National Trends in Tobacco Smoke Exposure and its Disruption on Vitamin D Levels Among U.S. Population, 2001-2014

Lei Yuan (leiy@tongji.edu.cn)  
Shanghai First Maternity and Infant Hospital  
https://orcid.org/0000-0002-4493-701X

Jingyi Ni  
Nanjing Medical University Affiliated Healthcare Hospital for Women and Infants: Nanjing Maternity and Child Health Care Hospital

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Abstract

Background: Persuasive evidence suggests that tobacco smoking is endocrine-disrupting and may interfere with vitamin D (VD) endocrine systems, but supporting research is limited and results vary greatly.

Methods: Data from the National Health and Nutrition Examination Survey, 2001-2014, was used to evaluate the trends in tobacco smoke exposure among U.S. general participants aged ≥3 yr (n=49338). 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 yr) or ethnicity/race groups were disproportionately impacted.

Results: During 2001-2004, the trends of active smoking rates stabilized between 17.2% to 19.6%. Serum cotinine was significantly and inversely associated with 25(OH)D in adult participants (≥20 yr). 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 additionally related to enhanced risk of VD inadequacy. These associations showed somewhat gender difference, with consistent and stronger associations observed in female adults. In contrast, effects of tobacco smoke exposure on VD levels were mostly protective or non-significant among children and adolescents aged 3-19 yr.

Conclusion: The percentage of U.S. general population with active smoking exposure stabilized over the 14-yr period and was still high. Tobacco smoke exposure may disrupt VD levels. Our results also provided initial evidence of active smoking exposure on VD intoxication, which needs to be further verified.

Implication: Convincing studies have linked tobacco use exposure, including active and passive smoking 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 there were no researches to date that estimated their relationship in children and adolescents. This study analyzed national survey data, to evaluate the national trends in tobacco smoke exposure over a decade, and to comprehensively assess the impacts of tobacco smoke exposure on VD levels across specific gender-, age- and ethnicity/race- groups. The evidence suggests that the prevalence of active smoking exposure stabilized over the 14-yr period and was still high. Moreover, tobacco smoke exposure may disrupt vitamin D levels among general population, with age- and gender- differences observed.

1. 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 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 2009). 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).
Substantial declines in smoking rates have been achieved through efforts in public consciousness, education and public policy since 1964 in the United States (National Institute on Drug Abuse, 2020). However, 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 U.S. market since 2007, together with increased flavor choices for both traditional and electronic cigarettes. Recent studies have consistently indicated that the tobacco use exposure in the U.S. general population are 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 U.S. adults aged 20 years or older were active smokers according to their serum cotinine values (Benowitz 2009); meanwhile, differences of age, gender, and ethnicity/race were seen in serum cotinine concentration. Moreover, data from NHANES 2009–2010 reported that about 42% of the U. S. 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 2018).

Emerging evidence suggests that tobacco use smoke is an endocrine disrupter interfering with Vitamin D endocrine systems (VDES) (Mousavi 2019). 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 2020), autoimmune diseases (Sharief 2011; Ahmed 2021), cardiometabolic disorders (Marquina 2018; Pott-Junior 2020), and even worse, coronavirus disease 2019 (COVID-19) risk and severity (Mitchell 2020; Pereira 2020). Substantial evidence also indicates that VD intoxication induces calcium and phosphorus dysregulation, causing damage to tissues and organs (Razzaque 2017). Although VD level was thought to be closely related to sun exposure and dietary intake, accumulating studies have linked tobacco use exposure to dysfunctional VDES accompanied with declined serum levels of VD metabolites (Banihosseini 2013; Iwaniec 2015; Manavi 2015; Nwosu 2018). A previous NHANES 2009–2010 analysis found that tobacco smoke exposure among U.S. children (3–17 years) was independently associated with VD deficiency (VDD) (Nwosu 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 2015). However, a nationwide study from Korea found no association between cotinine-verified smoking and serum VD in adolescents of 10–18 years old (Byun 2017). In addition, these estimations did not consider impacts of exposure on VD intoxication.

To date, there has been limited evidence measuring associations between tobacco use exposure and VD levels, and results varied greatly by time periods, age and gender groups. Therefore, these existing links prompted us to use NHANES data over the entire 14-year period (2001–2014) to: 1) evaluate the trends in tobacco smoke exposure of U.S. general participants, 2) and to comprehensively assess the impacts of tobacco smoke exposure on VD levels across specific gender-, age- and ethnicity/race- groups to identify susceptibility.

2. Methods

2.1 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 U.S. residents (https://www.cdc.gov/nchs/nhanes). Representative participants of all ages were randomly selected through a statistical process using U.S. census information, and were then personally contacted for a home interview concerning sociodemographic characteristics, health history and behaviour. 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 two-year cycle. Currently, serum cotinine was only available among participants aged ≥ 3 years, thus we included a total of 49338 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.

2.2 Measurement of tobacco use 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 hours; nicotine: 2 hours), and wide detection in biological fluids, including blood, urine, saliva, hair and nails (Benowitz 1996; Benowitz 2009; Akinkugbe 2018).

In each survey cycle, about ninety percent 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 two-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/√2). The detection rates of cotinine were summarized in Table 1.
Table 1
Population characteristics with serum cotinine and VD levels in NHANES 2001-2014\textsuperscript{a}.

| NHANES cycle (n %) | All (N = 49338) | 3–11 y (N = 4099) | 12–19 y (N = 4265) | 20–59 (N = 5031) | ≥ 60 (N = 5041) |
|-------------------|-----------------|-------------------|--------------------|------------------|-----------------|
|                   | Female          | Male              | Female             | Male             | Female          | Male             | Female           | Male             | Female           | Male             |
| 2001–2002         | 7017 (14.2)     | 463 (11.3)        | 462 (10.9)         | 1024 (21.2)      | 971 (19.3)      | 1514 (13.8)      | 1343 (13.4)      | 621 (12.2)       | 619 (12.3)       |
| 2003–2004         | 7291 (14.8)     | 609 (14.9)        | 604 (14.2)         | 940 (19.5)       | 994 (19.8)      | 1370 (12.5)      | 1270 (12.7)      | 755 (14.9)       | 749 (14.9)       |
| 2005–2006         | 7343 (14.9)     | 633 (15.4)        | 612 (14.4)         | 941 (19.5)       | 939 (18.7)      | 1583 (14.4)      | 1359 (13.6)      | 612 (12.1)       | 664 (13.2)       |
| 2007–2008         | 6160 (12.5)     | 532 (13.0)        | 579 (13.6)         | 392 (8.1)        | 471 (9.4)       | 1376 (12.5)      | 1283 (12.8)      | 765 (15.1)       | 762 (15.1)       |
| 2009–2010         | 7434 (15.1)     | 602 (14.7)        | 643 (15.1)         | 488 (10.1)       | 577 (11.5)      | 1809 (16.5)      | 1655 (16.5)      | 835 (16.5)       | 825 (16.4)       |
| 2011–2012         | 6726 (13.6)     | 608 (14.8)        | 655 (15.4)         | 480 (10.0)       | 509 (10.1)      | 1586 (14.4)      | 1525 (15.2)      | 679 (13.4)       | 684 (13.6)       |
| 2013–2014         | 7367 (14.9)     | 652 (15.9)        | 701 (16.5)         | 561 (11.6)       | 570 (11.3)      | 1751 (15.9)      | 1588 (15.8)      | 806 (15.9)       | 738 (14.6)       |
| Age [year, mean (SD)] | 35.2 (23.1) | 7.5 (2.5)        | 7.4 (2.5)          | 15.4 (2.3)       | 15.5 (2.3)      | 38.3 (11.3)      | 39.1 (11.3)      | 70.4 (7.0)       | 70.4 (6.9)       |
| Ethnicity/Race (n %) |                   |                   |                   |                   |                   |                   |                   |                   |                   |
| Hispanic          | 13880 (28.1)    | 1493 (36.4)       | 1481 (34.8)        | 1752 (36.3)      | 1705 (33.9)     | 2834 (25.8)      | 2592 (25.9)      | 1062 (20.9)      | 961 (19.1)       |
| Non-Hispanic Black | 11434 (23.2)    | 1126 (27.5)       | 1169 (27.5)        | 1405 (29.1)      | 1529 (30.4)     | 2307 (21.0)      | 2013 (20.1)      | 919 (18.1)       | 966 (19.2)       |
| Non-Hispanic White | 20257 (41.1)    | 1125 (27.4)       | 1236 (29.0)        | 1326 (27.5)      | 1453 (28.9)     | 4880 (44.4)      | 4549 (45.4)      | 2833 (55.8)      | 2855 (56.6)      |
| Other Race        | 3767 (7.6)      | 355 (8.7)         | 370 (8.7)          | 343 (7.1)        | 344 (6.84)      | 968 (8.8)        | 869 (8.7)        | 259 (5.1)        | 259 (5.1)        |
| BMI [kg/m\textsuperscript{2}, mean (SD)] | 26.1 (7.40) | 18.4 (4.2)       | 18.1 (4.0)         | 24.4 (6.3)       | 23.7 (5.9)      | 29.3 (7.8)       | 28.5 (6.2)       | 29.1 (6.5)       | 28.4 (5.3)       |
| BMI category (n %) |                   |                   |                   |                   |                   |                   |                   |                   |                   |
| Normal weight     | 19012 (38.5)    | 2372 (57.9)       | 2410 (56.1)        | 2613 (54.1)      | 2721 (54.1)     | 3459 (31.5)      | 2823 (28.2)      | 1350 (26.6)      | 1264 (25.1)      |
|                              | All          | 3–11 y       | 12–19 y       | 20–59        | ≥ 60         |
|------------------------------|--------------|--------------|--------------|--------------|--------------|
|                              | Female       | Male         | Female       | Male         | Female       | Male         | Female       | Male         |
| Obese                        | 16293 (33.0) | 1112 (27.1)  | 1211 (28.5)  | 1410 (29.2)  | 1447 (28.8)  | 4295 (39.1)  | 3259 (32.5)  | 1948 (38.4)  | 1611 (32.0)  |
| Overweight                   | 13191 (26.7) | 553 (13.5)   | 554 (13.0)   | 717 (14.9)   | 743 (14.8)   | 2994 (27.2)  | 3830 (38.2)  | 1696 (33.4)  | 2104 (41.7)  |
| Underweight                  | 842 (1.7)    | 62 (1.5)     | 81 (1.9)     | 86 (1.8)     | 120 (2.4)    | 241 (2.2)    | 111 (1.1)    | 79 (1.6)     | 62 (1.2)     |
| PIR [median (IQR)]           | 1.9 (2.7)    | 1.3 (2.0)    | 1.4 (2.0)    | 1.5 (2.3)    | 1.6 (2.4)    | 2.1 (3.1)    | 2.3 (3.3)    | 2.0 (2.4)    | 2.3 (2.9)    |
| Alcohol consumption (n %) b  |              |              |              |              |              |              |              |              |              |
| Yes                          | 20805 (65.8) | —            | —            | 104 (40.9)   | 133 (53.6)   | 6438 (58.6)  | 7955 (79.4)  | 2352 (46.4)  | 3823 (75.8)  |
| No                           | 8502 (26.9)  | —            | —            | 142 (55.9)   | 107 (43.1)   | 3437 (31.3)  | 1407 (14.0)  | 2444 (48.2)  | 965 (19.1)   |
| Missing                      | 2321 (7.3)   | —            | —            | 8 (3.1)      | 8 (3.2)      | 1114 (10.1)  | 661 (6.6)    | 277 (5.5)    | 253 (5.0)    |
| Serum cotinine detection rate (n %) c |              |              |              |              |              |              |              |              |              |
| Serum cotinine               | 0.06 (1.13)  | 0.05 (0.32)  | 0.05 (0.33)  | 0.06 (0.55)  | 0.09 (1.06)  | 0.05 (3.45)  | 0.20 (128.97)| 0.03 (0.10)  | 0.04 (0.74)  |
| [ng/mL, median (IQR)]        |              |              |              |              |              |              |              |              |              |
| Cotinine exposure category (n %) |              |              |              |              |              |              |              |              |              |
| Active smokers (> 10 ng/mL)  | 9102 (18.4)  | 19 (0.5)     | 15 (0.4)     | 424 (8.8)    | 761 (15.1)   | 2590 (23.6)  | 3644 (36.4)  | 612 (12.1)   | 1037 (20.6)  |
| Passive smokers (1–10 ng/mL) | 3631 (7.4)   | 562 (13.7)   | 604 (14.2)   | 518 (10.7)   | 586 (11.6)   | 457 (4.2)    | 587 (5.9)    | 127 (2.5)    | 190 (3.8)    |
| Nonsmokers (< 1 ng/mL)       | 36605 (74.2) | 3518 (85.8)  | 3637 (85.5)  | 3884 (80.5)  | 3684 (73.2)  | 7942 (72.3)  | 5792 (57.8)  | 4334 (85.4)  | 3814 (75.7)  |
| Tobacco/nicotine use (n %) d |              |              |              |              |              |              |              |              |              |
| Yes                          | 8441 (20.6)  | —            | —            | 444 (9.20)   | 686 (13.6)   | 2351 (21.4)  | 3644 (36.4)  | 519 (10.2)   | 910 (18.1)   |
| No                           | 29696 (72.5) | —            | —            | 4101 (85.0)  | 4063 (80.8)  | 7529 (68.5)  | 587 (5.9)    | 4284 (84.4)  | 3888 (77.1)  |
|                  | All     | 3–11 y  | 12–19 y | 20–59   | ≥ 60    |
|------------------|---------|---------|---------|---------|---------|
|                  | Female  | Male    | Female  | Male    | Female  | Male    | Female  | Male    | Female  | Male    |
| Missing          | 2846 (6.9) | —       | —       | 281 (5.8) | 282 (5.6) | 1109 (10.1) | 5792 (57.8) | 270 (5.3) | 243 (4.8) |
| **Serum 25(OH)D** | 59.2 (30.4) | 63.1 (23.5) | 66.5 (22.1) | 51.5 (28.0) | 56.1 (26.0) | 58.0 (34.8) | 3644 (36.4) | 64.1 (38.5) | 63.0 (29.6) |
| (ng/mL, median (IQR)) |         |         |         |         |         |         |         |         |         |
| **Continued Table** |         |         |         |         |         |         |         |         |         |
| **VD status category (n %)** |         |         |         |         |         |         |         |         |         |
| Deficiency       | 3764 (7.6) | 89 (2.2) | 39 (0.9) | 606 (12.6) | 342 (6.8) | 1176 (10.7) | 837 (8.4) | 397 (7.8) | 278 (5.5) |
| (< 30nmol/L; <12ng/mL) |         |         |         |         |         |         |         |         |         |
| Inadequacy       | 12718 (25.8) | 773 (18.9) | 601 (14.1) | 1699 (35.2) | 1536 (30.5) | 3020 (27.5) | 2774 (27.7) | 1161 (22.9) | 1154 (22.9) |
| (30-50nmol/L; 12-20ng/mL) |         |         |         |         |         |         |         |         |         |
| Adequacy         | 32176 (65.2) | 3221 (78.6) | 3594 (84.4) | 2474 (51.3) | 3133 (62.3) | 6571 (59.8) | 6350 (63.4) | 3302 (65.1) | 3531 (70.0) |
| (≥ 50nmol/L; ≥20ng/mL) |         |         |         |         |         |         |         |         |         |
| Intoxication     | 680 (1.4) | 16 (0.4) | 22 (0.5) | 47 (1.0) | 20 (0.4) | 222 (2.0) | 62 (0.6) | 213 (4.2) | 78 (1.6) |
| (>125nmol/L; >50ng/mL) |         |         |         |         |         |         |         |         |         |
| **VD consumption during past 24h (n %)** |         |         |         |         |         |         |         |         |         |
| Yes              | 25565 (92.3) | 2173 (90.8) | 2312 (89.7) | 1788 (93.1) | 2007 (94.4) | 6024 (92.4) | 5637 (93.2) | 2827 (91.6) | 2797 (93.0) |
| No               | 454 (1.6) | 16 (0.7) | 17 (0.7) | 56 (2.9) | 42 (2.0) | 135 (2.1) | 105 (1.7) | 43 (1.4) | 40 (1.3) |
| Missing          | 1668 (6.0) | 205 (8.6) | 249 (9.7) | 77 (4.0) | 78 (3.7) | 363 (5.6) | 309 (5.1) | 215 (7.0) | 172 (5.7) |
| **Oral contraceptives use (n %)** |         |         |         |         |         |         |         |         |         |
| Yes              | 10590 (50.7) | —       | —       | 786 (16.3) | —       | 7501 (68.3) | —       | 2303 (45.4) | —       |
| No               |         |         |         |         |         |         |         |         |         |
| Missing          |         |         |         |         |         |         |         |         |         |
|                         | All   | 3–11 y | 12–19 y | 20–59  | ≥ 60   |
|-------------------------|-------|--------|---------|--------|--------|
|                         | Female | Male   | Female  | Male   | Female | Male   | Female  | Male   | Female  | Male   |
| No                      | 8361   | (40.0) | 3513    | (72.8) | 2366   | (21.5) | 2482    | (48.9) |         |        |
| Missing                 | 1937   | (9.3)  | 527     | (10.9) | 1122   | (10.2) | 288     | (5.7)  |         |        |
| Self-reported kidney health (n %)\(\text{a}\) |       |        |         |        |        |        |         |        |         |        |
| Healthy                 | 30233  | (97.1) |         |        | 10750  | (97.8) | 9873    | (98.5) | 4834    | (95.3) |
|                         |        |        | 3513    | (72.8) | 2366   | (21.5) | 2482    | (48.9) |         |        |
| Weak/fail               | 841    | (2.7)  |         |        | 223    | (2.0)  | 141     | (1.4)  | 223     | (4.4)  |
|                         |        |        | 527     | (10.9) |        |        | 9       | (0.1)  |         |        |
| Missing                 | 52     | (0.2)  |         |        | 16     | (0.2)  | 9       | (0.1)  | 16      | (0.3)  |
| Vigorous activity (n %)\(\text{d}\) |       |        |         |        |        |        |         |        |         |        |
| Yes                     | 16496  | (40.3) | 2675    | (55.4) | 3396   | (30.9) | 6134    | (61.2) | 2293    | (45.2) |
|                         |        |        | 3835    | (76.2) | 5029   | (50.2) | 2432    | (48.2) |         |        |
| No                      | 24258  | (59.2) | 2041    | (42.3) | 7593   | (69.1) | 4994    | (49.8) | 4513    | (89.0) |
|                         |        |        | 1079    | (21.4) |        |        | 4038    | (80.1) |         |        |
| Missing                 | 229    | (0.6)  |         |        | 110    | (2.3)  | 0       | (0.0)  | 1       | (0.0)  |
| Moderate activity (n %)\(\text{d}\) |       |        |         |        |        |        |         |        |         |        |
| Yes                     | 23604  | (57.6) | 3020    | (62.6) | 6389   | (58.1) | 2293    | (45.2) | 2607    | (51.7) |
|                         |        |        | 3161    | (62.8) | 6134   | (61.2) |         |        |         |        |
| No                      | 17141  | (41.8) | 1697    | (35.2) | 4599   | (41.9) | 2778    | (54.8) | 2432    | (48.2) |
|                         |        |        | 1748    | (34.7) | 3887   | (38.8) |         |        |         |        |
| Missing                 | 238    | (0.6)  |         |        | 109    | (2.3)  | 1       | (0.0)  | 2       | (0.0)  |

Notes: IQR: Inter quartile range. BMI: body mass index. PIR: Ratio of family income to poverty.

\(\text{a}\) The number of included participants were 49338, with complete data on age, ethnicity/race, BMI, PIR, serum cotinine and 25 (OH) D levels in NHANES 2001–2014.

\(\text{b}\) Only participants aged \(\geq\) 20 years in NHANES 2001–2010, and participants aged \(\geq\) 18 years in NHANES 2011–2014 have data on the variable.

\(\text{c}\) Detection rate: at or above detection limit.

\(\text{d}\) Only participants aged \(\geq\) 12 years have data on the variable.
|                | All | 3–11 y | 12–19 y | 20–59 | ≥ 60 |
|----------------|-----|--------|---------|-------|------|
|                |     | Female | Male    | Female | Male  |
|                |     |        |         |        |      |

Only those participated in NHANES 2007 and later have data on vitamin D consumption during past 24-hours.

Only female participants aged ≥ 12 years have data on the variable.

Only participants aged ≥ 20 years have data on the variable.

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).

### 2.3 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).

U.S. 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/).

### 2.4 Statistical analysis

Because cotinine levels can vary greatly by gender and age, the analyses were 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). 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. We fitted multiple linear regression models to evaluate the linear association between cotinine levels and serum 25(OH)D concentrations. Then logistic regression models were applied to investigate relationship between individual tobacco smoke exposure with VD status within each gender-age group.
For the regression analyses, numbers of potential confounding factors were considered according to previous researches (Juonala 2019; Luo 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 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 was presented in Table 1.

We also performed the stratified analyses by ethnicity/race and BMI categories to examine potential modifying effects as well as to verify the robustness of our findings. Besides, the dietary vitamin D intakes variable has been added to NHANES survey using a 24-hour 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).

3. Results

3.1 Descriptive characteristics
Table 1 summarized the demographic characteristics, indices related to tobacco smoke exposure and VD status of all participants and by gender-age status. Among 49338 participants, there were 24987 (50.6%) females and 24351 (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, 21012 (42.6%) for 20–59, 10114 (20.5%) for ≥ 60 years. The detection frequency was 77.5% for serum cotinine and the overall median concentrations of serum cotinine and 25(OH)D were 0.06 and 59.2 ng/mL, respectively. The overall prevalence of active smoking, passive smoking and nonsmoking exposure were 18.4, 7.4 and 74.2%. Figure 1 illustrated the trends of serum cotinine measurement through the NHANES 2001–2014 period. As expected, the percentage of NHANES participants aged 3 years and older with active smoking exposure (serum cotinine level > 10 ng/mL) stabilized between 17.2–19.6% over the 14-year period (Supplementary Table 1). The proportion of participants with passive smoking exposure (1–10 ng/mL) showed the comparatively downward trends over time and ranged from 5.8–9.3%. 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 (Table 1). In addition, compared with other age groups, children aged 3–11 have a higher percentage of passive smoking exposure (32.1%).

Table 2 described the population characteristics by vitamin D status. The overall prevalence of VD deficiency, inadequacy, sufficiency and intoxication is 7.6, 25.8, 65.2 and 1.4%, respectively.
Table 2
Population characteristics by VD status in NHANES 2001–2014.

|                         | Deficiency N = 3764 | Inadequate N = 12718 | Adequate N = 32176 | Adverse effects 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)          | 15568 (48.4)        | 498 (73.2)             |
| Male                    | 1496 (39.7)         | 6065 (47.7)          | 16608 (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)          | 16511 (51.3)        | 531 (78.1)             |
| Other Race              | 283 (7.5)           | 1071 (8.4)           | 2367 (7.4)          | 46 (6.8)               |
| BMI [kg/m², 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)          | 14013 (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 %)      |                     |                      |                     |                        |
| 01–02                   | 490 (13.0)          | 2105 (16.6)          | 4388 (13.6)         | 34 (5.0)               |
| 03–04                   | 709 (18.8)          | 1860 (14.6)          | 4662 (14.5)         | 60 (8.8)               |
| 05–06                   | 522 (13.9)          | 2362 (18.6)          | 4421 (13.7)         | 38 (5.6)               |
| 07–08                   | 494 (13.1)          | 1425 (11.2)          | 4164 (12.9)         | 77 (11.3)              |
| 09–10                   | 544 (14.5)          | 1661 (13.1)          | 5096 (15.8)         | 133 (19.6)             |
| 11–12                   | 488 (13.0)          | 1682 (13.2)          | 4397 (13.7)         | 159 (23.4)             |
| 13–14                   | 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) |
|                                   | Deficiency | Inadequate | Adequate | Adverse effects |
|-----------------------------------|------------|------------|----------|-----------------|
| N = 3764                          | 2380 (63.2)| 9149 (71.9)| 24545 (76.3)| 531 (78.1)      |
| N = 12718                         |            |            |          |                 |
| N = 32176                         |            |            |          |                 |
| N = 680                           |            |            |          |                 |
| Nonsmokers (< 1 ng/mL)            | 24.4 (6.9) | 41.3 (9.9) | 68.5 (21.8)| 138 (19.0)      |
| Serum VD (ng/mL, median (IQR))    |            |            |          |                 |
| VD consumption during past 24h (n %) |            |            |          |                 |
| Yes                               | 1851 (96.8)| 5868 (97.8)| 17339 (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)| 18704 (78.7)| 485 (81.9)      |
| Alcohol consumption (n %)         |            |            |          |                 |
| Yes                               | 1603 (64.5)| 5014 (66.3)| 13800 (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)| 19232 (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)| 10702 (42.4)| 246 (38.5)      |
| No                                | 2431 (67.3)| 6906 (61.3)| 14528 (57.6)| 393 (61.5)      |
| Moderate activity (n %)           |            |            |          |                 |
| Yes                               | 1711 (47.4)| 5930 (52.6)| 15555 (61.7)| 408 (63.8)      |
| No                                | 1901 (52.6)| 5341 (47.4)| 9668 (38.3)| 231 (36.2)      |

### 3.2 Associations between serum cotinine and 25(OH)D concentrations by gender-age groups

Figure 2 and Supplementary Table 2 presented the associations of continuous serum cotinine with VD indicator by gender-age 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), there were consistent trends in decreasing 25(OH)D with increasing levels of continuous cotinine, and the significant inverse associations were more evident for females.

### 3.3 Associations of tobacco smoke exposure with VD status by gender-age groups

In children, the estimates for active smokers could not be derived due to small sizes (34, 0.4%). There was no evidence of significant associations of passive smoking exposure in children with VD status (Fig. 3 and Supplementary Table 3). For adolescents aged 12–19 years, a significantly protective effect of active smoking was proved on VD deficiency (OR = 0.62, 95% CI: 0.47–0.81). In gender-stratified analyses, the protective effects of active smoking remained consistent 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 active smoking and 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).

For adults aged between 20–59 years, passive smoking exposure was positively associated with VD deficiency (OR = 1.60, 95% CI: 1.28, 2.00). Meanwhile, 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. Furthermore, female adults exposed to higher levels of passive smoking was associated with a higher risk of VD intoxication (OR = 1.97, 95% CI: 1.02, 3.80). In male adults, only positive association between active smoking and VD deficiency remained (OR = 1.41, 95% CI: 1.17, 1.70).

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). Besides, active smoking 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). When stratified by gender, consistent relations and trends remained.

Of note, the associations of tobacco smoke exposure with VD status were stronger in male children and adolescents when compared with females, whereas the association with VD status was stronger in female adults than that in males.

### 3.4 Associations of tobacco smoke exposure with VD status by ethnicity/race and BMI groups

When stratifying by ethnicity/race, 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 between active smoking and VD deficiency were significant in all race groups in Table 3. 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).

Table 3
Associations between tobacco use exposure and VD status by ethnicity/race groups in NHANES 2001–2014.

| Race            | Exposure | Deficiency       | Inadequacy       | Intoxication   |
|-----------------|----------|------------------|------------------|----------------|
|                 |          | OR (95% CI)      | OR (95% CI)      | OR (95% CI)    |
| Hispanic        | Nonsmokers | Reference  |                  |                |
| (N = 13880)     | 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 | Nonsmokers | Reference  |                  |                |
| (N = 11434)     | 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 | Nonsmokers | Reference  |                  |                |
| (N = 20257)     | 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      | Nonsmokers | Reference  |                  |                |
| (N = 3767)      | 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) |

Notes: 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.

The associations of the active smoking exposure and VD deficiency as well inadequacy were consistently positive for participants across all BMI categories (Table 4). Meanwhile, passive smoking exposure of obese participants was also positively associated with VD deficiency (OR = 1.31, 95% CI: 1.07, 1.59).
### Table 4
Associations between tobacco use exposure and VD status by BMI groups in NHANES 2001–2014.

| BMI       | Exposure | Deficiency OR (95% CI) | Inadequate OR (95% CI) | Adverse effects OR (95% CI) |
|-----------|----------|------------------------|------------------------|----------------------------|
| Normal\(^a\) | Nonsmokers | reference |            |                          |
| (N = 19854) | 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 | Nonsmokers | reference |            |                          |
| (N = 13191) | 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 | Nonsmokers | reference |            |                          |
| (N = 16293) | 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) |

Notes: Estimates were adjusted for gender (categorical), age (continuous), ethnicity/race (categorical), PIR (continuous) and NHANES cycle (categorical).

* 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.

### 3.5. 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 (Table 5). Significant associations were shown for all types of tobacco smoke exposure and VD deficiency.
Table 5
Associations between tobacco use exposure and VD status among participants aged 20–59 years in NHANES 2007–2014.

| Exposure       | Deficiency   | Inadequacy   | Intoxication |
|----------------|--------------|--------------|--------------|
|                | OR (95% CI)  | OR (95% CI)  | OR (95% CI)  |
| Total          | Nonsmokers   | reference    |              |
| Passive smokers| 1.37 (1.01, 1.85) | 0.94 (0.75, 1.18) | 1.06 (0.48, 2.33) |
| Active smokers | 1.60 (1.35, 1.88) | 1.08 (0.96, 1.21) | 0.83 (0.57, 1.20) |
| Female         | Nonsmokers   | reference    |              |
| Passive smokers| 1.68 (1.09, 2.59) | 1.27 (0.90, 1.78) | 1.20 (0.47, 3.07) |
| Active smokers | 1.65 (1.31, 2.09) | 1.18 (0.99, 1.40) | 0.76 (0.48, 1.19) |
| Male           | Nonsmokers   | reference    |              |
| Passive smokers| 1.19 (0.77, 1.84) | 0.75 (0.55, 1.07) | 0.92 (0.21, 3.99) |
| Active smokers | 1.52 (1.20, 1.93) | 0.99 (0.85, 1.16) | 1.07 (0.53, 2.17) |

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), vigorous and moderate activity (dichotomous), kidney health condition (dichotomous), NHANES cycle (categorical) and VD intake (continuous). Gender was also adjusted for total population, and oral use of contraceptives (dichotomous) was additionally adjusted for females.

4. Discussion

Our research was based on 49338 participants aged ≥ 3 years in NHANES, 2001–2014. 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 years subgroups. Moreover, active smokers in 20–59 years and ≥ 60 years 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 analyses indicated that there was somewhat age- and gender- difference for the effects of tobacco smoke exposure on VD levels. 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 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 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 2011). A study of 181 Greece males aged 20–50 found that 25(OH)D was significantly lower in smokers compared to nonsmokers (Kassi 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 2016). Contrary to our positive relations found for tobacco smoke exposure with 25(OH)D concentrations in young participants aged 3–11 years and 12–19 years 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 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 2006). Whereas a non-significantly positive relation between smoking exposure and 25(OH)D was shown for pregnant women in an Iranian historical cohort (Banihosseini 2013).

Evidence on the association between tobacco smoke exposure and VD status was rather limited, and there were no researches to date that estimated their relationship in children and adolescents. Kassi et al. proved that young male smokers (20–29 years) had increased risk of VD deficiency (Kassi 2015). An increased risk of VD inadequacy was also detected among Spanish smokers aged 18–84 years (Cutillas-Marco 2012). The NHANES 2001–2006 analyses demonstrated that American female active smokers aged $\geq$ 18 years had higher prevalence of VD deficiency and inadequacy (Manavi 2015). Although these epidemiological studies were limited to adults, 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 mechanism 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 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 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. 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. Second, 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. Third, 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, 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 additionally 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.

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.

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. National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/nhanes/index.htm.

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Figures
Figure 1

Estimated prevalence (%) of active smoking (brown bars) and passive smoking (gray bars) exposure among U.S. population aged ≥3 years; 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.
Figure 2

Association between continuous serum cotinine and vitamin D by gender-age groups in NHANES 2001-2014. 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), 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.
Figure 3

Association between tobacco smoke exposure and VD status by gender-age 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.

Supplementary Files

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