Association Between Urine Uranium and Asthma Prevalence: NHANES 2007-2016

Dongdong Huang
Zhejiang University School of Medicine

Saibin Wang (✉ saibinwang@hotmail.com)
Zhejiang University School of Medicine, Jinhua Municipal Central Hospital

Research Article

Keywords: Uranium, Asthma, Heavy metal, Environmental pollution, NHANES

Posted Date: August 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-783343/v1

License: ☑️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Previous studies showed that urine uranium (U) is associated with asthma prevalence in adults. However, the association between them among the general population is unclear. Therefore, this study aimed at exploring this unclear association.

**Methods:** The data of the participants were collected from the 2007-2016 National Health and Nutrition Examination Survey (NHANES) performed in the United States. Continuous variables with skewed distribution were analyzed using Ln-transformation. The association between urine U and asthma prevalence was analyzed by multiple regression analysis, and the linear association between them was evaluated by the smooth curve fitting. The subgroup analysis was performed by the hierarchical multivariate regression analysis.

**Results:** A total of 13,581 participants were included in our analysis. The multivariate regression analysis showed that LnU was independently and positively correlated with asthma prevalence in the general population (OR=1.12; 95% CI:1.04,1.20; \(P=0.002\)). The subgroup analysis revealed that the College Graduate or above showed the stronger association between LnU and asthma prevalence (<9th Grade: OR=0.84; 95% CI: 0.61, 1.14; 9-11th Grade: OR=1.23; 95% CI: 0.99,1.52; High School Grade: OR=1.00; 95% CI: 0.84, 1.19; College: OR=1.04; 95% CI: 0.91,1.19; ≥ College Graduate: OR=1.32; 95% CI: 1.11, 1.57; \(P\) for interaction=0.0389).

**Conclusions:** Our research suggested that urinary U levels are positively correlated with asthma prevalence in the general population of the United States, and the association is especially strong among people with high level of education.

Introduction

Asthma is a chronic inflammatory disease of the airways affecting approximately 300 million people worldwide, and has become a serious global health problem affecting all mankind, as revealed by the Global Initiative for Asthma (GINA) report in 2021[1]. The control of asthma is not optimistic. The results of a survey on patients diagnosed with asthma indicate that this disease is still poorly controlled in the United States (U.S.), Canada, Europe[2], and Asia[3, 4]. In addition, Yaghoubi et al. estimated that the total economic burden of uncontrolled asthma among adolescents and adults in the U.S. will exceed $900 billion over the next 20 years [5].

The pathogenesis of asthma is relatively complicated. It is related to an early abnormal immune maturation, genomics, and environmental factors and it is a heterogeneous disease[6]. Environmental factors play a very important role in asthma prevalence. Indeed, an association between uranium (U) and asthma prevalence in adults was found in China and U.S.[7-9].

Exposure to harmful heavy metals such as lead (Pb), mercury (Hg) and arsenic (As) can cause a series of human diseases [10, 11], and among them, also U poisoning can cause serious health problems such as
respiratory diseases and lung cancer [7-10, 12], renal toxicity[13], as well as reproductive system toxicity[14] and immune system damage[15]. The sources of U pollution include mining, military activities, nuclear facilities, groundwater, and phosphate fertilizers[16]. At present, few studies reported the association between U exposure and the prevalence of asthma in adults[7-9], and the epidemiological association between U and asthma prevalence in the general population is not well known. In view of the enormous harm of asthma to human health and the economic burden, a large sample of epidemiological data on the impact of the environmental factors on asthma is necessary to carry out the primary prevention of asthma.

Therefore, this study was performed using data from the National Health and Nutrition Examination Survey (NHANES), which is a program of studies performed to assess the health and nutritional status of adults and children in the U.S, with the aim of investigating the association between urine U and asthma prevalence in the general population. The association between them in terms of age, gender, body mass index (BMI), economic level, race, education level, marital status, diabetes, hypertension, liver disease, smoking, alcohol consumption, and kidney function was also explored to evaluate the influence of these factors.

Methods

Study population

Our analysis was performed on NHANES data from 2007 to 2016. These data were obtained through a multi-level probability sampling of the nutrition and health status of the U.S. population representative of the general population in the U.S. We included participants aged 6-150 years in the 2007-2016 NHANES database. A total of 50588 participants were considered in this analysis. However, participants who met the following exclusion criteria were removed: participants who were unsure whether they had asthma (n = 2159); participants without urine U values (n = 3,4739); pregnant women (n=109).

Exposure variable

Urine U was the exposure variable in this study, detected by inductively coupled plasma mass spectrometry (ICP-MS). ICP-MS detects the U ion intensity and from that, it elaborates the concentration. The urine samples were collected, processed, and transported to the National Environmental Health Center, at the Department of Environmental Health Laboratory Science, and the Centers for Disease Control and Prevention to be analyzed. A detailed description of the method used for the urine uranium detection is available on the following website: https://wwwn.cdc.gov/Nchs/Nhanes/.

Outcome variable

The outcome variable in this study was the self-reported prevalence of asthma, and the participants were divided into asthma and non-asthma group according to the self-reported prevalence.

Covariates
The following covariates that can be considered as potential confounders associated with urine U and asthma prevalence were collected according to previous studies[7, 8] and clinical considerations: age, gender, race, BMI, poverty to income ratio (PIR), education level, marital status, blood sugar (diabetes), blood pressure (hypertension), liver diseases, smoking, and alcohol consumption. The following blood parameters were also collected: total protein (TP), albumin, globulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Scr), total bilirubin (TB), serum uric acid (SUA), and the content of the following metals in the urine were also collected: barium (Ba), cadmium (Cd), cobalt (Co), cesium (Cs), molybdenum (Mo), Pb, stibium (Sb), thallium (Tl), tungsten (Tu), and Hg.

The age, gender, race, PIR, education level, and marital status were obtained from the demographic data of NHANES. The race was divided into the following five categories: Mexican American, Non-Hispanic White, Non-Hispanic Black, Other Hispanic, Other Races. The BMI of the study population was calculated using the following formula: weight (Kg)/height (m$^2$). The education level included the following levels: <9$^{th}$ Grade, 9-11$^{th}$ Grade, High School Grade, College, ≥College Graduate. The marital status was classified as follows: married, divorced, widowed, separated, living with the partner, never married. The information regarding the presence of diabetes, hypertension, liver disease and whether they have smoking and drinking habits was obtained from the questionnaire filled by the participants. If the participant smoked at least 100 cigarettes during their life, this behavior was defined as smoking behavior. Alcohol use was defined as drinking at least 12 glasses of alcoholic beverages in the past 12 months. Moreover, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to convert the serum creatinine of the participants into the glomerular filtration rate (GFR) in order to assess and adjust the influence of renal function on the association between urine U and asthma prevalence [17, 18]. A GFR <60 ml/min/1.73 m$^2$ was defined as renal insufficiency[19-22].

**Statistical analysis**

Statistical analysis was performed using the R software (The R Foundation; https://www.r-project.org). The baseline characteristics of the study population was evaluated by the descriptive analysis. Since the levels of Ba, Cd, Co, Cs, Mo, Pb, Sb, Tl, Tu, Hg, and U in urine were characterized by a skewed distribution, the Ln-conversion was performed to improve the normality. Age was presented as median (Q1-Q3). Continuous variables were indicated as mean ± standard deviation (SD), while the categorical variables were indicated by numbers (percentages). The comparison between the asthma and non-asthma group was performed using the unpaired $t$-test or Mann-Whitney U test, Pearson chi-squared tests or the Fisher’s exact, as appropriate. The association between urine U and asthma prevalence was assessed by multiple regression model. Two adjustment models were used to explore the association between them in our study. The covariates that contribute to the odds ratio change greater than 10% such as age, gender, race, and BMI were included as the adjustment variables for the adjusted model I. The adjusted model 2 included the variables in the model I and the ones in which the $P$-value of the covariate to the dependent variable was less than 0.1, such as age, gender, race, BMI, education level, marital status, PIR, diabetes, hypertension, alcohol use, BUN, TB, TP, globulin, LnBa, LnCd, LnCo, LnCs, LnPb, LnSb, LnTI, LnTu, and
LnHg. LnU was transformed into a quartile categorical variable and the $P$-value for the trend was calculated to verify the possibility of non-linearity between LnU as a continuous variable and asthma prevalence. Furthermore, the correlation graph between urine U and asthma prevalence was shown using the smooth curve fitting (penalty spline method). Multiple imputation analysis was used to assess whether the missing values of the covariates were the cause of bias in the results[23]. Hierarchical multivariate regression analysis was used for subgroup analysis. A $P$-value < 0.05 was considered statistically significant.

**Results**

**Baseline characteristics of the subjects**

A total of 13,581 participants from the NHANES data from 2007 to 2016 were included in our analysis according to the inclusion and exclusion criteria of this study. The baseline characteristics of the study population are listed in Table 1. The participants in the asthma and non-asthma group were 2081 and 11500, respectively. Their Median age was 36.0 (15-57) and 29.0 (14-52) years, respectively ($P<0.001$). The mean LnU of the asthma and non-asthma group was -5.1 ± 1.0 and -5.0 ± 1.0 ug/L, respectively ($P<0.001$). In addition, the asthma and non-asthma group showed a statistically significant difference in BMI, PIR, race, education level, marital status, diabetes, hypertension, liver disease, smoking, alcohol consumption, TP, albumin, globulin, BUN, TB, GFR, LnBa, LnCd, LnCo, LnPb, LnSb, LnTI, LnTu, and LnHg (all $P<0.05$).

**Association between urinary U and asthma prevalence**

The association between urine U and asthma prevalence assessed by the logistic regression model is described in Table 2. The continuous variable urine U was associated with asthma prevalence in the non-adjusted model (OR=1.09; 95% CI: 1.04, 1.14; $P=0.0003$). Urine U was still associated with asthma after the adjustment of the model I (OR=1.10; 95% CI: 1.05, 1.15; $P<0.0001$) and model II (OR=1.12; 95% CI: 1.04,1.20; $P=0.002$) for different confounding factors. Moreover, participants in the second, third, and highest LnU quartile showed a statistically significantly higher asthma prevalence in the non-adjusted model ($P$ for trend=0.0007), adjustment model I ($P$ for trend=0.0002), and model II ($P$ for trend=0.0104) compared with the lowest-quantile LnU after converting LnU from a continuous variable to a categorical variable (quartile). $P$ for trends for all models was significant and consistent with the $P$-value of LnU as a continuous variable, thus suggesting a linear association between LnU and asthma prevalence. Further analysis with the smoothing curve fitting confirmed the linear association between urine LnU and asthma prevalence after the adjustment for confounding factors (adjustment model II) (Figure 1).

The effect of other covariates on the relationship between LnU and asthma prevalence was also evaluated in the subgroup analysis (Figure 2). The subgroup analysis revealed that College Graduate or above had the stronger association between LnU and asthma prevalence (<9th Grade: OR=0.84; 95% CI: 0.61, 1.14；9-11th Grade: OR=1.23; 95% CI: 0.99, 1.52; High School Grade: OR=1.00; 95% CI: 0.84, 1.19;
College: OR=1.04; 95% CI: 0.91, 1.19; ≥College Graduate: OR=1.32; 95% CI: 1.11, 1.57; P for interaction=0.0389). The association between urine LnU and asthma prevalence was consistent in the following subgroups: age, gender, BMI, PIR, race, marital status, diabetes, hypertension, liver disease, smoking, alcohol use, and GFR (P for interaction of all covariates > 0.05). The results of the imputed data set and the complete data were consistent.

**Discussion**

Our results demonstrated that urine uranium level was positively correlated with asthma prevalence in the whole population of the U.S., and this association was particularly significant in people with an education level ≥ college graduate.

The bioavailability of U compounds the human gastrointestinal tract is estimated between <0.1% and 6% [24]. The kidney is the main excretory organ of U compounds [25]. Since the urine U level is correlated with U exposure[26, 27], in this study urine U is used as a sign of U exposure.

A case-control study in a Chinese adult population (sample size 1:1 matched, 551 patients in both the asthma group and the control group) as well as an analysis considering 1857 American adults in the NHANES 2007-2008 survey suggested that the prevalence of asthma was positively correlated with the level of U in the urine [7][8, 9]. Since then, this conclusion has been confirmed by Li, X et al, who obtained consistent results after considering 3425 American adults aged 20-59 (2011-2014)[8, 9]. In this study, a sample size of 13,581 of American general population was considered as the study population (NHANES 2007-2016), and their age was ≥6 years old, which basically represents the general population in the United States. The results of this study not only confirmed the association between urinary U levels and the incidence of asthma in adults, but it was the first revealing the prevalence of asthma in adolescents and children (<18 years) positively correlated with urinary U levels. Our research has good clinical significance and represents a good reference value considering the high prevalence of asthma in adolescents and children, further revealing that this association cannot be ignored. In addition, our study also discovered that the education level of the general population had an interactive effect on the relationship between urinary U level and asthma prevalence, since this association was stronger in people with higher level of education, suggesting that their urinary U level (uranium exposure) needs a more stringent management in order to reduce the prevalence of asthma in this population.

The pathogenesis of asthma is a complex and incompletely clear process involving multiple cellular components [28-30]. Asthma caused by heavy metals is currently explained with the involvement of oxidative stress or airway inflammation[7]. For example, immunocompetent cells are induced by heavy metals to produce oxidants[31], which can cause airway hyper-responsiveness[32], airway spasm and contraction[33], and increase airway mucus secretion[34]. Additionally, Cr and Cd can induce airway inflammation, cause airway obstruction and airway hyperresponsiveness [35, 36]. Despite the above evidence, no research on the mechanism regulating the association between U and asthma prevalence is
available. Thus, further longitudinal studies between uranium and asthma are necessary to discover the potential mechanism.

O’Conor R et al. suggested that people with higher level of education have more awareness for asthma than people with lower level of education, and this aspect is more helpful in the control of asthma [37]. Our study revealed that the association between urine U and asthma prevalence in college graduates is more evident. This may be explained with the fact that people with high education level pay more attention to their own health, thus, allowing doctors or investigators to obtain information about their asthma prevalence. Hence, it is necessary to monitor urinary U levels in the general population, especially in the population with a high level of education.

The data from NHANES of a large sample survey with a random sampling of the general population in the U.S. was used in this work, since it has a good population representation. The multiple regression analysis was used to explore the independent relationship between urine U and asthma prevalence after adjusting for potential confounding factors. Despite this strength, this study has also some limitations. The simultaneous occurrence of U exposure and asthma cannot be considered a causal relationship between them since the design of this study is cross-sectional. A urine sample per participant was used to detect the urine U concentration, potentially causing measurement errors due to individual variability in short-term uranium excretion. Therefore, multiple or 24-hour urine samples should be used to reduce measurement errors. Self-reported asthma history may have recall bias.

Conclusions

Our research suggested that urinary U levels are positively correlated with asthma prevalence in the U.S. general population and the association is especially strong among people with high level of education. Therefore, the exposure should be prevented, the concentration of U in the urine should be monitored and U pollution should be removed from the environment.

Abbreviations

NHANES: National Health and Nutrition Examination Survey; Uranium: U; Odds ratio: OR; Confidence interval: CI; Global Initiative for Asthma: GINA; United States: U.S.; uranium: U; Lead: Pb; Mercury: Hg; Arsenic: As; Body mass index: BMI; Inductively coupled plasma mass spectrometry: ICP-MS; Poverty to income ratio: PIR; Total protein: TP; Alanine aminotransferase: ALT; Aspartate aminotransferase: AST; Blood urea nitrogen: BUN; Serum creatinine: Scr; Total bilirubin: TB; Serum uric acid: SUA; Barium: Ba; Cadmium: Cd; Cobalt: Co; Cesium: Cs; Molybdenum: Mo; Antimony: Sb; Thallium: Tl; Tungsten: Tu; Chronic Kidney Disease Epidemiology Collaboration: CKD-EPI; Glomerular filtration rate: GFR

Declarations
Acknowledgements
Special thanks to all NHANES participants and staff for their selfless dedication of time to make this research possible.

Competing interests
The authors declare that they have no competing interests.

Funding
This study was supported by the Medical and Health Science and Technology Plan Project of Zhejiang Province (No. 2020KY627)

Ethics approval and consent to participate
NHANES study protocols were approved by the research ethics review board of the National Center for Health Statistics. Written informed consent was acquired from each participant and obtained from the guardians of participants younger than 18 years of age, and assent was obtained from those aged 6 to 17 years.

Availability of data and materials
The data used in this study are publicly available on the Internet. https://www.cdc.gov/nchs/nhanes/

Authors' contributions
Dongdong Huang contributed to data collection and writing of the manuscript. Saibin Wang contributed to study design, data analysis, data interpretation, and manuscript revision. All authors read and approved the final manuscript.

Author details
1Department of Respiratory and Critical Care Medicine, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, No. N1 Avenue mall Road, Yiwu 322000, Zhejiang, China. E-mail address: 8016009@zju.edu.cn

2Department of Respiratory Medicine, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, No. 365, East Renmin Road, Jinhua 321000, Zhejiang, China. E-mail address: saibinwang@hotmail.com.

References
1. El-Husseini ZW, Gosens R, Dekker F, Koppelman GH: The genetics of asthma and the promise of genomics-guided drug target discovery. The Lancet Respiratory medicine 2020, 8(10):1045-1056.
2. Rabe KF, Vermeire PA, Soriano JB, Maier WC: Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *The European respiratory journal* 2000, 16(5):802-807.

3. Lai CK, De Guia TS, Kim YY, Kuo SH, Mukhopadhyay A, Soriano JB, Trung PL, Zhong NS, Zainudin N, Zainudin BM: Asthma control in the Asia-Pacific region: the Asthma Insights and Reality in Asia-Pacific Study. *The Journal of allergy and clinical immunology* 2003, 111(2):263-268.

4. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST: Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *The Journal of allergy and clinical immunology* 2004, 114(1):40-47.

5. Yaghoubi M, Adibi A, Safari A, FitzGerald JM, Sadatsafavi M: The Projected Economic and Health Burden of Uncontrolled Asthma in the United States. *American journal of respiratory and critical care medicine* 2019, 200(9):1102-1112.

6. von Mutius E, Smits HH: Primary prevention of asthma: from risk and protective factors to targeted strategies for prevention. *Lancet (London, England)* 2020, 396(10254):854-866.

7. Huang X, Xie J, Cui X, Zhou Y, Wu X, Lu W, Shen Y, Yuan J, Chen W: Association between Concentrations of Metals in Urine and Adult Asthma: A Case-Control Study in Wuhan, China. *PloS one* 2016, 11(5):e0155818.

8. Li X, Fan Y, Zhang Y, Huang X, Huang Z, Yu M, Xu Q, Han X, Lu C, Wang X: Association between selected urinary heavy metals and asthma in adults: a retrospective cross-sectional study of the US National Health and Nutrition Examination Survey. *Environmental science and pollution research international* 2021, 28(5):5833-5844.

9. Mendy A, Gasana J, Vieira ER: Urinary heavy metals and associated medical conditions in the US adult population. *International journal of environmental health research* 2012, 22(2):105-118.

10. Nemery B: Metal toxicity and the respiratory tract. *The European respiratory journal* 1990, 3(2):202-219.

11. Karakis I, Landau D, Gat R, Shemesh N, Tirosh O, Yitshak-Sade M, Sarov B, Novack L: Maternal metal concentration during gestation and pediatric morbidity in children: an exploratory analysis. *Environmental health and preventive medicine* 2021, 26(1):40.

12. Shumate AM, Yeoman K, Victoroff T, Evans K, Karr R, Sanchez T, Sood A, Laney AS: Morbidity and Health Risk Factors Among New Mexico Miners: A Comparison Across Mining Sectors. *Journal of occupational and environmental medicine* 2017, 59(8):789-794.

13. Yu L, Li W, Chu J, Chen C, Li X, Tang W, Xia B, Xiong Z: Uranium inhibits mammalian mitochondrial cytochrome c oxidase and ATP synthase. *Environmental pollution (Barking, Essex :*
1987) 2021, 271:116377.

14. Wang S, Ran Y, Lu B, Li J, Kuang H, Gong L, Hao Y: A Review of Uranium-Induced Reproductive Toxicity. Biological trace element research 2020, 196(1):204-213.

15. Dashner-Titus EJ, Schilz JR, Simmons KA, Duncan TR, Alvarez SC, Hudson LG: Differential response of human T-lymphocytes to arsenic and uranium. Toxicology letters 2020, 333:269-278.

16. Ma M, Wang R, Xu L, Xu M, Liu S: Emerging health risks and underlying toxicological mechanisms of uranium contamination: Lessons from the past two decades. Environment international 2020, 145:106107.

17. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL et al: Estimating glomerular filtration rate from serum creatinine and cystatin C. The New England journal of medicine 2012, 367(1):20-29.

18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T et al: A new equation to estimate glomerular filtration rate. Annals of internal medicine 2009, 150(9):604-612.

19. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet (London, England) 2010, 375(9731):2073-2081.

20. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, van der Velde M, Matsushita K et al: Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney international 2011, 79(12):1341-1352.

21. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J: Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney international 2011, 80(1):93-104.

22. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J, Astor BC, Matsushita K et al: Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney international 2011, 79(12):1331-1340.

23. Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, Seagle BL, Alexander A, Barber EL, Rice LW et al: Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. The New England journal of medicine 2018, 379(20):1905-1914.
24. Leggett RW, Harrison JD: Fractional absorption of ingested uranium in humans. *Health physics* 1995, 68(4):484-498.

25. Keith S, Faroon O, Roney N, Scinicariello F, Wilbur S, Ingerman L, Llados F, Plewak D, Wohlers D, Diamond G: Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles. In: *Toxicological Profile for Uranium*. edn. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); 2013.

26. Seldén AI, Lundholm C, Edlund B, Högdahl C, Ek BM, Bergström BE, Ohlson CG: Nephrotoxicity of uranium in drinking water from private drilled wells. *Environmental research* 2009, 109(4):486-494.

27. Karpas Z, Paz-Tal O, Lorber A, Salonen L, Komulainen H, Auvinen A, Saha H, Kurttio P: Urine, hair, and nails as indicators for ingestion of uranium in drinking water. *Health physics* 2005, 88(3):229-242.

28. Busse WW: Inflammation in asthma: the cornerstone of the disease and target of therapy. *The Journal of allergy and clinical immunology* 1998, 102(4 Pt 2):S17-22.

29. Sastre J, Vandenplas O, Park HS: Pathogenesis of occupational asthma. *The European respiratory journal* 2003, 22(2):364-373.

30. Bønnelykke K, Ober C: Leveraging gene-environment interactions and endotypes for asthma gene discovery. *The Journal of allergy and clinical immunology* 2016, 137(3):667-679.

31. Cohn L, Elias JA, Chupp GL: Asthma: mechanisms of disease persistence and progression. *Annual review of immunology* 2004, 22:789-815.

32. Zuo L, Clanton TL: Reactive oxygen species formation in the transition to hypoxia in skeletal muscle. *American journal of physiology Cell physiology* 2005, 289(1):C207-216.

33. Katsumata U, Miura M, Ichinose M, Kimura K, Takahashi T, Inoue H, Takishima T: Oxygen radicals produce airway constriction and hyperresponsiveness in anesthetized cats. *The American review of respiratory disease* 1990, 141(5 Pt 1):1158-1161.

34. Nabe T, Ikedo A, Hosokawa F, Kishima M, Fujii M, Mizutani N, Yoshino S, Ishihara K, Akiba S, Chaplin DD: Regulatory role of antigen-induced interleukin-10, produced by CD4(+) T cells, in airway neutrophilia in a murine model for asthma. *European journal of pharmacology* 2012, 677(1-3):154-162.

35. Oh CM, Oh IH, Lee JK, Park YH, Choe BK, Yoon TY, Choi JM: Blood cadmium levels are associated with a decline in lung function in males. *Environmental research* 2014, 132:119-125.

36. Schneider BC, Constant SL, Patierno SR, Jurjus RA, Ceryak SM: Exposure to particulate hexavalent chromium exacerbates allergic asthma pathology. *Toxicology and applied pharmacology* 2012, 259(1):38-44.
37. O’Conor R, Wolf MS, Smith SG, Martynenko M, Vicencio DP, Sano M, Wisnivesky JP, Federman AD: Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. Chest 2015, 147(5):1307-1315.

Tables
| Variables                          | Non-asthma (n=11500) | Asthma (n=2081) | P-value |
|-----------------------------------|----------------------|-----------------|---------|
| Age(years), Median (Q1-Q3)        | 36.0 (15-57)         | 29.0 (14-52)    | <0.001  |
| Gender (n), %                     |                      |                 | 0.056   |
| Male                              | 5816 (50.6%)         | 1005 (48.3%)    |         |
| Female                            | 5684 (49.4%)         | 1076 (51.7%)    |         |
| BMI (Kg/m²), Mean ± SD            | 26.1 ± 7.3           | 27.5 ± 8.6      | <0.001  |
| PIR (Ratio), Mean ± SD            | 2.3 ± 1.6            | 2.2 ± 1.6       | <0.001  |
| Race (n), %                       |                      |                 | <0.001  |
| Mexican American                  | 2210 (19.2%)         | 247 (11.9%)     |         |
| Other Hispanic                    | 1259 (10.9%)         | 238 (11.4%)     |         |
| Non-Hispanic White                | 4186 (36.4%)         | 830 (39.9%)     |         |
| Non-Hispanic Black                | 2485 (21.6%)         | 539 (25.9%)     |         |
| Other Races                       | 1360 (11.8%)         | 227 (10.9%)     |         |
| Education (n), %                  |                      |                 | <0.001  |
| <9th Grade                        | 958 (8.3%)           | 94 (4.5%)       |         |
| 9-11th Grade                      | 1127 (9.8%)          | 182 (8.7%)      |         |
| High School Grade                 | 1742 (15.1%)         | 296 (14.2%)     |         |
| College                           | 2173 (18.9%)         | 443 (21.3%)     |         |
| ≥College Graduate                 | 1791 (15.6%)         | 269 (12.9%)     |         |
| Don't Know                         | 3709 (32.3%)         | 797 (38.3%)     |         |
| Marital status, N (%)             |                      |                 | <0.001  |
| Married                           | 4119 (35.8%)         | 556 (26.7%)     |         |
| Widowed                           | 625 (5.4%)           | 92 (4.4%)       |         |
| Divorced                          | 782 (6.8%)           | 180 (8.6%)      |         |
| Separated                         | 248 (2.2%)           | 43 (2.1%)       |         |
| Never married                     | 1371 (11.9%)         | 306 (14.7%)     |         |
| Living with partner               | 648 (5.6%)           | 107 (5.1%)      |         |
| Condition                        | Yes           | No            | Don't know   | p-value |
|--------------------------------|---------------|---------------|--------------|---------|
| **Diabetes, N (%)**            | 960 (8.3%)    | 10348 (90.0%) | 188 (1.6%)   | <0.001  |
| **Hypertension, N (%)**        | 2743 (23.9%)  | 5861 (51.0%)  | 2896 (25.2%) | <0.001  |
| **Liver Disease, N (%)**       | 278 (2.4%)    | 7502 (65.2%)  | 3720 (32.3%) | <0.001  |
| **Smoking, N (%)**             | 3401 (29.6%)  | 4554 (39.6%)  | 3545 (30.8%) | <0.001  |
| **Alcohol use, N (%)**         | 5124 (44.6%)  | 2138 (18.6%)  | 4238 (36.9%) | <0.001  |

**Blood test, Mean ± SD**

| Test | Mean ± SD   | p-value |
|------|-------------|---------|
| TP (g/dL) | 7.2 ± 0.5  | <0.001  |
| Albumin (g/dL) | 4.3 ± 0.3  | <0.001  |
| Globulin (g/dL) | 2.9 ± 0.5  | 0.049   |
| ALT (U/L) | 24.6 ± 18.4 | 0.47    |
| AST (U/L)  | 25.7 ± 16.1 | 0.603   |
| BUN (mg/dL) | 13.0 ± 5.5 | <0.001  |
|                  | Mean ± SD | Mean ± SD | p-value |
|------------------|-----------|-----------|---------|
| Scr (mg/dL)      | 0.9 ± 0.3 | 0.9 ± 0.3 | 0.361   |
| TB (mg/dL)       | 0.7 ± 0.3 | 0.7 ± 0.3 | <0.001  |
| SUA (mg/dL)      | 5.4 ± 1.4 | 5.4 ± 1.4 | 0.141   |
| GFR (mL/min/1.73 m2) | 98.3 ± 26.9 | 100.6 ± 27.3 | 0.002   |
| Urine metals, Mean ± SD |          |           |         |
| LnBa(µg/L)       | 0.2 ± 1.0 | 0.2 ± 1.0 | 0.032   |
| LnCd(µg/L)       | -1.9 ± 1.1 | -2.0 ± 1.1 | 0.008   |
| LnCo(µg/L)       | -1.0 ± 0.8 | -0.9 ± 0.8 | <0.001  |
| LnCs(µg/L)       | 1.4 ± 0.7 | 1.4 ± 0.7 | 0.852   |
| LnMo(µg/L)       | 3.8 ± 0.9 | 3.8 ± 0.9 | 0.112   |
| LnPb(µg/L)       | -0.9 ± 0.9 | -1.0 ± 0.9 | 0.002   |
| LnSb(µg/L)       | -2.9 ± 0.8 | -2.8 ± 0.8 | 0.003   |
| LnTl(µg/L)       | -1.9 ± 0.7 | -1.9 ± 0.7 | 0.039   |
| LnTu(µg/L)       | -2.5 ± 1.1 | -2.4 ± 1.1 | <0.001  |
| LnHg(ng/mL)      | -1.2 ± 1.1 | -1.3 ± 1.0 | 0.039   |
| LnU(µg/L)        | -5.1 ± 1.0 | -5.0 ± 1.0 | <0.001  |

**Abbreviations:** NHANES, National Health and Nutrition Examination Survey; SD, Standard deviation; BMI, Body mass index; PIR, Poverty to income ratio; TP, Total protein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, Blood urea nitrogen; Scr, Serum creatinine; TB, Total bilirubin; SUA, Serum uric acid; GFR, Glomerular filtration rate; Ba, Barium; Cd, Cadmium; Co, Cobalt; Cs, Cesium; Mo, Molybdenum; Pb, Lead; Sb, Stibium; Tl, Thallium; Tu, Tungsten; Hg, mercury; U, Uranium
Table 2 The association between LnU and asthma prevalence in NHANES 2007-2016

|                          | The prevalence of asthma OR (95% CI) p-value                   |
|--------------------------|----------------------------------------------------------------|
|                          | Non-adjusted                      | Adjusted Model I       | Adjusted Model II                      |
| LnU                      | 1.09 (1.04, 1.14) 0.0003           | 1.10 (1.05, 1.15) <0.0001 | 1.12 (1.04, 1.20) 0.0020               |
| Quartiles                |                                  |                        |                                           |
| LnU Q1                   | Ref. (1)                          | Ref. (1)               | Ref. (1)                                 |
| LnU Q2                   | 1.19 (1.04, 1.36) 0.0137           | 1.18 (1.03, 1.35) 0.0209 | 1.31 (1.09, 1.56) 0.0033               |
| LnU Q3                   | 1.24 (1.09, 1.42) 0.0016           | 1.24 (1.08, 1.43) 0.0020 | 1.24 (1.03, 1.50) 0.0250               |
| LnU Q4                   | 1.26 (1.10, 1.45) 0.0007           | 1.30 (1.13, 1.49) 0.0002 | 1.38 (1.12, 1.69) 0.0022               |
| P for trend              | 0.0007                            | 0.0002                 | 0.0104                                  |

**Adjusted Model I** age, gender, race, BMI

**Adjusted Model II** age, gender, race, BMI, education, marital status, PIR, diabetes, hypertension, alcohol use, BUN, TB, TP, globulin, LnBa, LnCd, LnCo, LnCs, LnPb, LnSb, LnTl, LnTu, LnHg

**Abbreviations**: U, Uranium; NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio; CI, Confidence interval; BMI, Body mass index; PIR, Poverty to income ratio; BUN, Blood urea nitrogen; TB, Total bilirubin; TP, Total protein; Ba, Barium; Cd, Cadmium; Co, Cobalt; Cs, Cesium; Pb, Lead; Sb, Stibium; Tl, Thallium; Tu, Tungsten; Hg, mercury

**Figures**
The smooth curve fitting showed the association between urine LnU and asthma prevalence after adjusting for the confounders (age, gender, race, BMI, education, marital status, PIR, diabetes, hypertension, alcohol use, BUN, TB, TP, globulin, LnBa, LnCd, LnCo, LnCs, LnPb, LnSb, LnTi, LnTu, LnHg). The area between the two dashed lines is expressed as 95% confidence interval. Abbreviations: U: uranium; BMI, Body mass index; PIR, Poverty to income ratio; BUN, Blood urea nitrogen; TB, Total bilirubin; TP, Total protein; Ba, Barium; Cd, Cadmium; Co, Cobalt; Cs, Cesium; Pb, Lead; Sb, Stibium; Tl, Thallium; Tu, Tungsten; Hg, mercury
### Figure 2

Subgroup analysis of the influence of LnU on the prevalence of asthma. Abbreviations: OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; PIR: Poverty to income ratio; GFR: Glomerular filtration rate

| Subgroups                              | N     | OR(95%CI)          | P for interaction |
|----------------------------------------|-------|--------------------|-------------------|
| **Age, years**                         |       |                    |                   |
| <18                                    | 1323  | 1.14 (0.97, 1.34)  | 0.8065            |
| ≥18                                    | 8064  | 1.11 (1.03, 1.20)  |                   |
| **Gender**                             |       |                    |                   |
| Male                                   | 4725  | 1.11 (1.01, 1.23)  | 0.8431            |
| Female                                 | 4662  | 1.10 (1.00, 1.21)  |                   |
| **BMI, kg/m²**                         |       |                    |                   |
| <18.5                                  | 333   | 1.48 (0.92, 2.40)  | 0.2711            |
| 18.5-24.9                              | 3038  | 1.04 (0.91, 1.18)  |                   |
| 25-29.9                                | 2669  | 1.20 (1.06, 1.37)  |                   |
| ≥30                                    | 3147  | 1.10 (0.98, 1.22)  |                   |
| **PIR, ratio**                         |       |                    |                   |
| <3                                     | 6153  | 1.08 (1.00, 1.18)  | 0.1762            |
| ≥3                                     | 3234  | 1.20 (1.05, 1.35)  | 0.5203            |
| **Race**                               |       |                    |                   |
| Mexican American                       | 1536  | 1.09 (0.88, 1.35)  |                   |
| Other Hispanic                         | 1003  | 1.10 (0.87, 1.40)  |                   |
| Non-Hispanic White                     | 3649  | 1.05 (0.94, 1.17)  |                   |
| Non-Hispanic Black                     | 1943  | 1.24 (1.06, 1.45)  |                   |
| Other Races                            | 1056  | 1.16 (0.93, 1.44)  |                   |
| **Education**                          |       |                    |                   |
| <9th Grade                             | 834   | 0.84 (0.61, 1.14)  | 0.0389            |
| 9-11th Grade                           | 1077  | 1.23 (0.99, 1.52)  |                   |
| High School Grade                      | 1716  | 1.00 (0.84, 1.19)  |                   |
| College                                | 2258  | 1.04 (0.91, 1.19)  |                   |
| ≥College Graduate                      | 1825  | 1.32 (1.11, 1.57)  |                   |
| **Marital status**                     |       |                    |                   |
| Married                                | 3988  | 1.06 (0.94, 1.19)  | 0.4822            |
| Widowed                                | 581   | 1.30 (0.98, 1.71)  |                   |
| Divorced                               | 835   | 1.14 (0.92, 1.43)  |                   |
| Separated                              | 265   | 0.91 (0.54, 1.53)  |                   |
| Never married                          | 1413  | 0.96 (0.80, 1.16)  |                   |
| Living with partner                    | 642   | 1.21 (0.90, 1.63)  |                   |
| **Diabetes**                           |       |                    |                   |
| Yes                                    | 963   | 1.06 (0.96, 1.31)  | 0.4835            |
| No                                     | 8235  | 1.13 (1.05, 1.22)  |                   |
| Border line                            | 185   | 0.59 (0.28, 1.26)  |                   |
| **Hypertension**                       |       |                    |                   |
| Yes                                    | 2744  | 1.14 (1.01, 1.28)  | 0.4523            |
| No                                     | 5756  | 1.07 (0.98, 1.18)  |                   |
| **Liver Disease**                      |       |                    |                   |
| Yes                                    | 294   | 1.24 (0.90, 1.72)  | 0.3935            |
| No                                     | 7406  | 1.07 (0.99, 1.17)  |                   |
| **Smoking**                            |       |                    |                   |
| Yes                                    | 3492  | 1.05 (0.94, 1.17)  | 0.3733            |
| No                                     | 4369  | 1.12 (1.01, 1.26)  |                   |
| **Alcohol use**                        |       |                    |                   |
| Yes                                    | 5259  | 1.11 (1.01, 1.21)  | 0.6939            |
| No                                     | 2053  | 1.07 (0.91, 1.25)  |                   |
| **GFR, mL/min/1.73 m²**                |       |                    |                   |
| <60                                    | 747   | 1.20 (0.94, 1.53)  | 0.3773            |
| ≥60                                    | 6967  | 1.07 (0.98, 1.16)  |                   |