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Gender and Sexual Orientation Disparities in Smoking, Cadmium Exposure, and Estimated GFR: National Health and Nutrition Examination Survey 2005-2014

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Master of Public Health

Global Environmental Health

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Bachelor of Science in Biological Sciences, University of Missouri, 2019.

Thesis Committee Chair: Dana Barr, PhD

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Abstract

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Chronic kidney disease (CKD) is a progressive disease characterized by structural, molecular, and functional nephron changes that eventually result in permanent loss of function. CKD can lead to heart disease, stroke, and end stage kidney disease. Studies have linked cadmium exposure to decreased glomerular filtration rate (GFR) and renal pathogenesis. The main non-occupational pathway for cadmium exposure is from tobacco smoke. Lesbian, gay, and bisexual (LGB) individuals have one of the highest subpopulation smoking rates, yet studies have not examined if they have higher cadmium exposure or renal disease burden. The aim of this study was to evaluate gender and sexual orientation disparities in cadmium exposure and estimated glomerular filtration rate (eGFR) in the National Health and Nutrition Examination Survey (NHANES) from 2005-2014 in 16,576 individuals. The analysis used a combination of geometric means and survey linear regression to evaluate cadmium burden and eGFR. The percentage of smokers among LGB participants was higher (44.2%) than in straight participants (28.7%). Comparing geometric mean blood cadmium of males showed that straight men have the lowest cadmium levels (0.297 ng/L) and bisexual men have the highest cadmium levels (0.347 ng/L). Among females, straight females have the lowest cadmium levels (0.354 ng/L) and gay females have the highest cadmium levels (0.446 ng/L). There were statistically significant differences between odds ratios of low eGFR by gender and sexual orientation. Compared to straight males, the odds ratio for low eGFR among gay males was 0.824 (95% CI 0.820, 0.827; $p<0.0003$) bisexual males was 0.634 (95% CI 0.549, 0.555; $p<0.0001$), straight females was 0.844 (95% CI 0.843, 0.845; $p<0.0001$), gay females was 0.783 (95% CI 0.778, 0.788; $p<0.0001$), and bisexual females was 1.092 (95% CI 1.089, 1.096; $p<0.0001$). This analysis highlights the need for additional research specifically addressing disparities related to gender identity and sexual orientation.

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Introduction

Chronic kidney disease (CKD) is a progressive and permanent disease that causes structural, molecular, and functional changes to the nephrons that eventually results in loss of function. Estimated glomerular filtration rate (eGFR), a biomarker for kidney function, is decreased and elimination of wastes and toxins from the body ceases. CKD leads to an array of health problems including but not limited to heart disease, stroke, and end stage kidney disease (ESKD)[1]. More than 1 in 7 adults, or 37 million people, are estimated to have CKD in the U.S[1].

A variety of environmental toxicants have been established as risk factors to CKD, including arsenic, lead, mercury, and cadmium[2]. Studies have shown cadmium is nephrotoxic and carcinogenic at high exposure levels[3-5]. Cadmium exists in abundance in the environment, both naturally and as a product of human activities around fossil fuel use, metal ore combustion, and waste burning[5]. Cadmium is primarily concentrated in soils, where it can accumulate in plants and as a result appears in the food system in vegetables, grains, and tobacco. It is often through the food chain that cadmium accumulates in human organs. Additionally, tobacco has been established as the main source of cadmium exposure in smokers[6]. Most cigarettes contain 1-2 ng of cadmium, and approximately 10% of that is inhaled per cigarette[7].

Higher smoking rates among lesbian, gay, and bisexual (LGB) individuals compared to straight individuals is well established by previous literature. According to a 2016 National Health Interview Survey of adults age 18 and older, about 1 in 5 LGB adults (20.5%) smoke cigarettes compared to about 1 in 6 heterosexual adults (15.3%)[8]. The objective of this study is to evaluate gender and sexual orientation disparities in the associations of blood cadmium with eGFR and CKD in United States adults from 2005-2014 who participated in the National Health and Nutrition Examination Survey (NHANES).

Literature Review

Our understanding of cadmium exposure has changed dramatically over the past century due to advancing research. The main routes of cadmium exposure are through diet, ambient air, occupational exposures, and smoking. Historically, diet was considered the major source of cadmium exposure, emanating to age-dependent cumulative increase in the body burden of cadmium[7].

In 1972, the contribution of cigarette smoking to cadmium accumulation in organs was established[9]. One of the first studies comparing cadmium burden in nonsmokers and smokers was from an analysis of human necropsy material, which showed non-smokers accumulate smaller amounts of cadmium in their organs than smokers[9]. The authors suggested this was linked to cadmium content in cigarettes being relatively high, and the pulmonary absorption of inhaled cadmium being much higher (10-50%) than the amount of cadmium absorbed through ingestion (1-10%)[7,10]. It is estimated that a person smoking 20 cigarettes per day will absorb 1 ng of cadmium daily[11]. Therefore, smokers have on average four to five times higher blood cadmium concentrations as nonsmokers[7] which leads to detrimental health effects given that cadmium accumulates in organs and ten to thirty year half-life.

Previous research reveals smoking rates are not equal among specific populations. Sexual minorities have a higher smoking prevalence than many other subpopulations[8]. A systematic review of tobacco usage among sexual minorities from 1987 to 2000, found that the prevalence of smoking among LGBT individuals is between 1.5 to 2.5 times higher than their straight counterparts[8]. Bisexual men and women appear to have the highest smoking rates across sexual orientation. The Behavioral Risk Factor Surveillance System (BRFSS) found that from 2003-2006, that among bisexual women, the odds of smoking ranged from 1.5 to 3.5 times higher than for straight women[12]. The odds of smoking for bisexual men were 0.9 to 2.6 times higher than compared to

straight men[12]. However, research has not established whether this populations higher smoking prevalence has led to higher cadmium exposure and associated health outcomes.

The earliest observations concerning cadmium induced health effects were from an clinical medicine report in 1858 on delayed respiratory symptoms and acute gastrointestinal symptoms in people using cadmium-carbonate powder as a polishing agent[13]. Damage to the lungs from occupational cadmium exposure was later documented in 1938[13]. In the 1940's, bone effects and proteinuria were connected to cadmium exposure. Following World War II citizens in Japan discovered a form of renal osteomalacia, Itai Itai disease, that stemmed from chronic cadmium exposure in rice fields with a cadmium-polluting mine upstream[14]. Anemia, gastrointestinal, and renal dysfunction were other findings in the same population[14,15].

Subsequently, the toxicokinetics and toxicodynamics of cadmium were described in animals, and showed the level of cadmium absorbed is initially highest in the liver, and then gradually increases in the kidneys over the following weeks after a single exposure[16]. After cadmium is absorbed into the blood plasma, it is bound to albumin and other high-molecular weight proteins, where it is then taken up by the liver. After the uptake in the liver, cadmium is released from albumin and binds to metallothionein (MT)[17] .The low molecular weight of the cadmium-binding protein MT allows for it to be carried to the kidney[18]. These findings led to the kidneys to be identified as the critical organs in the development of more severe health effects of cadmium[17].

The first sign of renal damage is typically irreversible tubular dysfunction, expressed by an increased excretion of low molecular weight proteins such as B2-microglobulin, a1-microglobulin, and retinol binding proteins, or enzymes such as lysosomal enzyme N-acetyl glycosaminidase[19]. Cellular and functional damage in the tubules result in a loss of calcium, amino acids, enzymes, and proteinuria. The tubular proteinuria may progress to decreased glomerular filtration rate (GFR) leading to reserve filtration capacity depletion[5,20]. Studies in environmentally exposed populations

indicate that decreased GFR and creatinine may occur at a similar cadmium doses as the tubular damage[21-23]. Severe cadmium toxicity induces nephrotoxicity that can result in renal failure, and a variety of complications such as aminoaciduria, glucosuria, hypophosphaturia, hypercalciuria, polyuria, and decreased buffering capacity[24].

Cadmium may also lead to diabetes- induced effects on the kidney[22,25,26]. An NHANES study of 8,722 adults ages 40 or older showed urinary cadmium levels are significantly associated with impaired fasting glucose and diabetes, suggesting that cadmium could contribute to prediabetes and diabetes mellitus in adults[27]. The same study found clear dose-response relationships between urinary cadmium, fasting glucose, and diabetes, with an odds ratio of 2.05 (95% CI 1.42-2.95) for fasting glucose and 1.45 (95% CI 1.07-1.97) for diabetes at urinary cadmium levels of 1 ng/g or above[27].

Renal damage may further progress to End Stage Renal Disease (ESRD), and in extreme cases death if exposure is high and prolonged or if exposure occurs with other predisposing health factors[11]. A study based on records of all persons of a population residing in cadmium-polluted areas found a double risk of ESRD in persons living close (<2 km) near the industrial cadmium emitting plants[28].

Studies have also established cadmium as a carcinogen. A review of 36 epidemiological and clinical studies of cadmium and renal cancer found that occupational exposures are associated with increased risk of renal cancer (OR: 1.2 – 5.0)[29]. A case-control study of bladder cancer found an odds ratio at increased blood cadmium concentration of 5.7 (95% CI 3.3-9.9) after adjusting for occupational exposures and cigarette smoking[30]. Increased overall mortality among residents in cadmium-polluted areas has been reported in Japan at urinary cadmium levels as low as >2 and >3 ng/g creatinine[31,32].

Renal disease burden is also not equal among subpopulations. One of the first documented cadmium-induced renal diseases, Itai-itai, affected almost exclusively multiparous or elderly women. Despite this, there was no change in the direction of the subsequent cadmium research and risk assessment to account for gender differences for decades. As for most other chemicals and environmental exposures, the health risk assessments on cadmium and other toxic metals have largely been based on data on occupationally-exposed men[33]. The gender-exclusive results have been used as if they were representative of the general population, including women, children and elderly. Even though many epidemiological studies of mixed gender population groups reported data separately for men and women, gender differences were seldomly reported. Gender differences in the toxic effect of chemicals are to be expected[33]. However, a review of publications in 1997 in occupational health epidemiology found that women are less often studied than men, and that gender factors are rarely investigated in many mixed studies[34].

The few studies on gender differences in cadmium-induced renal disease have found that at similar exposure levels, women have higher blood and urine cadmium concentrations[28,35-38]. In cadmium-polluted areas, cadmium-induced renal disease has been shown to be more common and severe in women[28,35-38]. Several risk factors for women have been proposed, including more serious types of renal tubular dysfunction, differences in calcium metabolism and its regulatory hormones, kidney sensitivity, pregnancy, body iron store status, and genetic factors[35]. Less is known about gender differences in cadmium susceptibility. An increasing number of studies point towards differences between men and women in uptake and distribution of cadmium. The main reason for the higher body burden in women is increased intestinal absorption of dietary cadmium at low iron stores[39,40]. These differences likely result in disparities in health effects. Thus, there is reason to believe that males and females may differ in susceptibility, but additional research is needed to confirm [33].

Social disparities related to race, ethnicity, low socioeconomic status, and poverty also contribute to a higher susceptibility to potential environmental nephrotoxicants, which in turn may partially explain the excess risk of kidney disease among racial and ethnic subpopulations[41-46]. There has been little research on whether sexual minorities face higher environmental burdens than their heterosexual counterparts. However, there has been research confirming sexual minorities exhibit significantly more adverse physical and mental health conditions than their heterosexual counterparts[47]. Minority stress theory[48] proposes that LGB individuals experience greater social stressors because of their stigmatized minority status. Several empirical studies evidence the importance of minority stress for understanding health (e.g., mental health, physical health problems, smoking, obesity)[49]. This suggests social determinants of health could also impact the biological processes of environmental exposures. The environment justice hypothesis, which is part of the Environmental Justice Movement, states that hazards in the physical and chemical environment disproportionately affect those individuals and households that also face hazards in their social environment[50]. Sexual minorities face a multitude of social hazards such as discrimination and prejudice. The CDC and Healthy People 2020 included LGBT health as a core topic area for the first time in efforts to increase overall societal health[51]. Other agencies, such as the National Institutes of Health, now recognize gender and sexual minorities as a health disparity population, and support efforts to reduce related health disparities[52]. Minorities of gender and sexual orientation may face increased risk of cadmium exposure and associated health outcomes because of compounded minority stress and other social determinants, but additional research is needed to quantify these risk differences and increase overall societal health. Understanding the interplay between genetic susceptibility, lifestyle and environmental exposures that underlie cadmium exposure and associated conditions is essential for shifting the focus on documenting disparities to eliminating them.

Materials and Methods

Study Population:

The National Health and Nutrition Examination Survey (NHANES) is a multi-level cross-sectional study of the United States civilian population conducted continuously since 1999 in 2 year cycles. NHANES participants were selected based on their age, sex, and racial/ethnic background through a complex statistical process of weighting and censoring using the most recent census information. Informed written consent was obtained from all participants. The National Centers for Health Statistics, CDC, Institutional Review Board reviewed and approved the study protocols from NHANES 1999 onward. NHANES is a deidentified and publicly available database, therefore no further IRB review for data analysis was necessary. Weighting was adjusted to include five NHANES cycles (2005-2014). For the purposes of this study, blood cadmium levels were analyzed from 16,576 individuals from five NHANES cycles spanning from 2005-2014. All participants age 18 and older that completed the sexual behavior survey and completed the laboratory cadmium measurements were included. Of these individuals, 15,727 self-identified as straight or heterosexual, and 744 self- identified as lesbian, gay, or bisexual (LGB) and 105 self-identified as other. Sociodemographic information and medical histories of survey participants and their families were collected during the household interview.

Gender and Sexual Orientation

A new variable was created that incorporated gender and self-identified sexual orientation to examine disparities in cadmium exposure and chronic kidney disease outcomes. Sexual orientation survey responses included “heterosexual/straight”, “homosexual/gay”, “bisexual”, “something else”, “not sure”, “refused”, or “don’t know”. Participants that responded “not sure”, “refused”,

"don't know", or no response were not included in the analysis. The following variables were included in the analysis: male heterosexual/straight, male homosexual/gay, male bisexual, male other, female heterosexual/straight, female homosexual/gay, female bisexual, or female other.

Blood cadmium

NHANES blood and urine sample collection and processing for metal analysis have been described previously[1]. Blood cadmium was measured using inductively coupled plasma-mass spectrometry techniques. Blood cadmium is considered the most valid marker of recent exposure and is usually assessed in whole blood[11,53]. The half-life of cadmium in blood displays a fast component of 3 to 4 months and a slow component of 10 years[54]. As a result, blood cadmium is a biomarker of both acute and long-term, low-level exposure[7]. The distributions of blood cadmium were right skewed and were natural log-transformed for the analysis. The limits of detection (LODs) for NHANES cycles 2005-2010 were 0.2 ng/L, 2011-2012 was 0.11 ng/L, and 2013-2014 was 0.10 ng/L. For statistical purposes, an imputed value of the LOD divided by the square root of 2 was used when data were <LOD[55].

Smoking assessment

Serum cotinine levels (ng/mL) were measured using an isotope dilution- high performance liquid chromatography/atmospheric pressure chemical ionization-tandem mass spectrometry method[56]. Blood cotinine measurements were used as an approximation for current smoking status. The strength of using the biomarker cotinine as a biomarker for smoking status is that 72% of nicotine is converted to cotinine, and it has a longer half-life (17 h) in comparison to nicotine (3 h)[57,58]. Blood cotinine levels ≤10 ng/ml were classified as non-smoking, and blood cotinine levels

>10 ng/ml were classified as smoking, per the recommendation of CDC's National Biomonitoring Program[59].

Measures of kidney outcomes

NHANES measured serum creatinine using the Jaffe method with the Beckman Synchron LX20 and Beckman UniCel® DxC800 Synchron[1]. The five NHANES cycles provided serum creatinine measures traceable to an isotope dilution-mass spectroscopy (IDMS) method. The CKD-EPI equation was used to estimate glomerular filtration rate (eGFR), as an indicator of glomerular function:

$$141 \text{ x } \min\left(\frac{\text{Scr}}{\text{k}}, 1\right)^{\alpha} \text{ x } \max\left(\frac{\text{Scr}}{\text{k}}, 1\right)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.018 \text{ [if female]} \text{ x } 1.159 \text{ [if Black]}$$

where α = -0.329 for females and -0.411 for males [60].

Chronic kidney disease stages were derived from eGFR estimates and used to create the categorical outcome. eGFR ≥ 90 mL/min/1.73m^2 was classified as normal, eGFR between 60-90 mL/min/1.73m^2 classified as risk of chronic kidney disease stage 1 and 2, eGFR between 30-59.9 mL/min/1.73m^2 classified as risk of chronic kidney disease stage 3, and eGFR ≤ 30 mL/min/1.73m^2 classified as risk of chronic kidney disease stage 4 and 5.

Covariates

Variables included from the NHANES surveys included self-reported sexual behavior, age (continuous; years), sex (male/female), race and ethnicity (non-Hispanic white, non-Hispanic black,

Hispanic, or other), household income (ratio of family income to poverty), education (less than high school, high school graduate, some college, or college graduate/added education beyond college), hypertension (yes/no), taking prescription for hypertension (yes/no), alcohol use (ever had 5 or more drinks per day), diagnosed diabetes (yes/no), insulin (yes/no), diabetic pills (yes/no), and weak/failing kidneys (yes/no). A combined gender and sexual orientation variable was created. Blood pressure was measured four times after 5 minutes of rest during the health examination, and the median of these four attempts was calculated. Smoking exposure was approximated using serum cotinine.

Statistical analysis

SAS software (version 9.4) was used to produce estimates, regression coefficients, and Spearman correlation coefficients. The distribution of cadmium was right skewed, and was natural log transformed for linear and logistic regression. Geometric means and 95% confidence intervals were calculated for normally distributed and skewed variables.

Multivariable linear regression models were built for continuous outcomes (eGFR and log-transformed blood cadmium) and logistic regression models were built for categorical outcomes (CKD and blood cadmium quartiles). Models were created using backward stepwise elimination with selection based on significance level (<p=0.05).

Results

In the sample of 16,576 participants, blood cadmium levels ranged from 0.07 ng/L to 9.3 ng/L. The geometric mean of cadmium for the study population was 0.326 ng/L (95% CI: 0.322, 0.331). As shown in Table 1, geometric mean levels of blood cadmium were highest among female

LGB (Table 1). When gender and sexual orientation were separated, male and female heterosexual individuals had geometric mean blood cadmium of 0.324 (95 % CI 0.318, 0.329) ng/L and male and female sexual LGB individuals had geometric mean blood cadmium 0.376 (95 % CI 0.346, 0.409), representing a 13% increase.

Table 1. Geometric mean blood cadmium levels across gender and sexual orientation. US population, National Health and Nutrition Examination Survey, 2005-2014.

Gender and Sexual Orientation	Blood Cadmium Geometric Mean (ng/L)
Male	
Straight	0.297 (95% CI 0.289, 0.305)
Gay	0.314 (95% CI 0.257, 0.383)
Bisexual	0.347 (95% CI 0.269, 0.449)
Other	0.303 (95% CI 0.240, 0.384)
Female	
Straight	0.354 (95% CI 0.346, 0.363)
Gay	0.446 (95% CI 0.356, 0.560)
Bisexual	0.422 (95% CI 0.374, 0.476)
Other	0.356 (95% CI 0.259, 0.489)

Smoking status was classified based on cotinine levels greater than 10 ng/L. The percentage of men classified as smokers was 35.5%, and the percentage of females classified as smokers were 23.3%. The percentage of straight people classified with smoke exposure was 28.7% and the percentage of LGB people classified as smokers was 44.2%.

Table 2. Number and percentage of smoking versus nonsmoking study participants by gender and sexual orientation. Smoking status was determined using blood cotinine levels with cotinine greater than 10 ng/ml classified as smoking. US population, National Health and Nutrition Examination Survey, 2005-2014.

	Males (n, %)				Females (n, %)			
	Straight	**Gay**	**Bisexual**	**Other**	**Straight**	**Gay**	**Bisexual**	**Other**
Cotinine >10 ng/mL	2657 (17%)	52 (0.3%)	54 (0.3%)	15 (0.0%)	1648 (10%)	45 (0.3%)	165 (1%)	12 (0%)
Cotinine ≤10 ng/mL	4851 (31%)	110 (0.7%)	64 (0.4%)	25 (0.2%)	5868 (37%)	57 (0.4%)	167 (1.1%)	49 (0.3%)

The eGFR was calculated using the equation above. The mean eGFR was 99.52 mL/minute/1.73m^2 (95% CI 99.14, 99.90). The number of participants with reduced eGFR, defined as eGFR < 90 mL/min/1.73m^2 or the 25th percentile, was 3,499 participants or 21.1% of population. The percentage of women with reduced eGFR was 25.4% and the percentage of men was 31%. The percentage of straight participants with reduced eGFR was 22.1%, and the percentage of LBG individuals was 28.4%, representing a 22% increase in reduced eGFR based on sexual orientation.

Demographic and clinical characteristics of the study sample by geometric mean eGFR and blood cadmium estimates are in Table 3. Geometric mean cadmium levels increased with age, hypertension, diabetes, weak/failing kidneys, and smoking, and was higher among women and LGB individuals. Geometric mean cadmium levels varied across race and decreased with higher education, increased poverty income ratio, and insulin use.

Estimated glomerular filtration rate decreased with age, higher education, poverty income ratio, hypertension, diabetes, insulin use, weak/failing kidneys, nonsmokers. Estimated glomerular filtration rate varied across gender, sexual orientation, and race.

Table 3. Weighted demographic and clinical characteristics of NHANES 2005-2014 participants overall and by outcome (N=16,576). US population, National Health and Nutrition Examination Survey, 2005-2014.

	Overall N (%)	*Continuous eGFR* Geometric Mean (95% CI)*	*Blood cadmium concentrations ng/L, Geometric Mean (95% CI)*
Age in Years			
18-39	9,000 (54.30)	109.39 (108.97, 109.82)	0.289 (0.281, 0.294)
40-59	7576 (45.70)	90.30 (89.80, 90.81)	0.370 (0.360, 0.380)
Gender and Sexual Orientation			
Male Straight	7,872 (47.49)	98.79 (98.28, 99.30)	0.297 (0.290, 0.305)
Male Gay	167 (1.01)	99.81 (96.71, 102.10)	0.314 (0.257, 0.383)
Male Bisexual	121 (0.73)	102.90 (99.07, 106.97)	0.347 (0.269, 0.449)
Male Other	43 (0.26)	98.51 (90.48, 107.24)	0.303 (0.240, 0.384)
Female Straight	7,855 (47.39)	99.98 (99.34, 100.59)	0.354 (0.346, 0.363)
Female Gay	109 (0.66)	101.04 (96.86, 105.39)	0.446 (0.356, 0.560)
Female Bisexual	347 (2.09)	104.66 (101.81, 107.58)	0.422 (0.374, 0.476)
Female Other	62 (0.37)	108.27 (103.68, 113.07)	
Race/Ethnicity	N= 16,576		
Mexican American	2,897 (17.5)	109.39 (108.62, 110.16)	0.267 (0.260, 0.275)
Other Hispanic	1,502 (9.1)	104.67 (103.49, 105.85)	0.291 (0.279, 0.304)
Non-Hispanic White	7,072 (42.7)	96.40 (95.87, 96.85)	0.325 (0.317, 0.333)
Non-Hispanic Black	3,578 (21.6)	106.27 (105.24, 107.29)	0.372 (0.361, 0.384)
Other	1,527 (9.2)	102.56 (101.30, 103.84)	0.396 (0.374, 0.419)
Education	N= 15,725		
< High School	3,361 (21.4)	104.00 (103.14, 104.86)	0.436 (0.417,0.455)
High School Graduate	3,544 (22.5)	99.39 (98.54, 100.25)	0.380 (0.365, 0.396)
Some college	5,045 (32.1)	99.34 (98.69, 100.03)	0.324 (0.314, 0.335)
College Graduate or above	3,775 (24)	95.81 (95.09, 96.54)	0.263 (0.256, 0.270)
Poverty Income Ratio (0-5)	N= 16,576		
< 1.5	7,226 (43.6)	104.00 (103.32, 104.68)	0.384 (0.373, 0.396)
< 3	3,533 (21.3)	101.29 (100.48, 102.11)	0.331 (0.318, 0.245)
> 3	5,817 (35.1)	95.97 (95.42, 96.52)	0.292 (0.285, 0.300)
Blood Pressure Measurements	N= 16,576		
Systolic < 140	15,367 (92.7)	93.49 (91.88, 95.13)	0.322 (0.316, 0.328)
Systolic > 140	1,209 (7.3)	99.98 (99.58, 100.37)	0.391 (0.363, 0.421)
Diastolic < 90	15,863 (95.7)	99.70 (99.31, 100.10)	0.325 (0.320, 0.331)
Diastolic > 90	713 (4.3)	95.31 (93.60, 97.05)	0.352 (0.324, 0.382)
Hypertension (survey)	N= 16,576		
Yes	3,651 (22)	92.34 (91.43, 93.25)	0.352 (0.338,0.366)
No	12,905 (77.9)	101.66 (101.25, 102.07)	0.319 (0.313, 0.326)
Don't Know	20 (0)		
Diabetes	N= 17026		
Yes	1,046 (6.1)	90.39 (87.98, 92.87)	0.316 (0.295, 0.339)
No	15,729 (92.4)	100.16 (99.78, 100.54)	0.327 (0.321, 0.333)
Borderline	241 (1.4)	93.93 (91.05, 96.91)	0.323 (0.283, 0.369)
Insulin Use	N= 16,576		
Yes	310 (1.9)	81.84 (76.66, 87.37)	0.293 (0.261, 0.328)
No	16,266 (98.1)	99.85 (99.48, 100.23)	0.327 (0.321, 0.333)
Weak/Failing Kidneys	N= 16,756		
Yes	293 (1.8)	74.92 (68.93, 81.43)	0.418 (0.367, 0.475)
No	15,421 (93)	99.41 (99.04, 99.78)	0.329 (0.323, 0.335)
Cotinine level	N= 16,576		
Nonsmoker (<10 ng/ml)	11,191 (67.5)	98.40 (97.92, 98.87)	0.230 (0.227, 0.233)
Smoker (>10ng/ml)	4,648 (28)	100.46 (99.78, 101.15)	0.772 (0.747, 0.790)
*eGFR = estimated glomerular filtration rate			

Initially, an empty linear model for cadmium was conducted with gender and sexual orientation separated. In this model, the gender parameter estimate for blood cadmium was 0.05

(95% CI 0.046, 0.143; p<0.0001) and the sexual orientation parameter estimate for blood cadmium was 0.09 (95% CI 0.029, 0.071; p<0.0001).

A linear model was created for associations between blood cadmium and demographic and clinical variables. The significant variables were gender/sexual orientation, hypertension, cotinine levels, age, poverty index, race, education, diabetes, and kidney failure (p<0.05). Insulin use, average systolic blood pressure, and average diastolic blood pressure were removed from the model based on significance level (p>0.05). Parameter estimates of cadmium are shown in table 4.

Table 4. Multivariable adjusted associations of blood cadmium by demographic and clinical characteristics. US population, National Health and Nutrition Examination Survey, 2005-2014.

	Continuous Blood Cadmium Parameter Estimates (95% CI)	***P-value***
Age in Years	0.01 (0.01, 0.01)	<0.0001*
Gender and Sexual Orientation		
Male Straight	Reference	
Male Gay	0.03 (-0.01, 0.07)	0.1512
Male Bisexual	0.00 (0.00, 0.48)	0.8290
Female Straight	0.15 (0.14, 0.16)	<0.0001*
Female Gay	0.14 (0.09, 0.20)	<0.0001*
Female Bisexual	0.15 (0.12, 0.18)	<0.0001*
Race/Ethnicity		
Mexican American	0.02 (0.00, 0.04)	0.0189
Other Hispanic	0.03 (0.00, 0.05)	0.0118
Non-Hispanic White	Reference	
Non-Hispanic Black	0.02 (0.00, 0.04)	0.0039
Other	0.14 (0.13, 0.16)	<0.0001*
Education		
< High School	0.02 (0.00, 0.04)	0.0243*
High School Graduate	0.00 (-0.02, 0.00)	0.1543
Some college	-0.01 (-0.02, 0.00)	0.0762
College Graduate or above	Reference	
Poverty Income Ratio (0-5)	-0.00 (-0.01, 0.00)	<0.0001*
Hypertension (survey)		
Yes	-0.02 (-0.03, -0.01)	0.0002*
No	Reference	
Don't Know	0.05 (-0.09, 0.21)	0.4666
Diabetes		

Yes	-0.07 (-0.09, -0.05)	<0.0001*
No	Reference	
Borderline	-0.04 (-0.08, -0.01)	0.0124
Weak/Failing Kidneys		
Yes	0.05 (0.02, 0.09)	0.0045*
No	Reference	
Cotinine level	0.14 (0.14, 0.15)	<0.0001*

*significant p-value of <0.0001

Blood cadmium associations were minimal across all demographic and clinical characteristics. The positive associations were highest among women of all sexual orientations and increasing cotinine levels.

A linear model was created for estimated glomerular filtration rate and predictor variables. The significant variables were gender/sexual orientation, average systolic blood pressure, average diastolic blood pressure, hypertension, cotinine levels, age, poverty index, race, education, diabetes, insulin use, and kidney failure. Parameter estimates of estimated glomerular filtration rate are shown in table 5.

Table 5. Multivariable adjusted associations of estimated glomerular filtration rate (eGFR by demographic and clinical characteristics. US population, National Health and Nutrition Examination Survey, 2005-2014.

	Continuous eGFR Parameter Estimates (95% CI)	***P-value***
Age in Years	-0.844 (-0.868, -0.822)	<0.0001*
Gender and Sexual Orientation		
Male Straight	Reference	
Male Gay	2.89 (0.72, 5.06)	0.0091*
Male Bisexual	4.12 (1.17, 7.08)	0.0062*
Male Other	-3.22 (-9.07, 2.62)	0.7011
Female Straight	2.86 (2.34, 3.38)	<0.0001*
Female Gay	1.15 (-2.00, 4.30)	0.475
Female Bisexual	0.90 (-0.85, 2.65)	0.313
Female Other	6.44 (1.49, 11.39)	0.0077*
Race/Ethnicity		
Mexican American	7.54 (6.61, 8.49)	<0.0001*
Other Hispanic	4.34 (3.21, 5.48)	<0.0001*

Non-Hispanic White	Reference	
Non-Hispanic Black	7.93 (7.12, 8.76)	<0.0001*
Other	3.62 (2.61, 4.63)	<0.0001*
Education		
< High School	2.81 (1.90, 3.74)	<0.0001*
High School Graduate	1.12 (0.46, 1.96)	0.0017*
Some college	-0.14 (-0.78, -0.50)	0.5867
College Graduate or above	Reference	
Poverty Income Ratio (0-5)	-0.38 (-0.56, -0.21)	<0.0001*
Blood Pressure Measurements		
Average Systolic Blood Pressure	0.05 (0.02, 0.07)	<0.0001*
Average Diastolic Blood Pressure	-0.07 (-0.09, -0.04)	<0.0001*
Hypertension (survey)		
Yes	-1.37 (-10.28, 7.37)	<0.0001*
No	Reference	
Don't Know	0.08 (-8.73, 8.89)	0.986
Diabetes		
Yes	2.27 (0.938, 3.61)	0.0008*
No	Reference	
Borderline	0.80 (-1.18, 2.78)	0.428
Insulin Use		
Yes	-5.05 (-7.30, -2.80)	<0.0001*
No	Reference	
Weak/Failing Kidneys		
Yes	-12.84 (-14.88, -10.80)	<0.0001*
No	Reference	
Cotinine level	0.17 (0.01, 0.32)	0.0327*
*eGFR = estimated glomerular filtration rate		

*significant p-value of <0.0001

Estimated glomerular filtration rate was negatively associated with age (-0.844), poverty income ratio (-0.38), hypertension (-1.37), insulin use (-5.05), and weak/failing kidneys (-12.84). Estimated glomerular filtration rate varied among gender and sexual orientation, race and ethnicity. Bisexual males had the highest eGFR association, at 4.12 times higher than straight males. LGB females had lower eGFR association (1.15, 0.90) than LGB males (2.89, 4.12). Non-Hispanic blacks had the highest eGFR association (7.93) between all race/ethnicities. Estimated glomerular filtration rate was inversely associated with education, with participants with less than high school education having the largest association and participants with college education having the smallest association.

A logistic model was conducted to explore Chronic Kidney Disease risk across gender and sexual orientation. The model adjusts for gender and sexual orientation, average systolic blood

pressure, average diastolic blood pressure, hypertension, cotinine levels, age, poverty index, race, education, diabetes, insulin use, and kidney failure. Odds ratio of low estimated glomerular filtration rate (eGFR <60) are shown in table 6.

Table 6. Multivariable adjusted odds ratios of low estimated glomerular filtration rate (eGFR <60) by gender and sexual orientation. US population, National Health and Nutrition Examination Survey, 2005-2014.

Gender and Sexual Orientation	***Low eGFR* (eGFR <60 vs >60) OR (95% CI)***	***p-value***
Male Straight	Reference	
Male Gay	0.824 (0.820, 0.827)	0.0003
Male Bisexual	0.634 (0.631, 0.638)	<0.0001
Male Other	1.574 (1.557, 1.591)	<0.0001
Female Straight	0.844 (0.843, 0.845)	<0.0001
Female Gay	0.783 (0.778, 0.788)	<0.0001
Female Bisexual	1.092 (1.089, 1.096)	<0.0001
Female Other	0.335 (0.331, 0.339)	<0.0001
Cadmium Quartiles		
Q1 (0-0.14 ng/L)	Reference	
Q2 (0.15-0.32 ng/L)	0.953 (0.952, 0.954)	<0.0001
Q3 (0.33-0.53 ng/L)	0.961 (0.959, 0.962)	0.0002
Q4 (0.54- 9.3 ng/L)	0.936 (0.973, 0.938)	<0.0001
*eGFR = estimated glomerular filtration rate		

Women who identified as bisexual and men who identified as other had increased odds of low eGFR ($p<0.0001$) of 1.092 and 1.574, respectively. Straight, gay, and bisexual men, and straight and gay women had decreased odds of low eGFR. Higher blood cadmium was associated with decreased odds of low eGFR ($p<0.0001$) but the difference was minimal.

Discussion

This study aimed to quantify the gender and sexual orientation disparities in smoking, cadmium exposure, and renal pathogenesis. Previous estimates found about 1 in 5 LGB adults

(20.5%) smoke cigarettes compared to about 1 in 6 heterosexual adults (15.3%)[8]. This analysis found the rate to be much higher, closer to 1 in 2 LGB individuals classified as smoking (44.2%) and 1 in 4 straight individuals (28.3%) classified as smoking.

The established differences in smoking rates lead to the hypothesis that cadmium burden would be different in straight individuals compared to sexual minorities. The geometric mean of blood cadmium (Table 3) was lower in males than in females, which has been supported by previous literature[28,35-38]. However, a comparison geometric mean blood cadmium of males by sexual orientation showed that straight men have the lowest cadmium levels (0.297 ng/L) and bisexual men have the highest cadmium levels (0.347 ng/L). Comparing females of difference sexual orientation showed that straight females have the lowest cadmium levels (0.354 ng/L) and gay females have the highest cadmium levels (0.446 ng/L). Additionally, the geometric mean blood cadmium for gay females was the highest among all demographic and clinical subgroups besides the smoking population as a whole (0.772 ng/L). The within-sex differences in blood cadmium is likely explained by differences in smoking rates in sexual minorities. The between-sex differences are likely due to the previously established risk factors faced by women including more serious type of renal tubular dysfunction, difference in calcium metabolism and its regulatory hormones, kidney sensitivity, pregnancy, body iron store status, and genetic factors[39,40,61].

A linear regression model was conducted to test how gender and sexual orientation influences cadmium burden. Compared to straight males, females had the highest parameter estimate of all demographic and clinical characteristics for cadmium burden. Straight females (0.15, $p<0.0001$*), gay females (0.14, $p<0.0001$*), and bisexual females (0.15, $p<0.0001$*) was an equal predictor of cadmium burden as cotinine levels (0.14, $p<0.0001$) . A linear regression was conducted to test if gender and sexual orientation influences eGFR. Compared to straight males, the parameter estimate compared to for gay males was 2.89 ($p<0.01$) and the parameter for bisexual males was 4.12

($p<0.01$), suggesting a slightly protective effect. The parameter estimate for straight females was 2.86 ($p<0.0001$), gay females was 1.15 (nonsignificant) and bisexual females was 0.90 (nonsignificant).

The logistic regression model tested whether gender and sexual orientation impacted kidney outcomes such as chronic kidney disease. Chronic kidney disease stage three or higher is characterized by low eGFR (<60). The logistic regression results for low eGFR suggest similar results of close to null odds ratios among gay males (OR: 0.824) and bisexual males (OR: 0.634). The odds ratios for females was highest among bisexual females (1.092).

To our knowledge, this is the first study to examine the sexual orientation association of blood cadmium concentration with kidney function using data from the U.S. NHANES. The results suggest a complex relationship between gender, sexual orientation, smoking, cadmium exposure, and renal disease. Smoking rates and cadmium burden was significantly higher in sexual minorities. Sexual orientation was significant in all of the models, but the effect modification in the eGFR linear regression was minimal. Within-sex comparisons of cadmium burden and eGFR show differences, but the biologically relevant impact of these differences is still to be determined. This analysis highlights the need for additional research specifically addressing disparities related to gender identity and sexual orientation.

There are several limitations to our study. The study relies on a single, cross-sectional sample to estimate kidney function using various parameters, and these measurements vary over time. Specifically, eGFR may be subject to extreme intra-individual variability due to intrinsic renal disease or extrinsic factors [62]. Given our interest in measures of kidney function, which may influence the urinary excretion of cadmium, we chose to use cadmium concentration as measured in blood. Blood cadmium concentration may be a useful indicator of longer-term exposure [63,64]; however, we cannot rule out that concentrations in blood were higher among individuals with decreased glomerular filtration due to defects in urinary cadmium excretion. Additionally, other environmental exposures

may have confounded the analysis. Despite an overall large sample size, there may be limited power to precisely estimate sexual orientation specific measures of association due to small within stratum samples. A cross-sectional study design is useful for exploratory and hypothesis generating analyses, but a prospective study of repeat measurements of kidney function parameters in relation to cadmium concentration is needed to validate our findings before any discussion on causality can take place. Although we assessed the association between cadmium concentration and low eGFR, a diagnosis of CKD requires multiple assessments of kidney function over weeks or months, further highlighting the need to replicate these findings in cohorts with multiple measures of kidney function over time. We cannot draw conclusions about the temporality of cadmium exposure and kidney function. Strengths of our study include use of objective laboratory measurements in the evaluation of kidney function by eGFR as calculated using the CKD-EPI equation. NHANES also provides self-reported information gender and sexual orientation. The sample size was large and representative of the population, although may not be representative of gender and sexual identity given the limited choices of NHANES surveys and exclusion of transgender or non-binary gender individuals and pansexual and asexual identity individuals.

Increasing attention to gender identity and sexual orientation is essential in research and clinical practice for the creation of public health prevention and treatment programs, especially in the context of environmental health disparities, which affect vulnerable populations. Gender identity and sexual orientation should be taken into account in environmental health research. We hope to highlight the need for a new environmental epidemiology framework that includes consideration of work on social determinants such as gender identity and sexual orientation disparities in environmental health.

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