)	4326 (96.7)	4724 (96.7)
Missing	52 (0.17)	12 (0.29)	5 (0.12)	12 (0.28)	7 (0.17)	7 (0.14)	3 (0.07)	6 (0.12)
Vigorous activity (n, %)[d]								
Yes	16,496 (40.3)	2660 (43.7)	2342 (38.5)	2663 (43.7)	1978 (39.2)	2338 (37.8)	2123 (38.9)	2392 (39.8)

Table 1 (continued)

	Overall (N = 49,338)	2001–2002 (N = 7017)	2003–2004 (N = 7291)	2005–2006 (N = 7343)	2007–2008 (N = 6160)	2009–2010 (N = 7434)	2011–2012 (N = 6726)	2013–2014 (N = 7367)
No	24,258 (59.2)	3386 (55.6)	3684 (60.6)	3386 (55.5)	3044 (60.3)	3830 (61.9)	3325 (60.9)	3603 (59.9)
Missing	229 (0.56)	46 (0.76)	52 (0.86)	49 (0.80)	27 (0.53)	21 (0.34)	15 (0.27)	19 (0.32)
Moderate activity (*n*, %)[d]								
Yes	23,604 (57.6)	3091 (50.7)	3429 (56.4)	3532 (57.9)	2999 (59.4)	3646 (58.9)	3272 (59.9)	3635 (60.4)
No	17,141 (41.8)	2952 (48.5)	2594 (42.7)	2517 (41.3)	2022 (40.0)	2521 (40.7)	2177 (39.8)	2358 (39.2)
Missing	238 (0.58)	49 (0.80)	55 (0.90)	49 (0.80)	28 (0.55)	22 (0.36)	14 (0.26)	21 (0.35)
VD consumption during past 24 h (*n*, %)[g]								
Yes	25,565 (92.3)	—	—	—	5845 (94.9)	7077 (95.2)	6150 (91.4)	6493 (88.1)
No	454 (1.64)	—	—	—	75 (1.22)	102 (1.37)	97 (1.44)	180 (2.44)
Missing	1668 (6.02)	—	—	—	240 (3.90)	255 (3.43)	479 (7.12)	694 (9.42)

IQR inter quartile range, *BMI* body mass index, *PIR* ratio of family income to poverty

[a]The number of included participants was 49,338, with complete data on age, ethnicity/race, BMI, PIR, serum cotinine, and 25 (OH) D levels within each cycle in NHANES 2001–2014

[b]Detection rate: at or above detection limit

[c]Only participants aged ≥ 12 years have data on the variable

[d]Only participants aged ≥ 20 years in NHANES 2001–2010, and participants aged ≥ 18 years in NHANES 2011–2014 have data on the variable

[e]Only female participants aged ≥ 12 years have data on the variable

[f]Only participants aged ≥ 20 years have data on the variable

[g]Only those participated in NHANES 2007 and later have data on vitamin D consumption during past 24 h

NHANES 2011–2014). The physical activity questionnaires were established on the basis of the Global Physical Activity Questionnaires (GPAQ) and included activity at different intensity (moderate, vigorous) cross multiple domains (recreational and at work). We have merged the activity across different domains (at work and recreational) into total physical activity category, that is, moderate activity and vigorous activity for participants aged 12 years and older when available. For participants aged 20 and over, self-reported kidney health condition was also collected from the question "Ever told you had weak/failing kidneys?" The variables adjusted in the final analyses included gender (female, male), age (continuous), ethnicity/race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race), PIR (continuous), BMI (categorical), alcohol use (dichotomous), vigorous activity (dichotomous), moderate activity (dichotomous), kidney health condition (weak, healthy), and NHANES cycle (categorical). Oral use of contraceptives (dichotomous) was additionally adjusted for females aged 12 and over. List of detailed variable characteristics is presented in Table 1.

Statistical analysis

The serum cotinine and 25(OH)D were natural-log transformed (ln-transformed) to improve the normality in the analyses. Cotinine and 25(OH)D were modeled as both continuous (ln-transformed) and categorical variables. In the base model, we fitted multiple linear regression models to evaluate the linear association between serum cotinine and 25(OH)D concentrations. We first applied the models by combining all seven cycles together without considering change in risk over time. The temporal variation of the association was then evaluated by a stratification model, which estimated and compared separate associations for each cycle to examine whether the associations were consistent across all cycles. Then logistic regression models were fitted to further investigate relationships between tobacco smoke exposure categories with different VD status. Meanwhile, all the analyses were performed for pooled cycles (2001–2014), and for each cycle separately to examine whether the associations are consistent over time.

Furthermore, we performed the stratified analyses by age, gender, ethnicity/race, and BMI categories to examine potential modifying effects of demographic factors as well as to verify the robustness of our findings. Because cotinine levels can vary greatly by gender and age, the analyses were further stratified by age group (3–11, 12–19, 20–59, ≥ 60 years) in both females and males, generally consistent with the age groupings defined in the NHANES Sample Design reports (CDC 2021). In addition, the dietary vitamin D intake variable has been added to NHANES survey using a 24-h dietary recall interview for participants of all age since 2007. Thus, we included the adjustment for self-reported VD intakes in the sensitivity analysis for NHANES 2007–2014. Results of all analyses were presented as β coefficients (continuous) and odds ratios (ORs; categorical), with corresponding 95% confidence intervals (CIs). All the statistical analyses were

conducted using R (version 3.4). *P* value < 0.05 was deemed as statistically significant (two-tailed).

Results

Table 1 summarizes the demographic characteristics, variables related to tobacco smoke exposure, and VD status of all participants across the seven survey cycles. A total of 49,338 participants were included in these study, with 7017 from 2001 to 2002, 7291 from 2003 to 2004, 7343 from 2005 to 2006, 6160 from 2007 to 2008, 7434 from 2009 to 2010, 6726 from 2011 to 2012, and 7367 from 2013 to 2014. The distributions of the general characteristics for overall sample by gender-age status are shown in Supplementary Table 1. Among 49,338 participants, there were 24,987 (50.6%) females and 24,351 (49.4%) males. The mean age of all participants was 35.2 years (± 23.1 years), and the distribution of age subgroups was 8355 (16.9%) for 3–11, 9857 (20.0%) for 12–19, 21,012 (42.6%) for 20–59, and 10,114 (20.5%) for ≥ 60 years.

Tobacco smoke exposure prevalence

Figure 1 illustrates the trends of serum cotinine levels through the NHANES 2001–2014 period. Comparing the overall median concentrations of serum cotinine in NHANES 2001–2002 (0.08 ng/mL) and NHANES 2013–2014 (0.04 ng/mL), a decrease of 50% was observed (Table 1). The percentage of NHANES participants with active smoking exposure (serum cotinine level > 10 ng/mL) stabilized between 17.2 and 19.6% over the 14-year period. Meanwhile, the proportion of participants with passive smoking exposure (1–10 ng/mL) showed the comparatively downward trends over time, with the prevalence in NHANES 2013–2014 decreased to 6.4% (compared to 8.5% in NHANES 2001–2002).

For the overall sample covering all the cycles, the percentage of active smokers across different age groups were 0.4% for children aged 3–11 years, 13.0% for adolescents aged 12–19 years, 68.5% for adults aged 20–59 years, and 18.1% for adults aged ≥ 60 years (Supplementary Table 1). In addition, compared with other age groups, children aged
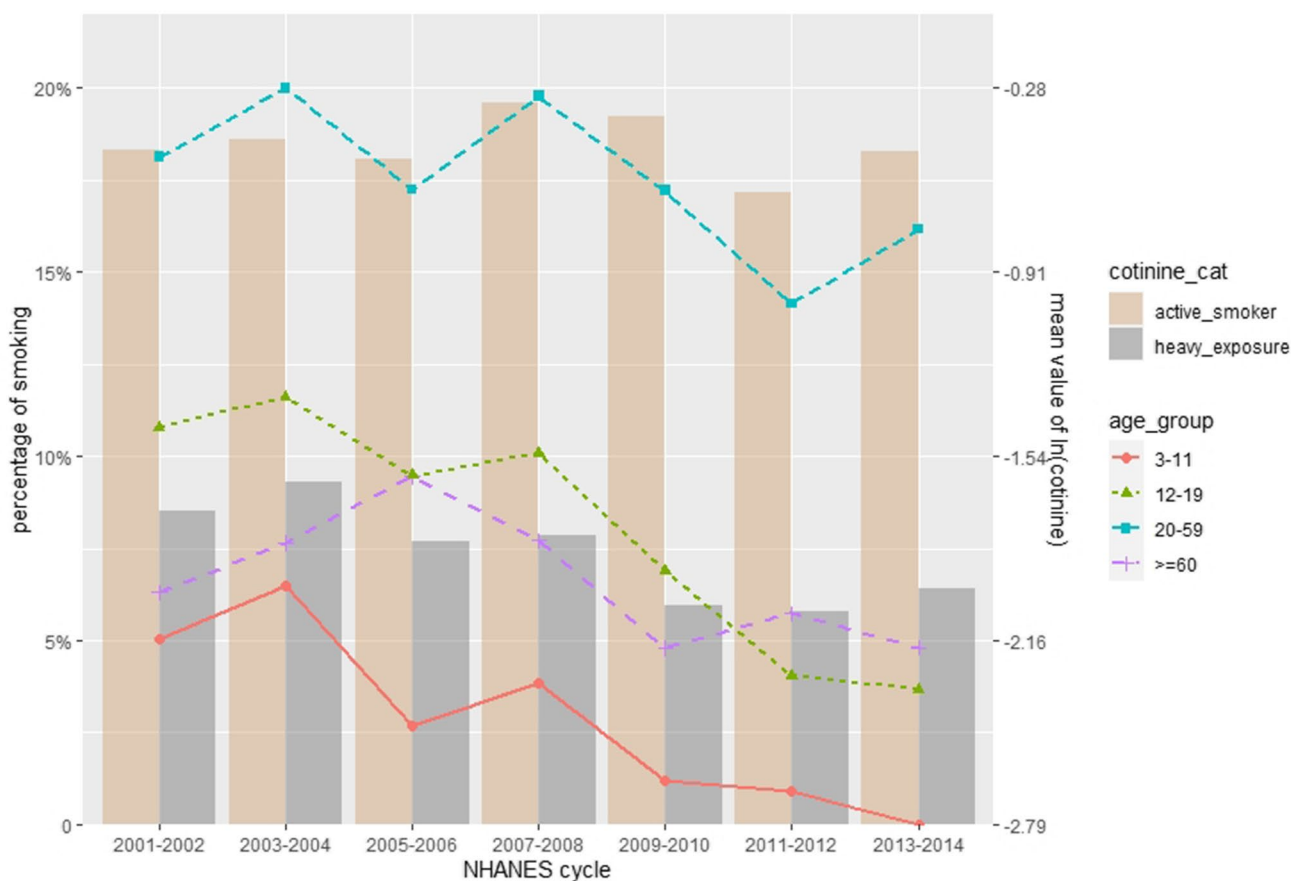
Fig. 1 Estimated prevalence (%) of active smoking (brown bars) and passive smoking (gray bars) exposure among US population aged ≥ 3 years. Notes: Geometric mean serum cotinine levels (ng/mL) plotted on the ln scale for children aged 3–11 years (orange circles, solid line) and adolescents aged 12–19 years (green triangles, dashed line), adults aged 20–59 years (blue squares, dashed line), and aged ≥ 60 years (purple crosses, dashed line) in the NHANES 2001–2014 by survey cycles; data shown in Supplementary Table 1

3–11 have a higher percentage of passive smoking exposure (32.1%).

Suboptimal VD status occurrence

Table 2 describes the population characteristics by vitamin D status. During the entire study period (2001–2014), the overall prevalence of VD deficiency, inadequacy and intoxication is 7.6, 25.8 and 1.4%, respectively. The median concentration was reported to be 24.4, 41.3, 68.5, and 138 nmol/L for VD deficiency, inadequacy, sufficiency, and intoxication, respectively. VD deficiency prevalence was relatively stable among different cycles. While the prevalence of VD inadequacy in the 1st cycle decreased from 30.0% to the end of the study (20.0%), with the prevalence of VD adequacy increased from 62.5 to 68.5% (Table 1). Obvious increasing trends for VD intoxication were also illustrated. Compared to VD intoxication in NHANES 2001–2002, the prevalence increased from 0.43 to 2.43% in 2013–2014. In particular, participants who were female, non-Hispanic Black, obese, and having higher levels of serum cotinine had higher percentage of VD deficiency or inadequacy. And the prevalence of VD intoxication was observed higher for female, non-Hispanic White, oral contraceptive users, and participants doing moderate activities.

Association between tobacco smoke exposure and VD levels

In the base model, we first calculated the associations between tobacco smoke exposure and VD levels for the entire study period without considering the temporal variation. The overall coefficient for the linear association between continuous serum cotinine and 25(OH)D was estimated to be -0.011 (95% CI: $-0.012--0.01$), which indicated that cotinine concentration was negatively associated with VD level (Table 3). Next we evaluated whether the risks varied over time using stratification models for different cycles. The coefficients were all negative for all datasets with slight increase in associations over time: for NHANES 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014, the adjusted coefficients were -0.007 (95% CI: -0.009 to -0.004), -0.008 (95% CI: -0.011 to -0.005), -0.006 (95% CI: -0.008 to -0.004), -0.008 (95% CI: -0.011 to -0.005), -0.014 (95% CI: -0.017 to -0.012), -0.015 (95% CI: -0.018 to -0.012), -0.013 (95% CI: -0.016 to -0.011), respectively.

More specifically, pooled analysis of associations between tobacco smoke categories and VD status showed adverse effects of active smoking on VD inadequacy (OR = 1.51, 95% CI: 1.43–1.61) and VD deficiency (OR = 2.24, 95% CI: 2.05–2.45). A positive association between passive smoking and VD deficiency was also observed (OR = 1.30, 95% CI: 1.14–1.48) for the entire study period (Table 4). Results for the stratified analysis indicated that the associations between tobacco smoke exposure and VD status within different cycles were mostly consistent with the pooled samples. We observed a similar temporal trend to the base model, namely, that the overall risk of VD deficiency and inadequacy related to active smoking exposure increased over time, whereas estimations for passive smoking exposure showed less pronounced and less consistent impacts on VD deficiency and inadequacy among different cycles. For NHANES 2001–2002, and 2010–2011, the associations were additionally positive for passive smoke exposure and VD deficiency; the odds ratios were evaluated to be 1.74 (95% CI: 1.25–2.42) and 1.59 (95% CI: 1.09–2.32), respectively. Moreover, the associations evidenced between tobacco smoke exposures and VD intoxication were not consistent for different NHANES datasets. For instance, in NHANES 2005–2006, both active and passive smoke exposures were positively associated with VD intoxication (OR$_{Active}$ = 2.17, 95%CI: 1.00–4.73; OR$_{Passive}$ = 3.35; 95%CI: 1.20–9.31), and a positive relationship was also proved for active smoking in NHANES 2013–2014 (OR = 1.50, 95%CI: 1.00–2.25). However, this positive relationship was weak since it was not supported by all sub-datasets.

Modification effects by age, gender, ethnicity/race and BMI

Since the associations between tobacco smoke exposure and VD levels were mostly consistent for the entire period and among cycles, the modification effects by demographic factors were examined combing all the cycles from 2001 to 2014. Figure 2 and Supplementary Table 2 present the linear associations between serum cotinine and VD concentrations by age-gender groups. Among children aged 3–11 years, serum cotinine was consistently positively associated with 25(OH)D concentrations, and showed a more pronounced estimate for females. Similarly, positive associations of serum cotinine with 25(OH)D were detected for all adolescents, and persisted only among male adolescents. For adults (20–59 and ≥ 60 years), significant inverse associations for decreasing 25(OH)D concentrations with increasing levels of continuous cotinine were revealed, and the associations were more evident for females.

Figure 3 and Supplementary Table 3 show associations between tobacco smoke exposure categories and varied VD status within age-gender groups. For active smoking exposure, the estimates for children could not be derived due to small sizes (34, 0.4%). Active smoking was proved to be related with decreased risk of VD deficiency for adolescents aged 12–19 years (OR = 0.62, 95% CI: 0.47–0.81). In gender-stratified analyses, the protective effects remained consistent

Table 2 Population characteristics by VD status in NHANES 2001–2014

	Deficiency N = 3764	Inadequacy N = 12,718	Adequacy N = 32,176	Intoxication N = 680
Age (year, mean (SD))	36.8 (20.1)	34.9 (21.6)	34.9 (23.9)	48.6 (23.5)
Sex (*n*, %)				
Female	2268 (60.3)	6653 (52.3)	15,568 (48.4)	498 (73.2)
Male	1496 (39.7)	6065 (47.7)	16,608 (51.6)	182 (26.8)
Race (*n*, %)				
Hispanic	795 (21.1)	4208 (33.1)	8833 (27.5)	44 (6.5)
Non-Hispanic Black	2220 (59.0)	4690 (36.9)	4465 (13.9)	59 (8.7)
Non-Hispanic White	466 (12.4)	2749 (21.6)	16,511 (51.3)	531 (78.1)
Other race	283 (7.5)	1071 (8.4)	2367 (7.4)	46 (6.8)
BMI (kg/m^2, mean (SD))	29.9 (9.2)	27.5 (7.5)	25.1 (6.9)	25.2 (5.8)
BMI category (*n*, %)				
Normal/underweight	1177 (31.3)	4298 (33.8)	14,013 (43.6)	366 (53.8)
Obese	1771 (47.1)	5116 (40.2)	9282 (28.8)	124 (18.2)
Overweight	816 (21.7)	3304 (26.0)	8881 (27.6)	190 (27.9)
NHANES cycle (*n*, %)				
2001–2002	490 (13.0)	2105 (16.6)	4388 (13.6)	34 (5.0)
2003–2004	709 (18.8)	1860 (14.6)	4662 (14.5)	60 (8.8)
2005–2006	522 (13.9)	2362 (18.6)	4421 (13.7)	38 (5.6)
2007–2008	494 (13.1)	1425 (11.2)	4164 (12.9)	77 (11.3)
2009–2010	544 (14.5)	1661 (13.1)	5096 (15.8)	133 (19.6)
2011–2012	488 (13.0)	1682 (13.2)	4397 (13.7)	159 (23.4)
2013–2014	517 (13.7)	1623 (12.8)	5048 (15.7)	179 (26.3)
PIR (median (IQR))	1.6 (2.1)	1.6 (2.3)	2.1 (3.0)	3.2 (3.6)
Serum cotinine (ng/mL, median (IQR))	0.18 (25.67)	0.08 (1.82)	0.05 (0.76)	0.03 (0.43)
Cotinine exposure category (*n*, %)				
Active smokers (> 10 ng/mL)	1016 (27.0)	2609 (20.5)	5354 (16.6)	123 (18.1)
Passive smokers (1–10 ng/mL)	368 (9.8)	960 (7.6)	2277 (7.1)	26 (3.8)
Nonsmokers (< 1 ng/mL)	2380 (63.2)	9149 (71.9)	24,545 (76.3)	531 (78.1)
Serum 25(OH)D (nmol/L, median (IQR))	24.4 (6.9)	41.3 (9.9)	68.5 (21.8)	138 (19.0)
VD consumption during past 24 h (*n*, %)				
Yes	1851 (96.8)	5868 (97.8)	17,339 (98.6)	507 (98.3)
No	61 (3.2)	135 (2.25)	249 (1.42)	9 (1.74)
Tobacco/nicotine use (*n*, %)				
Yes	904 (27.2)	2361 (22.6)	5069 (21.3)	107 (18.1)
No	2417 (72.8)	8090 (77.4)	18,704 (78.7)	485 (81.9)
Alcohol consumption (*n*, %)				
Yes	1603 (64.5)	5014 (66.3)	13,800 (73.7)	388 (72.7)
No	884 (35.5)	2546 (33.7)	4926 (26.3)	146 (27.3)
Oral contraceptives use (*n*, %)				
Yes	1006 (51.5)	2591 (49.0)	6668 (59.2)	325 (73.0)
No	946 (48.5)	2700 (51.0)	4595 (40.8)	120 (27.0)
Self-reported kidney health (*n*, %)				
Healthy	2603 (97.0)	7850 (97.0)	19,232 (97.5)	548 (95.3)
Weak/fail	81 (3.0)	239 (3.0)	494 (2.5)	27 (4.7)
Vigorous activity (*n*, %)				
Yes	1181 (32.7)	4367 (38.7)	10,702 (42.4)	246 (38.5)
No	2431 (67.3)	6906 (61.3)	14,528 (57.6)	393 (61.5)
Moderate activity (*n*, %)				
Yes	1711 (47.4)	5930 (52.6)	15,555 (61.7)	408 (63.8)
No	1901 (52.6)	5341 (47.4)	9668 (38.3)	231 (36.2)

Table 3 Association between continuous serum cotinine and 25(OH)D by survey cycle in NHANES 2001–2014

	Entire period (2001–2014)	Cycle 1 (2001–2002)	Cycle 2 (2003–2004)	Cycle 3 (2005–2006)	Cycle 4 (2007–2008)	Cycle 5 (2009–2010)	Cycle 6 (2011–2012)	Cycle 7 (2013–2014)
Crude model	−0.012 (−0.013, −0.011)	−0.012 (−0.015, −0.010)	−0.009 (−0.012, −0.006)	−0.007 (−0.010, −0.005)	−0.006 (−0.009, −0.003)	−0.014 (−0.016, −0.011)	−0.015 (−0.018, −0.012)	−0.016 (−0.019, −0.013)
Adjusted model[a]	−0.011 (−0.012, −0.010)	−0.007 (−0.009, −0.004)	−0.008 (−0.011, −0.005)	−0.006 (−0.008, −0.004)	−0.008 (−0.011, −0.005)	−0.014 (−0.017, −0.012)	−0.015 (−0.018, −0.012)	−0.013 (−0.016, −0.011)

Data are coefficients (95% confidence intervals)

[a] Estimates were adjusted for age (continuous), gender (categorical), ethnicity/race (categorical), PIR (continuous), and BMI (categorical)

for VD deficiency in both females and males. But some differences were displayed. Specifically, among female active smokers, an inverse association was also shown for VD inadequacy (OR = 0.70, 95% CI: 0.52–0.94). Moreover, we observed a strongly positive relationship of active smoking with VD intoxication in male adolescents (OR = 4.02, 95% CI: 1.36–11.90). Among adults aged between 20 and 59 years, active smoking was associated with increased risk of VD deficiency (OR = 1.67, 95% CI: 1.47–1.90) and inadequacy (OR = 1.21, 95% CI: 1.11–1.32). Among female adults, the positive associations and patterns across smoke exposure and VD categories were similar to those in all participants. In male adults, only positive effect on VD deficiency risk remained (OR = 1.41, 95% CI: 1.17–1.70). Besides, active smoking in participants aged ≥ 60 years was related with VD deficiency (OR = 2.30, 95% CI: 1.85–2.86) as well as inadequacy (OR = 1.75, 95% CI: 1.52–2.01). Consistent relations were shown after stratifying by gender.

For passive smoking exposures, there was no evidence of significant associations of passive smoking exposure with VD status among children and adolescents. For adults aged between 20 and 59 years, passive smoking exposure was positively associated with VD deficiency (OR = 1.60, 95% CI: 1.28–2.00). Furthermore, female adults exposed to higher levels of passive smoking were associated with a higher risk of VD intoxication (OR = 1.97, 95% CI: 1.02–3.80). Among participants aged ≥ 60 years, passive smoking exposure was positively associated with increased risk of VD deficiency (OR = 2.04, 95% CI: 1.37–3.03).

When stratified by ethnicity/race, the associations between active smoking and VD deficiency were significant in all race groups in Table 5. Specifically, the association was relatively stronger in non-Hispanic participants when compared with Hispanic and other races. Across ethnicity/race groups, the associations and patterns of active smoking and VD inadequacy were similar to those of VD deficiency. In addition, for Hispanic participants, a strongly positive association was shown between active smoking exposure and VD intoxication (OR = 3.41, 95% CI: 1.72–6.77). Passive smoking exposure was positively associated with VD deficiency among participants whose races are Hispanic (OR = 1.70, 95% CI: 1.25–2.31) and non-Hispanic black (OR = 1.22, 95% CI: 1.04–1.44).

The associations of the active smoking exposure and VD deficiency as well inadequacy were consistently positive for participants across all BMI categories (Table 5). Meanwhile, passive smoking exposure of obese participants was also positively associated with VD deficiency (OR = 1.31, 95% CI: 1.07–1.59).

Results of sensitivity analysis

To exclude the possible influence of VD intake, we further evaluated the effects of tobacco use exposure on VD status among participants aged 20–59 years with adjustment for

Table 4 Associations between tobacco use exposure and suboptimal VD status by survey cycle in NHANES 2001–2014

Exposure	Suboptimal VD status	Entire period (2001–2014)	Cycle 1 (2001–2002)	Cycle 2 (2003–2004)	Cycle 3 (2005–2006)	Cycle 4 (2007–2008)	Cycle 5 (2009–2010)	Cycle 6 (2011–2012)	Cycle 7 (2013–2014)
Active smokers	Deficiency	**2.24 (2.05, 2.45)**	**2.20 (1.69, 2.86)**	**2.12 (1.71, 2.64)**	**1.84 (1.43, 2.38)**	**1.69 (1.32,2.17)**	**2.58 (2.05, 3.23)**	**2.89 (2.28, 3.68)**	**2.78 (2.20, 3.50)**
	Inadequacy	**1.51 (1.43, 1.61)**	**1.48 (1.27, 1.72)**	**1.45 (1.25, 1.69)**	**1.59 (1.38, 1.85)**	**1.42 (1.20,1.68)**	**1.63 (1.40, 1.90)**	**1.55 (1.32, 1.83)**	**1.53 (1.31, 1.79)**
	Intoxication	1.11 (0.90, 1.36)	1.27 (0.53, 3.05)	1.48 (0.77, 2.85)	**2.17 (1.00, 4.73)**	1.26 (0.70,2.24)	0.71 (0.42, 1.18)	0.88 (0.54, 1.44)	**1.50 (1.00, 2.25)**
Passive smokers	Deficiency	**1.30 (1.14, 1.48)**	**1.74 (1.25, 2.42)**	0.98 (0.73, 1.32)	1.34 (0.97, 1.86)	0.93 (0.62,1.39)	1.30 (0.88, 1.90)	**1.59 (1.09, 2.32)**	1.25 (0.88, 1.79)
	Inadequacy	0.99 (0.91, 1.08)	1.01 (0.82, 1.25)	0.94 (0.77, 1.16)	0.95 (0.77, 1.18)	1.13 (0.88.1.45)	0.91 (0.70, 1.18)	1.00 (0.77, 1.29)	0.88 (0.69, 1.12)
	Intoxication	0.88 (0.59, 1.32)	NA	2.25 (0.98, 5.13)	**3.35 (1.20, 9.31)**	1.01 (0.41,2.49)	0.32 (0.08, 1.30)	0.22 (0.03, 1.61)	0.92 (0.33, 2.59)

Suboptimal VD levels were defined according to serum 25(OH)D concentration as deficiency (< 30 nmol/L), inadequacy (30–50 nmol/L), and intoxication (> 125 nmol/L). Data are odds ratios (95% confidence intervals). "NA" indicates the estimates could not be derived in the group due to limited cases. Estimates were adjusted for age (continuous), gender (categorical)), ethnicity/race (categorical), PIR (continuous), and BMI (categorical)

dietary vitamin D intakes (Supplementary Table 4). Significant associations were shown for all types of tobacco smoke exposure and VD deficiency.

Discussion

Our research was based on a national long-term cross-sectional study including 49,338 participants aged ≥ 3 years, revealing an increasing temporal trend in the association between tobacco smoke exposure and VD levels in the US

general population during 2001 to 2014. The regression analyses for both pooled and separate cycles showed consistent effects of tobacco smoke exposure on suboptimal VD levels, with a slight increase in risk over time. Our overall results proved a negative association between serum cotinine and 25(OH)D concentrations, and that tobacco smoke exposure was related to suboptimal VD status, including VD inadequacy and deficiency.

Modification effects by several demographic characteristics on the associations further indicated that there was somewhat age- and gender- difference for the effects of
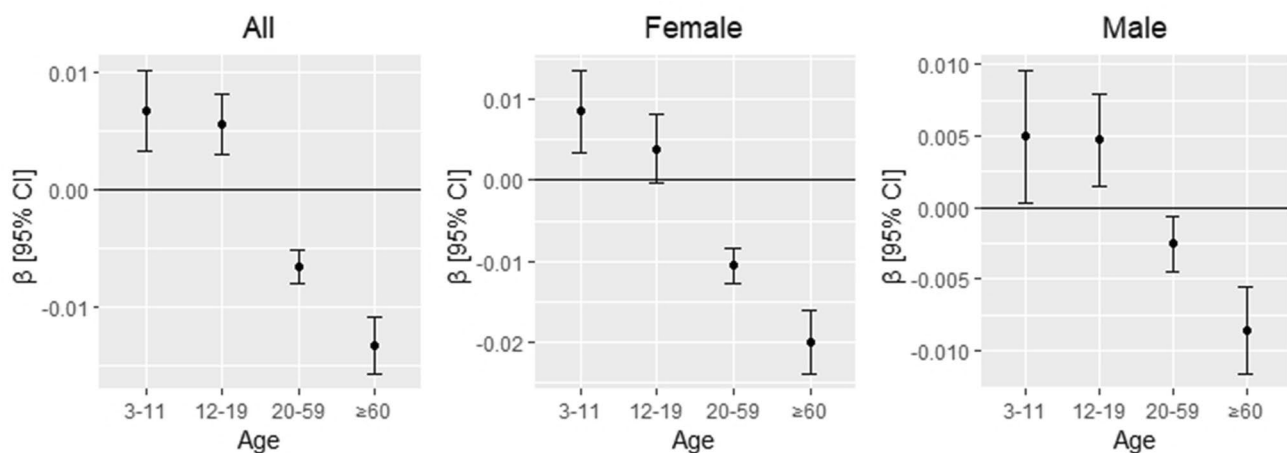
Fig. 2 Association between continuous serum cotinine and vitamin D by age-gender groups in NHANES 2001–2014. Notes: Both cotinine and vitamin D were ln-transformed. Estimates were presented as coefficients and 95% confidence intervals (CIs) and were adjusted for age (continuous), BMI (categorical), ethnicity/race (categorical), PIR (continuous), and NHANES cycle (categorical). Gender was also adjusted in the total population, oral contraceptive use was adjusted for females aged ≥ 12 years, and kidney health (categorical) was adjusted for participants aged ≥ 20 years
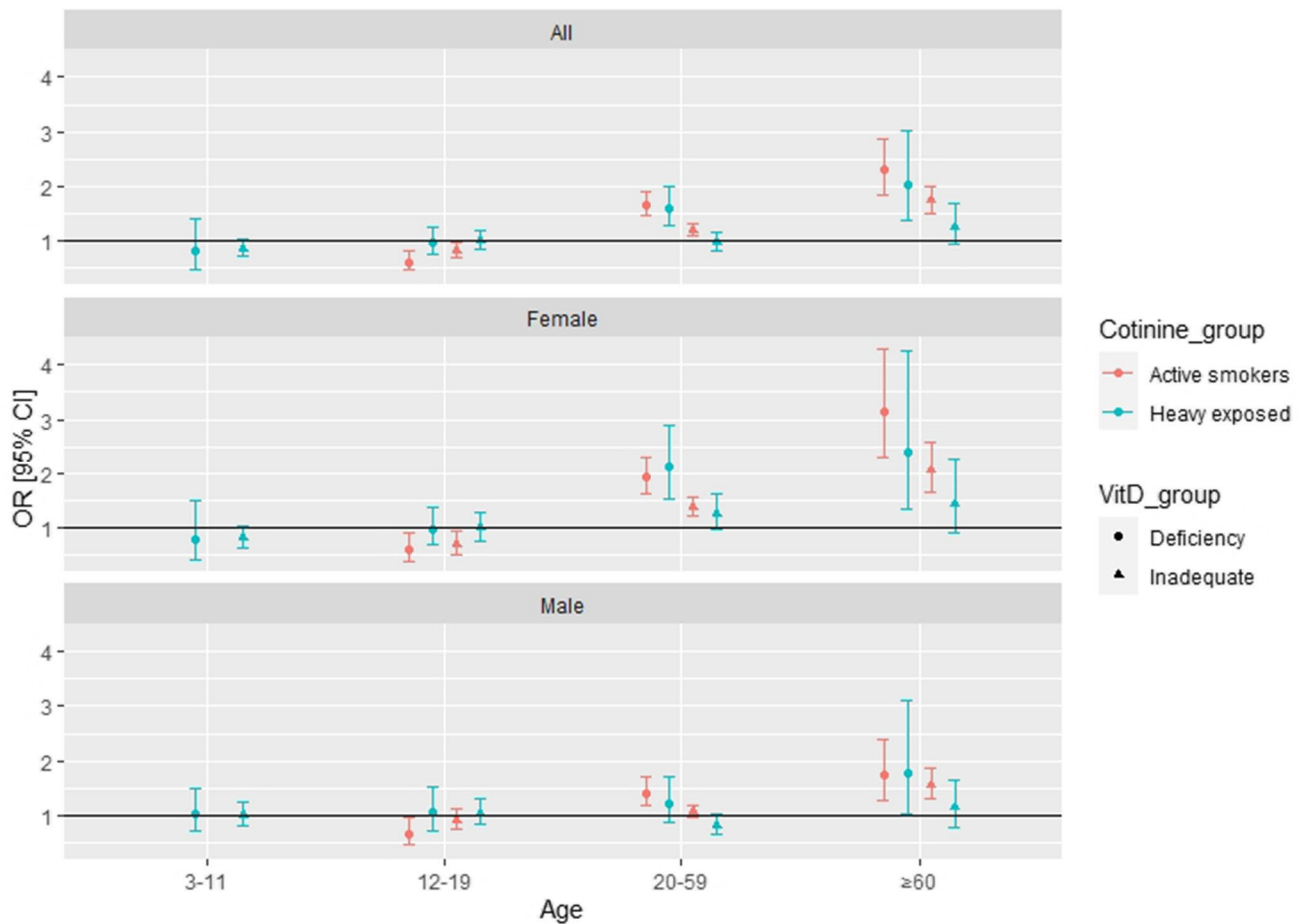
Fig. 3 Association between tobacco smoke exposure and VD status by age-gender groups in NHANES 2001–2014. Notes: Estimates were presented as odd ratios (ORs) and 95% confidence intervals (CIs) and were adjusted for age (continuous), ethnicity/race (categorical), PIR (continuous), BMI (categorical), alcohol use (dichotomous; ≥ 12 years), vigorous activity (dichotomous; ≥ 12 years), moderate activity (dichotomous; ≥ 12 years), kidney health condition (dichotomous; ≥ 20 years), and NHANES cycle (categorical). Gender was also adjusted for total population, and oral use of contraceptives (dichotomous) was additionally adjusted for females aged ≥ 12 years; the estimates could not be derived for active smoking exposure among children aged 3–11 years and passive smoking in adults aged ≥ 60 years due to limited case sizes

tobacco smoke exposure on VD levels. We found that serum cotinine presented a positive association with 25(OH)D concentrations in 3–11 years and 12–19 years old subgroups, whereas a negative relation was shown in 20–59 years and ≥ 60 years old subgroups. No significant relationships were found between tobacco smoke exposure and VD status for children aged 3–11 years. Among active smokers aged 12–19 years, protective effects of tobacco smoke exposure were observed on VD deficiency as well as inadequacy. Both active and passive smoking were significantly associated with enhanced risk of VD deficiency in 20–59 years and ≥ 60-year subgroups. Moreover, active smokers in 20–59-years and ≥ 60-year old subgroups also had increased risk of VD inadequacy. After stratifying by gender, most of the above-mentioned effects persisted for both genders and

were more pronounced in female participants. Our results also provided some evidence concerning impacts of tobacco smoke exposure on VD intoxication, which was rarely investigated in previous studies of the same content.

Our findings for linear relationship between tobacco smoke exposure and serum VD concentrations were partly supported by previous epidemiological studies. A Norwegian study on 205 participants aged ≥ 29 years found that serum 25(OH)D levels were significantly lower in smokers than nonsmokers (Jorde et al. 2005). Results from 293 American females aged 18–45 years demonstrated significant decrease in serum 25-hydroxy-vitamin D3 (25-OHD$_3$) in both active and passive smokers (Soldin et al. 2011). A study of 181 Greece males aged 20–50 found that 25(OH)D was significantly lower in smokers compared to

Table 5 Associations between tobacco use exposure and VD status by ethnicity/race groups in NHANES 2001–2014

	Exposure	Deficiency OR (95% CI)	Inadequacy OR (95% CI)	Intoxication OR (95% CI)
Ethnicity/race[a]				
Hispanic (N = 13,880)	Nonsmokers		Reference	
	Passive smokers	**1.70 (1.25, 2.31)**	1.08 (0.91, 1.29)	NA
	Active smokers	**1.50 (1.20, 1.88)**	**1.30 (1.15, 1.47)**	**3.41 (1.72, 6.77)**
Non-Hispanic Black (N = 11,434)	Nonsmokers		Reference	
	Passive smokers	**1.22 (1.04, 1.44)**	0.90 (0.79, 1.03)	1.15 (0.34, 3.90)
	Active smokers	**2.73 (2.39, 3.13)**	**1.84 (1.63, 2.06)**	1.52 (0.76, 3.01)
Non-Hispanic White (N = 20,257)	Nonsmokers		Reference	
	Passive smokers	1.21 (0.76, 1.93)	1.05 (0.87, 1.26)	0.94 (0.60, 1.47)
	Active smokers	**2.91 (2.37, 3.57)**	**1.64 (1.49, 1.80)**	0.97 (0.76, 1.22)
Other race (N = 3767)	Nonsmokers		Reference	
	Passive smokers	0.71 (0.38, 1.33)	0.85 (0.61, 1.18)	1.45 (0.18, 11.35)
	Active smokers	**2.04 (1.47, 2.81)**	**1.30 (1.05, 1.60)**	0.29 (0.04, 2.18)
BMI[b]				
Normal[c] (N = 19,854)	Nonsmokers		Reference	
	Passive smokers	1.23 (0.99, 1.53)	0.89 (0.77, 1.02)	1.04 (0.61, 1.76)
	Active smokers	**2.47 (2.11, 2.90)**	**1.59 (1.44, 1.76)**	1.20 (0.91, 1.59)
Overweight (N = 13,191)	Nonsmokers		Reference	
	Passive smokers	1.25 (0.93, 1.68)	0.96 (0.80, 1.16)	1.24 (0.59, 2.61)
	Active smokers	**1.98 (1.66, 2.37)**	**1.46 (1.31, 1.63)**	0.86 (0.57, 1.31)
Obese (N = 16,293)	Nonsmokers		Reference	
	Passive smokers	**1.31 (1.07, 1.59)**	1.03 (0.90, 1.19)	0.41 (0.10, 1.68)
	Active smokers	**2.11 (1.83, 2.43)**	**1.43 (1.29, 1.58)**	1.24 (0.75, 2.05)

[a] Estimates were adjusted for gender (categorical), age (continuous), BMI (categorical), PIR (continuous), and NHANES cycle (categorical). "NA" indicates that the analysis could not be derived due to limited cases

[b] Estimates were adjusted for gender (categorical), age (continuous), ethnicity/race (categorical), PIR (continuous), and NHANES cycle (categorical)

[c] Given that there were few cases (1.7%) in the underweight category, underweight and normal weight were combined into one class in the regression analyses

nonsmokers (Kassi et al. 2015). In a cross-sectional study examining the association of smoking status with VD in 612 Chinese males aged 50 years and older, smokers also presented lower serum VD levels than nonsmokers (Jiang et al. 2016). Contrary to our positive relations found for tobacco smoke exposure with 25(OH)D concentrations in young participants aged 3–11-year and 12–19-year subgroups, a cross-sectional study carried out in Italy reported that passive smoking exposure in 152 children aged 5–15 years had lower levels of 25(OH)D (Chinellato et al. 2018). A Sweden cohort study based on 1068 males aged 18–20 years also indicated adverse effects of smoking on 25(OH)D levels (Lorentzon et al. 2007), whereas a nonsignificantly positive relation between smoking exposure and 25(OH)D was shown for pregnant women in an Iranian historical cohort (Banihosseini et al. 2013).

Evidence on the association between tobacco smoke exposure and VD status was rather limited, and there were

no researches to date that estimated the effects of tobacco smoke on VD intoxication. Kassi et al. proved that young male smokers (20–29 years) had increased risk of VD deficiency (Kassi et al. 2015). An increased risk of VD inadequacy was also detected among Spanish smokers aged 18–84 years (Cutillas

-Marco et al. 2012). The NHANES 2001–2006 analyses demonstrated that American female active smokers aged ≥ 18 years had higher prevalence of VD deficiency and inadequacy (Manavi et al. 2015). Although these epidemiological studies were limited to specific populations, their findings supported our results that tobacco smoke exposure, including active and passive smoking, was associated with increased risk of VD deficiency and inadequacy. It is noteworthy that the associations for smoke exposure with VD status were significant for participants with different races and BMI categories, indicating the adverse effects of exposure were stable.

The mechanisms behind the disrupting effects of tobacco smoke on VD are unclear. On the ground of the foregoing experimental and epidemiological evidence, possible mechanisms for tobacco smoke exposure to interfere with VD were recently summarized as several highly likely pathways (Mousavi et al. 2019). First of all, smoking could induce skin aging, and smoking-derived aging may disturb the cutaneous production of VD. Second, dysfunctional VD-parathyroid hormones (PTH) axis due to tobacco smoke exposure could result in disruption of the VD metabolism. In addition, it appears that tobacco smoke is associated with dysregulation of enzymes genes related to the metabolism of VD. Another possible pathway is renal tubular dysfunction caused by tobacco smoke exposure. Heavy metals contained in tobacco may accumulate in kidneys, inhibiting VD activation through impairing kidney function. Besides, it is also hypothesized that tobacco smoke could depress intake of VD due to changed dietary taste. Although the exact explanation related to age difference is unknown, we assume that the observed protective effects of tobacco smoke exposure on VD levels in young people in our study might due to the very small numbers of exposed subjects. Nonetheless, further investigation is warranted to clearly ascertain mechanisms responsible for the reported smoking-VD associations as well as age- and gender- differences.

Our study has multiple strengths. First, our study used a nationally representative sample with a large sample size, which allowed for exploring age- and gender-difference in the associations between tobacco smoke exposure and VD levels as well as potential modifying effects of several important factors. Second, the study provided important evidence for long-term trends in health impacts of tobacco smoke exposure over a 14-year period. Of note, smoking rates were consistently high over time, especially for active smoking among male adults and passive smoking among children. Moreover, protecting public health from tobacco smoke exposure could be made much more effective with understanding of this risk trend. Third, our study was the first to investigate effects of tobacco smoke exposure on VD intoxication, giving more clues on the disruptive role of tobacco smoke.

Our results, however, should be interpreted with caution due to following limitations. First, given the cross-sectional nature of this study, no causal inference could be derived. Future evidence from prospective study design is warranted. Second, cotinine has a short half-life, and the measurement was based on a single spot serum sample. Therefore, the indicators detected could only represent a short-term level and the variation of individuals might be overlooked. In addition, the lack of data on sun exposure such as season and latitude, and dietary intake of VD in NHANES 2001–2006 hindered us from elaborating the possible biological mechanisms. However, after our further adjustment for dietary VD intake for participants with full dietary data in NHANES 2007–2014, significant

associations between tobacco smoke and VD deficiency persisted. Also, although stratified analyses by age, gender, ethnicity/race, and BMI would help identify susceptible population, the multiple testing may also increase the chance of false positive findings. Thus, the current results from stratified analyses were exploratory.

In conclusion, the study indicated an increased trend for associations between tobacco smoke exposure and VD levels during 2001 to 2014. Serum cotinine was significantly and inversely associated with 25(OH)D in adult participants. Tobacco smoke exposure, including both active and passive smoking exposure, was associated with increased risk of VD deficiency in adults. Moreover, active smoking of adults was also related to increased risk of VD inadequacy. These associations showed somewhat gender difference, with consistent and stronger associations observed in female adults. In contrast, the effect of tobacco smoke exposure in children and adolescents aged 3–19 years on VD levels were mostly protective or non-significant. More researches are needed to verify our results.

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Availability of data and materials The data underlying this article will be shared on reasonable request to the corresponding author. The datasets were derived from sources in the public domain: CDC, NCSH, and National Health and Nutrition Examination Survey, https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate The NCHS Research Ethics Review Board (ERB) approval and documented consent was obtained from all participants.

Consent for publication Not applicable.

Competing interest The authors declare no competing interests.

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