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Urinary 2,5-dichlorophenol and 2,4-dichlorophenol concentrations and prevalent disease among adults in the National Health and Nutrition Examination Survey (NHANES)

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Abstract

OBJECTIVE: To test cross-sectional associations between urinary concentrations of 2,5-dichlorophenol (2,5-DCP) and 2,4-dichlorophenol (2,4-DCP) with the prevalence of cardiovascular disease (CVD), cancer, lung disease, thyroid problems and liver conditions.

METHODS: Logistic regression was used to evaluate associations of urinary concentrations of 2,5-DCP and 2,4-DCP with prevalence of various medical conditions among 3,617 National Health and Nutrition Examination Survey participants from 2007–08 and 2009–10. Odds ratios (OR) and 95% confidence intervals (CI) for each disease were estimated. All regression models were adjusted for urinary creatinine.

RESULTS: We observed a monotonically increasing association between quartiles of 2,5-DCP and prevalence of CVD. After adjustment for sociodemographic and lifestyle characteristics, participants with the highest versus lowest quartile of urinary 2,5-DCP had an OR=1.84 (95% CI: 1.26–2.70) (p-linear trend=0.006). The association was similar with further adjustment for established clinical CVD risk factors. Higher 2,5-DCP was also associated with prevalence of all cancers combined [OR_{Q4 v Q1}=1.50 (1.00, 2.26); p-trend=0.05] and, in exploratory analyses, with gynecologic cancers [OR_{Q4 v Q1}=4.15 (1.51, 11.40; p-trend=0.01)]. No associations were detected between 2,5-DCP and lung diseases, thyroid problems or liver conditions, nor between 2,4-DCP and prevalent disease.

CONCLUSION: In this nationally representative study, higher urinary 2,5-DCP concentrations were associated with greater prevalence of CVD and all cancers combined. Further examination

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Disclosures

None

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may be warranted to assess whether chronic exposure to 2,5-DCP is associated with incidence of adverse health outcomes.

INTRODUCTION

Dichlorophenols (DCPs) and their precursors are known endocrine disruptors commonly found in a variety of consumer and industry products.¹ Exposure to DCPs, such as 2,5-dichlorophenol (2,5-DCP) and 2,4-dichlorophenol (2,4-DCP) generally occurs through inhalation, and they are excreted primarily via urination.¹ 2,5-DCP is a metabolite of para-dichlorobenzene (*p*-DCB, also known as 1,4-DCB),² which has been detected in indoor ambient air³⁴ as it is commonly used for synthesis of dyes and resins and is used in moth balls as well as in room and toilet deodorizers.⁵ Urinary measures of 2,5-DCP are a reliable marker of *p*-DCB exposure.⁶ 2,4-DCP is an intermediate in pesticide production as well as in the manufacturing of triclosan.⁷ The precursor of 2,4-DCP—2,4-dichlorophenoxyacetic acid (2,4-D)—is common in herbicides. Both 2,5-DCP and 2,4-DCP are also byproducts of chlorination of drinking and waste water.²⁷ Between 2003–2010, 2,5-DCP and 2,4-DCP were detected in 81% of urinary samples collected in National Health and Nutrition Examination Survey (NHANES), a nationally representative survey, which is indicative of the ubiquity of these compounds in the environment.⁸

Prior NHANES analyses have reported associations of higher concentrations of 2,5-DCP with greater prevalence of asthma (among atopic wheezers),⁹ allergies,¹⁰ and metabolic abnormalities such as diabetes,¹¹ metabolic syndrome,¹² obesity,¹³¹⁴ adverse concentrations of thyroid function biomarkers among both adult¹⁵ and adolescent¹⁶ participants, and with younger age of menarche among adolescent girls.¹⁷ 2,4-DCP has been included in only some of these NHANES analyses. Higher urinary concentrations of 2,4-DCP were associated with greater prevalence of allergies⁹ and olfactory dysfunction¹⁸ but were not associated with prevalence of metabolic syndrome¹² or obesity in adults¹³ or children,¹⁴ or with age of menarche among adolescent girls.¹⁷ In addition to NHANES, 2,5-DCP has been positively associated with prevalent respiratory diseases among boys (but not girls) aged 6–7 years old,¹⁹ while 2,5-DCP and 2,4-DCP were not associated with inflammatory biomarkers among pregnant Puerto Rican women.²⁰ Little is known about associations of these environmental exposures with other health conditions, such as lung diseases, cardiovascular diseases (CVD) and cancer in adult humans. Considering the pervasiveness of exposure to these chemicals,⁸ and laboratory animal studies suggesting that they have metabolic effects,²¹²² there is a need to comprehensively evaluate whether these chemicals are associated with common medical conditions.

Using data from adult participants of NHANES 2007–2010, we tested the hypotheses that elevated concentrations of urinary 2,5-DCP and 2,4-DCP are associated with higher prevalence of cancer, CVD, lung disease, liver disease and thyroid disease.

MATERIALS AND METHODS

NHANES 2007–2010

Publicly available data from NHANES were used for the present analyses. NHANES is a repeated cross-sectional study that is administered by the U.S. National Center for Health Statistics. Participants were selected using a complex sampling design with certain demographic groups over-represented and to allow for non-response. Participants provided written informed consent. NHANES data collection includes numerous components including computer-assisted questionnaires, anthropometric measurements, non-fasting phlebotomy, and urine collection in a random subset.

For our analyses, two consecutive survey periods were combined (2007–2008, 2009–2010) in order to yield a greater sample size. These survey cycles were chosen as they yielded the largest sample size for the present analyses. The overall response rates were ~80% in 2007–2008 and 2009–2010. A total of 10,149 participants took part in the 2007–2008 survey, and 10,537 in the 2009–2010 survey.

Urinary Measurements

A random sub-sample (one-third) of participants provided spot urine samples that were frozen at -20°C until testing. These samples were used to quantify biomarkers of several phenols, including 2,5-DCP and 2,4-DCP. While 2,4,5-trichlorophenol, 2,4,6-trichlorophenol and o-phenyl phenol were also measured in both survey cycles, over 70% of participants had concentrations below the limit of detection. Therefore, we did not include these phenols in the present analyses.

2,5-DCP and 2,4-DCP were measured at the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention (CDC) as previously described.²³²⁴ Briefly, urinary 2,5-DCP and 2,4-DCP concentrations were quantified using on-line solid phase extraction coupled to high-performance liquid chromatography-isotope dilution tandem mass spectrometry with peak focusing. The lower limit of detections for both 2,5-DCP and 2,4-DCP was $0.2\text{ }\mu\text{g/L}$. Concentrations below the limit of detection were replaced with a value of $0.14\text{ }\mu\text{g/L}$ (equal to limit of detection divided by the square root of two) by NHANES staff. Urinary creatinine was measured at the University of Minnesota Advanced Research and Diagnostic Laboratory (ARDL) using enzymatic methods.²⁵²⁶ No notable changes in laboratory analyzing results or assay methods were reported between the two study periods (2007–2008, 2009–2010).

Prevalent diseases

Participants aged 20 years and older were asked, via questionnaire, “Has a doctor or other health professional ever told you that you have....?” for a variety of conditions, including: asthma, chronic bronchitis, emphysema, coronary heart disease, heart attack, chronic heart failure stroke, cancer, liver disease, and thyroid disease. Participants who reported a previous diagnosis of “cancer or a malignancy” were asked to report the type of cancer they were diagnosed with (up to 3 cancer types could be reported). In addition to examining

associations with all cancers combined, exploratory analyses were conducted for breast and prostate cancers individually as well as groupings consisting of obesity-related cancers [kidney, colon, liver, uterine, breast cancer before menopause (age of diagnosis <50 years)] and gynecological cancers [ovarian, uterine, cervical]. A composite CVD variable was created, which included coronary heart disease, heart attack, chronic heart failure and stroke.

Covariates

Participants self-reported their sociodemographic characteristics and health behaviors. Income and household size data was used to estimate an income-to-poverty ratio. Education was categorized as less than high school, high school graduate, or higher education (e.g. some college, college graduate, graduate school). Based on responses to questions about smoking, we created three groups: current, former (based on lifetime >100 cigarettes but not current), and never. Participants were asked whether they consumed at least 12 alcoholic drinks per year. Participants were also asked to report if they engaged in moderate or vigorous recreational physical activity. For our analyses, we used 2 indicator variables based on whether they said yes to doing any moderate physical activity or yes to doing any vigorous physical activity.

Participants were asked to bring their medication bottles to the exam, where the bottles were transcribed and coded. Diabetes medication use was defined by use of 1 medication classified as an anti-diabetic agent, and blood pressure lowering medication use as 1 medication classified as an anti-hypertensive agent²⁷ [e.g. diuretic, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, calcium-channel blocker, β -blocker, or other antihypertensive agents]. A physiologic exam was also performed, with all measurements conducted using standard protocols by trained staff. Anthropometric measures, including height and weight, were obtained and were used to calculate body mass index (BMI in kg/m²). Blood pressure measurements were performed after participants sat quietly for 4 minutes; 3 consecutive readings were conducted, and the average of the second and third measurement were used for these analyses.

Fasting and non-fasting serum samples were obtained, frozen at -20°C and shipped to ARDL. High-density lipoprotein (HDL-c) and total cholesterol were measured using enzymatic methods. HbA1c was measured in whole blood at the Fairview-University Medical Center in Minneapolis, Minnesota. In 2007–2008, HbA1c was measured using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (for the first 6 months of 2007) and Tosoh G7 HPLC Glycohemoglobin Analyzer for the rest of 2007–2008 and 2009–2010. Diabetes was defined by HbA1c $\geq$ 6.5%, use of an anti-diabetic agent, or self-reported physician diagnosis of diabetes.

Statistical Analysis

Of the 20,686 individuals who participated in the NHANES 2007–2008 and 2009–2010 cycles, we excluded those who were less than 20 years old (n=8,533), pregnant (n=125), had missing 2,5-DCP and 2,4-DCP measurements (n=8,346), and those with missing responses to any health status questions (n=65). The final analytic sample included 3,617 participants; sample weights for the 2007–2008 and 2009–2010 survey cycles were combined per

NHANES guidelines.²⁸ The environmental sub-sample weights were applied to produce nationally representative estimates. Taylor series linearization was used for variance estimation.

2,5-DCP and 2,4-DCP were categorized into quartiles with the lowest quartile serving as the referent group. Unconditional logistic regression was used to generate odds ratios (OR) and 95% confidence intervals (CI) for 2,5-DCP and 2,4-DCP in relation to prevalent disease. All analyses were adjusted for urinary creatinine to account for the influence of hydration. Multiple logistic regression models were used to adjust for confounding characteristics. The first model was adjusted for urinary creatinine, age, race/ethnicity and sex. Due to limited numbers for some subgroups, race/ethnicity was categorized as non-Hispanic white, non-Hispanic black and other. The second model additionally adjusted for other potential confounding characteristics such as income-to-poverty ratio, BMI, smoking, alcohol use, and moderate or vigorous physical activity. BMI was categorized as follows: underweight/normal ($<24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), obese ($\geq 30 \text{ kg/m}^2$). For analyses looking at cardiovascular diseases, a third model was additionally adjusted for total cholesterol, HDL-c, systolic blood pressure (all modeled continuously), antihypertensive medication use and diabetes. In a sensitivity analysis, we restricted our analyses to participants aged 50+ years; since for most diseases in our analyses, prevalence is highest in this sub-group. We also mutually adjusted the final (fully-adjusted) 2,5-DCP models for 2,4-DCP quartiles (and vice versa) when examined in relation to prevalent CVD and cancer.

STATA version 14.1 (StataCorp; College Station, TX) was used for all analyses. Two-tailed p-values of 0.05 were used for tests of statistical significance.

RESULTS

Among the 3,617 NHANES 2007–2010 participants included in our analyses, the weighted mean $\pm$ SD age was 46.9 $\pm$ 16.6 years; 51.2% of included participants were female, 69.5% were non-Hispanic white and 22.3% were non-Hispanic black. The geometric mean concentration of urinary 2,5-DCP was 7.03 ug/L (95% CI: 6.04–8.19) and, in our analytic sample, 2.4% of measurements were below the limit of detection. For urinary 2,4-DCP, the geometric mean concentration was 0.84 ug/L (0.78–0.91) and, in our analytic sample, 12.7% were below the limit of detection. The correlation between ln-transformed 2,4-DCP and ln-transformed 2,5-DCP was high [coefficient of correlation $r=0.83$ ($p<0.001$)].

As shown in Table 1, participants with higher concentrations of 2,5-DCP and 2,4-DCP tended to be obese, have a lower income-to-poverty ratio and were less likely to be non-Hispanic white. Geometric mean concentrations of urinary 2,5-DCP and 2,4-DCP are presented in Supplemental Table 1 by disease status. Briefly, 2,5-DCP concentrations—and to a lesser extent 2,4-DCP—tended to be higher in those with CVD (composite and individual diseases).

Table 2 presents adjusted ORs (95% CIs) for diseases across 2,5-DCP quartiles. Across the various models, we consistently observed a monotonically increasing association between 2,5-DCP quartiles and prevalence of CVD. After adjusting for age, race/ethnicity, sex and

urinary creatinine, participants with the highest compared to lowest quartile of 2,5-DCP had an OR=1.76 (95% CI: 1.22, 2.53; p-linear trend=0.007). The association was similar with further adjustment for sociodemographic and lifestyle characteristics [$OR_{Q4 \text{ v } Q1}=1.84$ (1.26, 2.70); p-trend=0.006], and established clinical CVD risk factors [1.81 (1.19, 2.74); p-trend=0.01]. Considering CVD phenotypes separately, the association was largely driven by prevalent CHD [Model 3 $OR_{Q4 \text{ v } Q1}=2.38$ (1.35, 4.19)]. Higher 2,5-DCP was not statistically significantly associated with prevalent cancer in Model 1 but was statistically significantly associated with prevalent cancer after accounting for sociodemographic and lifestyle characteristics [Model 2 $OR_{Q4 \text{ v } Q1}=1.50$ (1.00, 2.26); p-trend=0.05]. No statistically significant associations were found between 2,5-DCP and lung diseases (asthma, chronic bronchitis, emphysema), thyroid problems or liver conditions. When we added 2,4-DCP quartiles to the final (fully-adjusted) models, 2,5-DCP remained statistically significantly associated with the prevalent CVD composite [$OR_{Q4 \text{ v } Q1}=2.76$ (1.60, 4.76)] but was no longer associated with prevalent cancer [$OR_{Q4 \text{ v } Q1}=1.40$ (0.77, 2.54)]. As shown in Table 3, no statistically significant associations were found between 2,4-DCP and any of the diseases under consideration. After additional adjustment for 2,5-DCP quartiles, 2,4-DCP was still not associated with prevalent cancer [$OR_{Q4 \text{ v } Q1}=0.51$ (0.30, 0.89)] but was inversely associated with CVD composite [$OR_{Q4 \text{ v } Q1}=0.51$ (0.30, 0.89)]

In a sensitivity analysis, we restricted analyses to participants aged ≥ 50 years. Results were largely similar to the main analyses, except in the multivariable-adjusted model, 2,5-DCP concentrations were no longer statistically significantly associated with prevalent cancer (Supplemental Table 2). In exploratory analyses, we looked at associations of 2,5-DCP and 2,4-DCP with prevalent cancer sub-types (Supplemental Table 3). For gynecologic cancers, participants with the highest compared to lowest 2,5-DCP quartile had an OR=4.15 (95% CI: 1.51, 11.40; p-trend=0.01) in the fully adjusted model. No other statistically significant associations were observed between 2,5-DCP and other cancer sub-types, or between 2,4-DCP and any cancer sub-type.

DISCUSSION

In this nationally representative cross-sectional study, higher urinary 2,5-DCP concentrations were associated with greater prevalence of heart disease and greater prevalence of all cancers combined, after accounting for numerous potential covariates. No statistically significant associations were observed between 2,5-DCP and lung, thyroid or liver conditions, nor were any associations found between 2,4-DCP and prevalence of any disease. To our knowledge, this is the first study to examine the association of exposure to 2,5-DCP and 2,4-DCP with a wide array of common chronic diseases in a large, nationally representative study. Of note, both DCPs were associated with BMI in our study, however, only 2,5-DCP was associated with greater prevalence of CVD or cancer.

Prior NHANES studies have examined urinary 2,5-DCP in relation with allergies,⁹ asthma,¹⁰ diabetes,¹¹ obesity,¹³¹⁴ metabolic syndrome,¹² and thyroid function,¹⁵¹⁶ while 2,4-DCP has been examined in relation to allergies,⁹ asthma,¹⁰ diabetes,¹¹ obesity¹³¹⁴ and olfactory dysfunction.¹⁸ In the prior NHANES analysis of DCP and diabetes there was a dose-dependent association between urinary 2,5-DCP quartiles and higher diabetes prevalence;

2,4-DCP was not related to diabetes prevalence.¹¹ Higher 2,5-DCP concentrations were also associated with a greater prevalence of metabolic syndrome in non-diabetic adults; 2,4-DCP was not associated with prevalence of metabolic syndrome.¹² In addition, higher 2,5-DCP concentrations have been associated with elevated thyroid stimulating hormone levels¹⁶ which may predispose individuals to hypothyroidism and subsequent weight gain.²⁹ In the Mount Sinai Children's Environmental Health Study (aged 6–7 years), 2,5-DCP was positively associated with prevalence of a self-reported (by parents) physician diagnosis of asthma (as well as wheezing or atopic skin conditions) among boys but not girls.¹⁹ Our findings did not suggest an overall association between 2,5-DCP and prevalent asthma in the 2007–2010 survey cycles. This is in contrast with a prior publication¹⁰ which examined asthma during the 2005–2006 cycle and reported a positive association between 2,5-DCP and a doctor-diagnosed asthma among atopic wheezers. The discrepancy between findings is mostly likely explained by the fact that the other study examined association in a specific subgroup of asthmatics - those who self-reported wheezing and were defined as atopic. Additionally, prior publications^{15,16} have reported associations between high 2,5-DCP and adverse concentrations of thyroid function biomarkers, while the present study evaluated self-reported thyroid disease, and therefore had less precision to detect associations.

Understanding potential health effects of 2,5-DCP and 2,4-DCP is critical, given the high prevalence (81%) of Americans with evidence of exposure to these chemicals.⁸ The specific mechanisms by which 2,5-DCP and 2,4-DCP may influence health are not fully understood. In occupational settings where *p*-DCB, the precursor to 2,5-DCP, is manufactured or processed, high serum transaminase and white blood cell concentrations have been reported,³⁰ as has liver necrosis.³¹ The International Agency for Research on Cancer considers *p*-DCB a possible human carcinogen (Group 2B), though there is a lack of evidence for carcinogenicity of 2,4-DCP.²² *p*-DCB, is an endocrine disruptor that exerts physiologic influence by mimicking natural hormones in the body.^{32,33} It has been suggested that this endocrine-disruption in turn could contribute to associations with obesity, diabetes and CVD.^{34–36}

Findings from *in vitro* studies and animal models provide additional insight into mechanisms by which DCPs could potentially induce cardio metabolic or carcinogenic effects. After intravenous-administration to rats (10 mg/kg), higher concentrations of 2,4-DCP were found in the kidney as well as in the liver and adipose tissue.³⁷ *In vitro* studies indicate that chlorinated phenols are prone to uncoupling oxidative phosphorylation reactions which can result in ATP depletion within cells.²⁷ In animal studies, *p*-DCB was found to exert *in vitro* and *in vivo* estrogenic activity²¹ and chronic *p*-DCB exposure has been shown to contribute to liver and kidney damage.²² Administration of *p*-DCB at both high (300 mg/kg/day) and low (150 mg/kg/day) doses lead to increased cell proliferation in the livers of rats and mice. While cell proliferation was increased in the kidneys of male rats, no changes were detected at low doses (150 mg/kg/day). No changes in cell proliferation were noted in the kidneys of female rats or in mice of either sex.³⁸ While *p*-DCB has been associated with carcinogenic effects in animal models, these findings may not be applicable to humans.³⁹ For example, acute *p*-DCB exposure contributed to increased frequency of micronuclei formation in rat hepatocytes but not in human hepatocytes.⁴⁰ Based on current literature, we are unaware of specific mechanisms or explanations as to the different findings

between 2,5-DCP and 2,4-DCP, particularly in relation to cardiovascular diseases. Thus, the exact mechanism underlying the potential associations of 2,5 DCP with CVD and cancer in humans are yet to be determined, and these results should be viewed as hypothesis generating.

NHANES is a large nationally representative survey with a wealth of high-quality data, including measures of numerous environmental pollutants that are of potential public health importance. However, given that this is a cross-sectional survey, it is possible that individuals may have had the disease prior to exposure to these chemicals and/or that reverse causality occurred, in that those with the disease may metabolize these chemicals differently. Also, it is unclear whether one-time measurement reflects long-term exposure to DCP. For instance, the half-life of 2,4-DCP is relatively short (4 to 30 minutes).³⁷ Additionally, disease status was not objectively measured in this analysis as participants were asked to self-report disease status. Due to small numbers of individual cancer types, we were largely limited to examining 2,5-DCP and 2,4-DCP in relation to all cancers combined. Intriguingly, in exploratory analysis with cancer sub-types, higher 2,5-DCP was related to greater odds of prevalent gynecological cancers, though effect estimates were imprecise. Next, these findings may not be reflective across the total spectrum of risk as people who died of the diseases could not have taken part in the NHANES survey. Additionally, our results for the CVD composite and cancer were not entirely consistent when we adjusted 2,5-DCP for 2,4-DCP (and vice versa). Of note, these two dichlorophenols had high collinearity [i.e. $r=0.83$ ($p<0.001$)], which complicates interpretation of mutually adjusted results. Lastly, given the number of hypotheses examined, the potential for false positives are worth noting. Taken together, we consider these analyses hypothesis generating.

CONCLUSION

In conclusion, higher urinary concentrations of 2,5-DCP were associated with greater prevalence of cardiovascular diseases and all cancers combined. Further examination is warranted to assess whether chronic exposure to 2,5-DCP is associated with incidence of adverse health outcomes and to assess the pathophysiologic mechanisms through which this may occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGES**What is already known about this subject?**

- Dichlorophenols and their precursors are known endocrine disruptors commonly found in a variety of consumer and industry products.
- Laboratory animal studies suggest that these compounds may have metabolic effects.

What are the new findings?

- Higher urinary 2,5-dichlorophenol concentrations were associated with greater prevalence of heart disease and greater prevalence of all cancers combined.

How might this impact on policy or clinical practice in the foreseeable future?

- Understanding potential health effects of 2,5-dichlorophenol and 2,4-dichlorophenol is critical, given the high prevalence of Americans with evidence of exposure to these chemicals.

Table 1.

Sample sizes and weighted descriptive characteristics stratified by quartiles of 2,5-dichlorophenol and 2,4-dichlorophenol among NHANES participants aged ≥ 20 years, 2007–2010^a

	2,5 DCP Quartiles			
	1	2	3	4
N	881	926	902	908
2,5 DCP, ug/L ^{b, c}	0.79 (0.75–0.84)	3.80 (3.71–3.90)	13.47 (12.95–14.01)	157.44 (137.22–180.63)
2,4 DCP, ug/L ^b	0.32 (0.30–0.34)	0.56 (0.52–0.60)	0.95 (0.91–0.99)	5.07 (4.48–5.74)
Creatinine, g/L	0.73 ± 0.02	1.26 ± 0.03	1.47 ± 0.04	1.51 ± 0.03
Age	48.4 ± 0.6	46.1 ± 0.7	45.9 ± 0.6	47.1 ± 0.7
Sex				
Men	409 (41.5)	473 (49.4)	483 (53.5)	445 (52.4)
Women	472 (58.5)	453 (50.6)	419 (46.5)	463 (47.8)
Race/ethnicity				
Non-Hispanic White	567 (79.7)	511 (76.0)	416 (69.0)	254 (46.6)
Non-Hispanic Black	65 (3.8)	148 (8.8)	198 (12.9)	284 (23.4)
Other	249 (16.5)	267 (15.2)	288 (18.1)	370 (30.0)
Income to poverty ratio	3.3 ± 0.1	3.0 ± 0.1	3.1 ± 0.1	2.6 ± 0.1
Education				
<HS	2124 (14.9)	256 (16.8)	251 (21.0)	314 (25.3)
HS	210 (21.1)	224 (26.3)	226 (23.9)	238 (28.5)
>HS	456 (64.0)	445 (56.8)	425 (55.1)	355 (46.2)
Moderate physical activity (y/n)	368 (48.6)	357 (45.7)	325 (41.1)	296 (37.8)
Vigorous physical activity (y/n)	197 (27.7)	188 (26.4)	192 (24.1)	134 (17.5)
Smoking				
Current	193 (19.2)	209 (22.8)	210 (22.1)	205 (20.7)
Former	248 (27.1)	241 (25.5)	216 (24.1)	195 (22.7)
Never	440 (53.7)	476 (51.7)	476 (53.9)	507 (56.6)
Alcohol (y/n)	603 (76.4)	632 (79.5)	616 (77.4)	559 (71.8)
Body mass index				
Obese	259 (27.2)	316 (32.2)	372 (41.8)	403 (43.5)
Overweight	293 (32.6)	334 (35.7)	291 (32.6)	279 (30.7)
Normal	291 (38.3)	249 (31.5)	215 (24.5)	195 (24.7)
Underweight	18 (1.9)	7 (0.6)	8 (1.1)	10 (1.1)

	2,4 DCP Quartiles			
	1	2	3	4
N	806	893	1,000	918
2,4 DCP, ug/L ^{b, cd}	0.19 (0.18–0.20)	0.52 (0.51–0.53)	1.14 (1.11–1.17)	6.08 (5.47–6.76)
2,5 DCP, ug/L ^b	1.23 (1.10–1.37)	3.82 (3.38–4.33)	8.55 (7.51–9.74)	94.77 (77.16–116.40)
Creatinine, g/L	0.67 ± 0.02	1.13 ± 0.03	1.46 ± 0.03	1.65 ± 0.03

	2,4 DCP Quartiles			
	1	2	3	4
Age	48.0 ± 0.7	46.7 ± 0.7	46.4 ± 0.5	46.5 ± 0.7
Sex				
Men	355 (40.0)	450 (49.7)	559 (55.4)	446 (49.1)
Women	451 (60.0)	443 (50.3)	441 (44.6)	472 (50.9)
Race/ethnicity				
Non-Hispanic White	484 (76.7)	480 (74.4)	499 (71.2)	285 (52.2)
Non-Hispanic Black	81 (5.3)	146 (9.3)	193 (11.2)	275 (21.2)
Other	241 (18.0)	267 (16.3)	308 (17.6)	358 (26.6)
Income to poverty ratio	3.2 ± 0.1	3.1 ± 0.1	3.1 ± 0.1	2.7 ± 0.1
Education				
<HS	208 (15.7)	267 (19.7)	250 (18.1)	310 (23.4)
HS	188 (22.6)	213 (23.7)	256 (24.5)	241 (28.7)
>HS	409 (61.6)	412 (56.6)	494 (57.4)	366 (47.9)
Moderate physical activity (y/n)	325 (47.8)	331 (43.0)	385 (44.5)	305 (38.9)
Vigorous physical activity (y/n)	185 (29.8)	169 (23.5)	212 (25.5)	145 (17.8)
Smoking				
Current	174 (20.0)	219 (22.7)	210 (20.2)	214 (22.1)
Former	226 (26.7)	212 (23.7)	263 (26.8)	199 (22.4)
Never	406 (53.2)	462 (53.6)	526 (53.1)	505 (55.6)
Alcohol (y/n)	540 (77.0)	611 (75.2)	679 (79.3)	580 (74.0)
Body mass index				
Obese	254 (28.6)	313 (34.1)	378 (36.9)	405 (43.3)
Overweight	269 (32.5)	310 (35.5)	349 (34.3)	269 (28.8)
Normal	251 (37.7)	238 (29.5)	247 (27.5)	214 (26.6)

^aWeighted mean ± SE or N (weighted %) unless otherwise indicated

^bGeometric mean (95% CI)

^cRange of 2,5-DCP concentrations by quartiles: Q1 = 0.14–2.0 ug/L; Q2 = 2.1–7.0 ug/L; Q3 = 7.1–30.9 ug/L; Q4 = 31.2–47200.0 ug/L

^dRange of 2,4-DCP concentrations by quartiles: Q1 = 0.14–0.3 ug/L; Q2 = 0.4–0.7 ug/L; Q3 = 0.8–1.9 ug/L; Q4 = 2.0–933.0 ug/L

Table 2.

Weighted odds ratios (95% confidence intervals) for associations between 2,5-DCP quartiles and prevalent disease among NHANES participants aged ≥ 20 years, 2007–2010^a

	2,5 DCP Quartiles				p-linear trend
	1	2	3	4	
N	881	926	902	908	
2,5 DCP, ug/L ^b	0.79 (0.75–0.84)	3.80 (3.71–3.90)	13.47 (12.95–	157.44 (137.22–180.63)	
Lung Diseases					
Asthma, N	130	117	126	118	
Model 1	1 (ref)	0.76 (0.57, 1.03)	0.87 (0.62, 1.23)	0.88 (0.62, 1.24)	0.64
Model 2	1 (ref)	0.74 (0.56, 0.98)	0.91 (0.61, 1.34)	0.84 (0.54, 1.31)	0.65
Chronic Bronchitis, N	56	50	53	59	
Model 1	1 (ref)	0.87 (0.42, 1.79)	1.24 (0.68, 2.25)	1.34 (0.71, 2.53)	0.21
Model 2	1 (ref)	0.93 (0.40, 2.19)	1.36 (0.71, 2.59)	1.30 (0.72, 2.35)	0.15
Emphysema, N	24	20	18	20	
Model 1	1 (ref)	0.98 (0.35, 2.77)	0.72 (0.33, 1.57)	1.18 (0.58, 2.42)	0.93
Model 2	1 (ref)	0.94 (0.33, 2.69)	0.54 (0.24, 1.23)	1.02 (0.43, 2.41)	0.72
Cardiovascular Diseases					
Composite, N ^c	82	101	101	108	
Model 1	1 (ref)	1.34 (0.92, 1.95)	1.48 (0.94, 2.32)	1.76 (1.22, 2.53)	0.007
Model 2	1 (ref)	1.41 (0.95, 2.07)	1.61 (1.00, 2.57)	1.84 (1.26, 2.70)	0.006
Model 3	1 (ref)	1.28 (0.84, 1.95)	1.71 (1.02, 2.88)	1.81 (1.19, 2.74)	0.01
CHD, N ^d	53	70	65	71	
Model 1	1 (ref)	1.45 (0.93, 2.26)	1.44 (0.89, 2.32)	1.97 (1.25, 3.13)	0.007
Model 2	1 (ref)	1.73 (1.04, 2.88)	1.56 (0.93, 2.60)	2.18 (1.24, 3.83)	0.01
Model 3	1 (ref)	1.58 (0.95, 2.63)	1.84 (1.08, 3.16)	2.38 (1.35, 4.19)	0.005
Chronic Heart Failure, N	26	27	27	36	
Model 1	1 (ref)	0.99 (0.49, 2.01)	1.14 (0.54, 2.38)	1.64 (0.83, 3.24)	0.15
Model 2	1 (ref)	0.88 (0.37, 2.06)	1.03 (0.46, 2.31)	1.40 (0.65, 3.02)	0.32
Model 3	1 (ref)	0.69 (0.27, 1.76)	0.85 (0.36, 2.03)	0.95 (0.36, 2.47)	0.94
Stroke, N	31	30	39	38	
Model 1	1 (ref)	0.88 (0.40, 1.93)	1.46 (0.77, 2.76)	1.20 (0.65, 2.21)	0.22
Model 2	1 (ref)	0.65 (0.31, 1.35)	1.30 (0.67, 2.53)	0.98 (0.54, 1.79)	0.74
Model 3	1 (ref)	0.56 (0.25, 1.26)	1.20 (0.56, 2.54)	0.79 (0.41, 1.52)	0.94
Cancer, N	83	90	87	84	
Model 1	1 (ref)	1.00 (0.65, 1.54)	1.29 (0.89, 1.88)	1.29 (0.91, 1.83)	0.08
Model 2	1 (ref)	1.04 (0.66, 1.64)	1.34 (0.91, 1.97)	1.50 (1.00, 2.26)	0.05
Thyroid problems, N	91	88	76	78	
Model 1	1 (ref)	1.00 (0.67, 1.47)	1.13 (0.74, 1.74)	1.02 (0.65, 1.60)	0.75
Model 2	1 (ref)	0.89 (0.62, 1.30)	1.14 (0.71, 1.83)	0.82 (0.51, 1.33)	0.79
Liver Conditions, N	36	32	34	28	

	2,5 DCP Quartiles				p-linear trend
	1	2	3	4	
Model 1	1 (ref)	0.71 (0.40, 1.26)	0.96 (0.57, 1.61)	0.74 (0.39, 1.39)	0.55
Model 2	1 (ref)	0.70 (0.38, 1.29)	0.95 (0.53, 1.71)	0.61 (0.26, 1.44)	0.40

^aModel 1 = age, race/ethnicity, sex, urinary creatinine

Model 2 = Model 1 + BMI category (underweight+normal, overweight, obese), moderate recreational physical activity (yes/no), vigorous recreational physical activity (yes/no), income/poverty ratio, education (<HS, HS, >HS), Smoker (current/former/never), alcohol use (12 drinks per year)

Model 3 = Model 2 + total cholesterol, high-density lipoprotein, systolic blood pressure, antihypertensive medication use, diabetes

^bGeometric mean (95% CI)

^cComposite variable for Cardiovascular Diseases includes coronary heart disease, heart attack, chronic heart failure and stroke

^dCHD = coronary heart disease or heart attack

Table 3.

Weighted odds ratios (95% confidence intervals) for associations between 2,4-DCP quartiles and prevalent disease among NHANES adult participants aged ≥ 20 years, 2007–2010^a

	2,4 DCP Quartiles				p-linear trend
	1	2	3	4	
N	806	893	1000	918	
2,4 DCP, ug/L ^b	0.19 (0.18–0.20)	0.52 (0.51–0.53)	1.14 (1.11–1.17)	6.08 (5.47–6.76)	
Lung Diseases					
Asthma, N	121	122	135	113	
Model 1	1 (ref)	0.90 (0.59, 1.38)	0.78 (0.53, 1.14)	0.83 (0.59, 1.18)	0.21
Model 2	1 (ref)	0.80 (0.51, 1.24)	0.72 (0.46, 1.10)	0.71 (0.47, 1.07)	0.08
Chronic Bronchitis, N	52	42	66	58	
Model 1	1 (ref)	0.84 (0.40, 1.73)	1.24 (0.72, 2.15)	1.51 (0.92, 2.48)	0.07
Model 2	1 (ref)	0.72 (0.35, 1.46)	1.19 (0.65, 2.17)	1.34 (0.79, 2.26)	0.13
Emphysema, N	23	15	18	26	
Model 1	1 (ref)	0.41 (0.15, 1.12)	0.53 (0.28, 1.00)	1.09 (0.45, 2.67)	0.92
Model 2	1 (ref)	0.36 (0.12, 1.06)	0.50 (0.22, 1.11)	0.99 (0.28, 3.48)	0.92
Cardiovascular Diseases					
Composite, N ^c	88	102	102	100	
Model 1	1 (ref)	1.02 (0.64, 1.62)	0.98 (0.61, 1.57)	1.03 (0.73, 1.47)	0.93
Model 2	1 (ref)	1.03 (0.63, 1.69)	0.94 (0.55, 1.62)	0.98 (0.64, 1.49)	0.80
Model 3	1 (ref)	1.02 (0.62, 1.68)	1.08 (0.61, 1.93)	1.07 (0.69, 1.64)	0.73
CHD, N ^d	54	72	70	63	
Model 1	1 (ref)	1.25 (0.73, 2.15)	1.01 (0.61, 1.68)	1.20 (0.82, 1.75)	0.70
Model 2	1 (ref)	1.23 (0.67, 2.28)	1.00 (0.55, 1.81)	1.12 (0.67, 1.87)	0.97
Model 3	1 (ref)	1.34 (0.68, 2.64)	1.29 (0.68, 2.43)	1.34 (0.77, 2.32)	0.41
Chronic Heart Failure, N	27	24	29	36	
Model 1	1 (ref)	0.86 (0.30, 2.42)	0.96 (0.42, 2.18)	1.53 (0.67, 3.54)	0.25
Model 2	1 (ref)	0.89 (0.31, 2.54)	0.83 (0.34, 2.03)	1.31 (0.54, 3.16)	0.55
Model 3	1 (ref)	0.89 (0.28, 2.84)	0.86 (0.31, 2.39)	1.22 (0.44, 3.42)	0.63
Stroke, N	34	31	35	38	
Model 1	1 (ref)	0.66 (0.39, 1.13)	0.80 (0.41, 1.56)	0.81 (0.45, 1.46)	0.67
Model 2	1 (ref)	0.57 (0.32, 1.01)	0.64 (0.30, 1.36)	0.66 (0.31, 1.39)	0.39
Model 3	1 (ref)	0.47 (0.24, 0.92)	0.64 (0.29, 1.43)	0.62 (0.29, 1.35)	0.41
Cancer, N	78	83	102	81	
Model 1	1 (ref)	0.86 (0.60, 1.24)	1.15 (0.77, 1.70)	1.07 (0.69, 1.66)	0.43
Model 2	1 (ref)	0.88 (0.60, 1.28)	1.16 (0.75, 1.80)	1.33 (0.81, 2.18)	0.15
Thyroid problems, N	83	81	88	81	
Model 1	1 (ref)	1.01 (0.67, 1.53)	1.34 (0.86, 2.07)	1.07 (0.67, 1.70)	0.37
Model 2	1 (ref)	1.01 (0.66, 1.54)	1.18 (0.74, 1.88)	0.89 (0.53, 1.49)	0.94

	2,4 DCP Quartiles				p-linear trend
	1	2	3	4	
Liver Condition, N	32	35	30	33	
Model 1	1 (ref)	0.84 (0.47, 1.50)	0.70 (0.35, 1.40)	0.70 (0.41, 1.19)	0.19
Model 2	1 (ref)	0.83 (0.43, 1.59)	0.79 (0.37, 1.71)	0.63 (0.33, 1.23)	0.24

^aModel 1 = age, race/ethnicity, sex, urinary creatinine

Model 2 = Model 1 + BMI category (underweight+normal, overweight, obese), moderate recreational physical activity (yes/no), vigorous recreational physical activity (yes/no), income/poverty ratio, education (<HS, HS, >HS), Smoker (current/former/never), alcohol use (12 drinks per year)

Model 3 = Model 2 + total cholesterol, high-density lipoprotein, systolic blood pressure, antihypertensive medication use, diabetes,

^bGeometric mean (95% CI)

^cComposite variable for Cardiovascular Diseases includes coronary heart disease, heart attack, chronic heart failure and stroke

^dCHD = coronary heart disease or heart attack