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Antimony and sleep health outcomes: NHANES 2009-2016

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ABSTRACT

Objectives: Following an earlier National Health and Nutrition Examination Survey (NHANES) 2005-2008 analysis, we investigated the association between urine antimony and sleep health using more recent data, new measures of sleep health, and multiple measures of urine density adjustment in NHANES 2009-2016.
Design: A cross-sectional study.
Setting: United States, national population-based survey.
Measurements: Multinomial logistic regression (sleep duration) and a generalized linear model with log-binomial regression (OSA, daytime sleepiness, sleep problems) were used to analyze the association of urinary antimony with sleep health outcomes. Urine creatinine and osmolality were considered, combined with statistical adjustment and standardization to account for urine density.
Participants: A total of 8133 adult participants over 20 years of age were used using NHANES 2009-2016.
Results: We did not observe associations between urine antimony and short sleep duration or sleep problems. We observed mixed results for long sleep duration; there was a negative association in NHANES 2015-2016 and no association in NHANES 2009-2014. For self-reported symptoms of OSA, which were only available in 2015-2016, we observed a positive association for upper quartile urine antimony compared with the first quartile (RR = 1.24; 95% CI: 1.03, 1.50) and a test for trend, P= .02.
Conclusion: Urinary antimony was not consistently associated with short sleep duration, long sleep duration, or sleep problems, despite the findings from a relatively recent scientific article using earlier waves of NHANES. We observed a positive association between antimony and symptoms of OSA; this cross-sectional analysis requires confirmation.

Introduction

Antimony (Sb) is a naturally occurring brittle silvery-white metalloid that can pollute the environment through coal-fired power plants, incineration, and mining, along with natural sources such as volcanic eruptions, forest fires, or sea spray.[33] High antimony exposure is common in process and mining industries, as measured through elevated biomarker antimony levels, although occupational exposure in the United States has declined over the past 3 decades.[19] Worldwide daily exposure to antimony is considered to be at generally low levels, with higher concentrations in denser urban countries.[11] For example, in the United States, the general population exposure to antimony is common but at very low levels, allowing urinary excretion to be used to monitor biomarker antimony levels within the body.[5] General antimony exposure is common through tobacco smoke, flame retardants, and therapies used in endemic areas for schistosomiasis and leishmaniasis infections.[29,33] Oral absorption of antimony is uncommon, but is possible through drinking water.[28]

Antimony exposure may lead to acute and chronic respiratory, cardiovascular, gastrointestinal, developmental, and neurological effects. Oral exposure to antimony over 0.5 mg/kg can be emetic, resulting in vomiting and other gastrointestinal effects.[33] Environmental concentrations of antimony are generally lower than the levels needed to cause acute health problems, however there is early evidence of associations with low level chronic exposure. Chronic exposure may be associated with cardiac arrhythmias, dermal

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antimony spots, pneumoconiosis, among other health problems.[33] Increased risk of disease may be present at antimony levels as low as 0.01 μg/L in urine.[21]

Sleep disturbance is one of the potential acute health effects of antimony trioxide exposure (NJDH, 2004).[26] In an early case study conducted in 1846, Dr. Mayerhofer describes his personal experiences with his own ingestion of antimony linked with disturbed sleep experiences.[18] A much more recent population-based study indicated an association between low level antimony exposure and sleep outcomes.[30] Their analysis of the National Health and Nutrition Examination Survey (NHANES) 2005-2008 waves showed that urine antimony was positively associated with a range of poorer sleep health outcomes, including short sleep, increased sleep onset latency, obstructive sleep apnea (OSA), and increased daytime sleepiness.[30] Sleep deprivation and OSA are linked to a wide range of psychological and medical conditions including depression, obesity, diabetes, and cardiovascular disease (Centers for Disease Control and Prevention,[3] 2019) suggesting antimony's association with sleep health may be a pathway by which antimony impacts other health conditions.

To the best of our knowledge,[30] is the only population-based study to investigate antimony in relation to sleep outcomes at population-level exposures. The objective of our study is to extend the work of[30] in 3 distinct and important ways: (1) we will replicate the analyses conducted in the 2017 study using more recently collected data in NHANES 2009-2016 waves; (2) we will utilize 2 new measures of sleep health (Doctor-Diagnosed sleep problems and self-reported sleep problems) and new questions about sleep duration that are available in the more recent NHANES data; and (3) we will incorporate measures of osmolality and creatinine to test sensitivity of results to different measures used to adjust for urine dilution.

Methods

Study population

NHANES is a cross-sectional survey of citizens of the United States released in two-year waves.[22] The NHANES study sample was recruited through multistage sampling from selected households of chosen counties with the goal of being nationally representative. We merged four waves (2009-2010, 2011-2012, 2013-2014, and 2015-2016) of publicly available NHANES data.[23]

Our dataset is restricted to those individuals who provided urine samples which were measured for antimony, our primary predictor of interest, and those who answered questions about sleep outcomes (n = 8133); this restricts our population to those 20 years and older. Informed consent was obtained prior to data collection as per approval by NCHS Research Ethics Review Board.

Outcome measures

Five outcomes were considered in relation to sleep health; some of these were not available in each wave of data, and some were collected using different instruments across the waves of data collection. They will be described for each of the following health outcomes:

- Sleep duration: Sleep duration was evaluated separately for different waves. For 2009-2014, sleep duration was determined by the question "How much sleep do you get in hours?", with categories of short sleep (≤6 hours/night), mid-range sleep (7-8 hours/night) and long sleep (≥9 hours/night). For the years 2015-2016, sleep duration was determined by the question "How much sleep {do you/does SP} usually get at night on weekdays or workdays?" and analyzed using the same categories as 2009-2014 waves.[20,27]

  Obstructive sleep apnea (OSA) symptoms: OSA is defined based on answers to three dichotomous questions; these three questions were only available for 2015-2016. These include (1) Snoring 3 or more nights per week; (2) snorting, gasping, or stopping breathing 3 or more nights per week; or (3) Feeling excessively sleepy during the day 16-30 times per month despite sleeping around 7 or more hours per night on weekdays or work nights.[9] Individuals positive for symptoms of OSA answered yes to at least one of the preceding 3 questions.
- Daytime Sleepiness: Defined as a single categorical item in response to the question "In the past month, how often did you feel excessively or overly sleepy during the day?" asked only in 2015-2016 wave; responses were coded dichotomously with ≥5 times/month being considered an indicator of daytime sleepiness.[27]

  Doctor-diagnosed sleep problems: Participants reported whether or not a doctor had ever diagnosed them with a sleep problem for 3 waves of 2009-2014.

  Self-reported sleep problem: Participants reported whether or not they had ever told a doctor they had trouble sleeping for all 4 waves of 2009-2016.

Urinary biomarkers

Participants provided spot urine samples which were stored at −20°C before being analyzed by inductively coupled plasma-mass spectrometry to measure urinary antimony. The lower limits of detection (LODs) for urinary antimony were 0.032 ug/L for 2009-2010, 0.04 μg/L for 2011-2012, and 0.022 μg/L for 2013-2014 and 2015-2016. Urinary concentrations of antimony below the LOD were assigned the LOD divided by the square root of 2, as recommended by NHANES.[24] To account for differences in urine dilution across samples, urine creatinine and osmolality were extracted from the NHANES database. Urine creatinine was measured using the Jaffe creatinine rate method. Osmolality was available for 2009-2012 data only and measured by standard osmolality tests. Additional details of detection and measurement can be found in the NHANES laboratory method.[24]

Covariates

We considered the following covariates based on evidence of associations with urine antimony and/or sleep health: age (continuous variable in years), gender (male/female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), education level (<than high school, completed high school, and completed >high school),[34,6,7,15,17,8,12] body mass index (BMI),[1,35] alcohol consumption (no alcohol use, 1-4 drinks per week, and >4 drinks per week),[13,32] smoking status (never-smoker (smoke <100 cigarettes)), former smoker (not currently smoking, but has smoked ≥100 cigarettes ever), and current smoker (currently smoking and has smoked ≥100 cigarettes ever),[4,14] serum cotinine (log-transformed), and ratio of family income to poverty level (continuous variable).[16,6,7,15]

Disease outcomes were considered as possible confounders: cardiovascular disease (CVD),[25] diabetes, kidney health, and general health status.[36] CVD was defined by having hypertension or having a positive response to any of the following three questions: "Have you ever had angina/angina pectorals?"; "Ever told you had a stroke?"; or "Ever told you had a heart attack?". Participants self-reported whether or not a doctor ever said they have a weak failing kidney, or said they have diabetes. General health condition was coded as a categorical variable based on the open-ended question "Would you say {your/SP's} health in general is…" with participants reporting excellent, very good, good, fair, or poor condition.

Statistical methods

SAS 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses. For our primary analysis, antimony was categorized into quartiles and statistically adjusted for creatinine.[2,10] In secondary analyses, we standardized antimony by creatinine, and replaced creatinine with osmolality both using statistical adjustment and standardization. We also repeated all analyses treating antimony as a log-transformed continuous variable. We further repeated all analyses using NHANES laboratory sampling weights; results were minimally different and are not reported.

Three models were evaluated for each sleep-related outcome: model 1 only adjusting for urine dilution marker (creatinine or osmolality); model 2 added adjustment for demographic and socio behavioral variables including BMI, gender, age, race/ethnicity, education, serum cotinine, smoking status, family income to poverty, and weekly alcohol drinking; and model 3 further added adjustment for CVD, kidney health, diabetes, and general health status. Adjustment for health outcomes in model 3 has the potential to mask antimony's effects on sleep if sleep mediates the relationship between antimony and health outcomes; we considered this when interpreting results of model 3.

Dichotomous dependent variables (OSA, daytime sleepiness, sleep problems) were analyzed using a generalized linear model with log-binomial regression which allowed for estimates of relative risks (RRs), more appropriate than estimates of ORs since the outcomes are not rare.[31] Dependent variables with 3 categories (sleep duration) were investigated using multinomial logistic regression and odds ratios (ORs) were reported. ORs and RRs were reported along with their 95% confidence intervals.

A series of sensitivity analyses were also conducted. We incorporated laboratory sample weights in the analysis using proc surveylogistic to apply results to the general population; we note that RRs could not be estimated from this procedure, only ORs. We also re-ran the regression analyses using (a) different cutoffs for the antimony quartiles so that values below detection limit were only included in the lowest quartile and (b) added urine metals as additional covariates to account for potential occupational confounders (cadmium, cobalt, cesium, molybdenum, lead, thallium, uranium, manganese, tin, strontium, tungsten).

Results

The study population was 8,133 (n = 8133) adults aged 20 years and older. Demographics and characteristics of the population by quartile of urine antimony can be seen in Table 1. More women and non-Hispanic whites were in the lowest quartile of urine antimony. The 2015-2016 data indicate more people in the ≥9 hours of sleep category, and fewer in the ≤6 hours of sleep category, compared with the 2009-2014 data.

Sleep duration

In both the 2009-2014 NHANES and the 2015-2016 NHANES, there was no association between antimony and short sleep duration (≤6 hours) compared with mid-range sleep duration (7-8 hours), regardless of whether antimony is analyzed in quartiles or as a log-transformed continuous variable (Table 2). For long sleep (≥9 hours), there was no association in fully adjusted models for the upper quartile of antimony in 2009-2014; however, in 2015-2016 there was a negative association between upper quartile antimony and excessive sleep, with a significant test for trend (P= .01) in models 2 and 3. In all years, continuous antimony was not associated with long sleep duration. Results were similar when we standardized antimony by creatinine (Supplementary Table 1) or when controlled for urine dilution using osmolality (results available upon request).

Obstructive sleep apnea symptoms and other sleep-related problems

We did not observe any associations between antimony and sleep-problems or daytime sleepiness (Table 3). There was a small association between antimony and symptoms of obstructive sleep apnea, with an increased risk in the upper quartile (RR = 1.24, 95% CI: 1.03-1.50), a significant test of trend (P= .02), and a borderline association with log-transformed antimony (RR = 1.02, 95% CI: 1.00-1.05). Results were similar when we standardized antimony by creatinine (Supplementary Table 2).

Sensitivity analyses

Results did not meaningfully change when adjusting for urine metals or when using different quartile cutoffs for urine antimony (results not shown). When the sampling weights were included the confidence intervals were wider for the OSA and sleep duration results, but the effect estimates were very similar to those reported in the primary analyses reported in Tables 2 and 3 (Supplementary Tables 3 and 4). In the fully adjusted model (model 3) there were still no associations with daytime sleepiness or sleep problems.

Discussion

Urine antimony was observed to have no association with self-reported short sleep duration or sleep problems. Long sleep duration produced mixed results; NHANES 2009-2014 exhibited a significant association in model one. As more covariates were added in models 2 and 3, this association decreased and was no longer significant. There was, however, a starker negative association between antimony and long sleep duration in NHANES 2015-2016 waves for all 3 models; that is people with higher antimony concentrations were less likely to report long sleep duration**.** Even in models that incorporated the sampling weights, the size of this negative association was similar. This result is in contrast to the findings from,[30] which reported null findings (consistently elevated ORs with wide CIs) between antimony and long sleep. Sleep problems, either based on self-report of symptoms, or self-report of doctor diagnosis, were not associated with urine antimony. A strong association was observed for symptoms of OSA, although this association was only present in the fully adjusted model and was most pronounced when urine antimony was analyzed in quartiles. Results were consistent regardless of the method of urine density adjustment, be it statistical adjustment, standardization, or choice of osmolality or creatinine.

To our knowledge, there are only two studies that investigated the relationship between antimony exposure and sleep issues. The first was an 1846 self-reported case study where Dr. Mayerhofer ingested antimony and documented his subsequent sleep trouble.[18] Because this was a self-reported case-study, we cannot verify the validity of these results. The second study,[30] reported positive associations between urine antimony and both short sleep and long sleep duration using NHANES 2005-2008. Analyzing the NHANES 2009-2014 data which utilize the same question regarding sleep duration, our results are more attenuated toward the null and are not significant in adjusted models.[30] also reported associations with sleep problems and daytime sleepiness; we did not find strong associations with those outcomes. Both our study and the[30] study are cross-sectional in nature, however, there were differences in the design that can account for the inconsistencies across the studies.

Sleep problems were defined differently from[30] because of changes in NHANES questions between the years.[30] reported sleep problems as answering yes to at least one of the following questions:

Table 1
NHANES 2009-16 data set, sample size (N) and sample weighted characteristics.

NHANES 2009-2016	Total	Antimony Q1 (≤ 0.028 μg/L)		Antimony Q2 (0.029-0.046 μg/L)		Antimony Q3 (0.047-0.081 μg/L)		Antimony Q4 (> 0.081 μg/L)	
	N	GM	SE	GM	SE	GM	SE	GM	SE
Urinary antimony (μg/L)	8133	0.02	0.00	0.03	0.00	0.06	0.00	0.15	0.00
Age (years)	8133	48.43	0.39	48.03	0.37	46.77	0.37	44.99	0.36
Urinary creatinine	8129	48.25	0.69	77.14	1.08	128.85	1.35	169.20	1.84
BMI (kg/m2)	8040	27.06	0.13	27.58	0.13	28.58	0.15	28.35	0.15
Ratio of family income to poverty	7384	1.04	0.04	0.87	0.04	0.74	0.04	0.58	0.03
Serum cotinine (ng/mL)	7703	0.14	0.01	0.20	0.02	0.26	0.02	0.70	0.06
	N	**%**		**%**		**%**		**%**	
Gender									
Male	4002	39.4		48.1		52.3		56.1	
Female	4131	61.6		51.9		47.7		44.0	
Race/ethnicity									
Mexican American	1291	16.4		13.4		17.3		16.5	
Other Hispanic	863	11.0		12.1		11.0		8.4	
Non-Hispanic White	3157	44.3		39.4		35.6		36.5	
Non-Hispanic Black	1727	11.1		18.2		24.6		30.1	
Other race - including multi-racial	1095	17.2		16.9		11.5		8.6	
Smoking status									
Current smokers	1484	15.5		18.2		18.9		26.4	
Former smokers	1752	21.8		25.2		24.5		21.6	
Never smokers	4279	62.7		56.7		56.6		52.0	
Education level									
Less than high school	1777	20.3		22.7		21.9		22.2	
Completed high school	1607	17.3		17.7		21.6		22.3	
More than high school	3931	55.4		50.5		46.2		41.8	
Alcohol consumption									
No alcohol	1115	13.6		15.5		14.3		11.4	
1-4 drinks per week	4187	51.8		48.9		51.8		53.5	
>4 drinks per week	491	6.2		6.9		5.2		6.0	
Diabetes[1]									
Yes	944	10.8		12.2		12.7		10.6	
No	6998	86.9		85.1		84.8		87.5	
CVD[2]									
Yes	2817	32.9		37.1		35.1		33.1	
No	5316	67.1		62.9		64.9		66.9	
Kidney status[3]									
Yes	243	2.6		3.7		3.4		3.5	
No	7063	97.1		96.1		96.5		96.3	
General health condition									
Excellent	721	10.7		10.1		9.2		9.1	
Very good	1939	29.4		27.6		24.8		23.4	
Good	3028	38.5		39.0		40.5		45.6	
Fair	1451	18.1		20.1		21.6		18.5	
Poor	255	3.3		3.2		3.8		3.4	
Sleep duration 2009-2014									
Short sleep (≤6 hours/night)	2356	35.3		37.0		38.0		42.1	
Mid-range sleep (7-8 hours/night)	3292	57.7		54.9		53.3		48.4	
Long sleep (≥9 hours/night)	517	7.0		8.1		8.7		9.6	
Sleep duration 2015-2016									
Short sleep (≤6 hours/night)	426	19.4		20.4		22.1		25	
Mid-range sleep (7-8 hours/night)	1069	56.7		56.8		54.7		28.9	
Long sleep (≥9 hours/night)	473	24.0		22.8		23.3		26.1	
Obstructive sleep apnea symptoms, 2015-2016									
Yes	914	53.7		51.7		45.3		51.1	
No	899	46.3		48.3		54.7		49.0	
Daytime sleepiness, 2015-2016									
Yes	1453	73.1		74.6		76.6		71.3	
No	513	26.9		25.4		23.5		28.7	
Sleep problems (told by a doctor), 2009-2014									
Yes	474	6.6		7.6		8.1		8.3	
No	5685	93.4		92.4		91.9		91.7	
Sleep problems (self-reported), 2009-2016									
Yes	1953	24.8		24		23.8		23.5	
No	6180	75.2		76		76.2		76.5	

GM: geometric mean; N:sample size; SE: standard error; NHANES: The National Health and Nutrition Examination Survey
[1] Doctor told you have diabetes.
[2] CVD: cardiovascular disease: Ever told by doctor you had angina pectoris, a heart attack, or a stroke.
[3] Ever told by doctor you have weak or failing kidneys.

Table 2
Adjusted multinomial logistic regression (OR and 95% CI) of sleep duration with urine antimony, 2009-2014 and 2015-2016, NHANES.

	Sleep duration 2009-2014			Sleep duration 2015-2016		
	Model 1 (n = 6163)	Model 2 (n = 4866)	Model 3 (n = 4385)	Model 1 (n = 1966)	Model 2 (n = 1561)	Model 3 (n = 1381)
Short sleep (≤6 hours) vs Mid-range sleep duration (7-8 hours)						
Antimony Q1	1.00	1.00	1.00	1.00	1.00	1.00
Antimony Q2	1.08 (0.93, 1.26)	1.02 (0.86, 1.21)	1.03 (0.86, 1.24)	1.00 (0.73, 1.39)	0.78 (0.54, 1.14)	0.67 (0.45, 1.01)
Antimony Q3	1.06 (0.89, 1.27)	1.00 (0.82, 1.72)	1.02 (0.83, 1.26)	1.03 (0.73, 1.46)	0.83 (0.55, 1.24)	0.76 (0.49, 1.17)
Antimony Q4	**1.25 (1.03, 2.23)**	1.13 (0.90, 1.41)	1.14 (0.90, 1.45)	1.18 (0.79, 1.76)	0.94 (0.58, 1.49)	0.93 (0.56, 1.54)
p-trend	0.05	0.35	0.34	0.46	0.80	0.85
LN antimony	1.02 (0.99, 1.05)	1.03 (0.99, 1.06)	1.03 (0.99, 1.07)	1.00 (0.95, 1.05)	0.99 (0.94, 1.05)	1.05 (0.97, 1.13)
Long sleep (≥9 hours) vs Mid-range sleep duration (7-8 hours)						
Antimony Q1	1.00	1.00	1.00	1.00	1.00	1.00
Antimony Q2	1.21 (0.92, 1.60)	1.25 (0.90, 1.72)	1.30 (0.92, 1.84)	0.87 (0.64, 1.19)	0.65 (0.45, 0.93)	**0.63 (0.42, 0.92)**
Antimony Q3	1.34 (0.98, 1.83)	1.33 (0.92, 1.23)	1.43 (0.97, 2.12)	0.78 (0.55, 1.09)	0.83 (0.55, 1.24)	**0.44 (0.29, 0.69)**
Antimony Q4	**1.59 (1.13, 2.23)**	1.31 (0.86, 1.99)	1.45 (0.93, 2.27)	0.81 (0.54, 1.19)	**0.54 (0.33, 0.87)**	**0.53 (0.32, 0.90)**
p-trend	**0.01**	0.21	0.10	0.21	**0.01**	**0.01**
LN antimony	1.02 (0.97, 1.07)	1.02 (0.96, 1.08)	1.04 (0.98, 1.10)	1.02 (0.97, 1.06)	1.00 (0.95, 1.04)	1.02 (0.94, 1.10)

Model 1: adjusted for urinary creatinine.
Model 2: adjusted for model 1 covariates including BMI, gender, race/ethnicity, age, serum cotinine, smoking status, ratio of family to poverty income, education level, and alcohol intake.
Model 3: adjusted for model 1 and model 2 covariates including general health condition, CVD, diabetes, weak/failing kidneys.
Antimony Quartiles: Q1: ≤ 0.028 μg/L; Q2: 0.029-0.046 μg/L; Q3: 0.047-0.081 μg/L; Q4: > 0.081 μg/L.
LN Antimony: Natural log-transformed urinary antimony; NHANES: The National Health and Nutrition Examination Survey.

Table 3
Adjusted log-binomial regression (RR and 95% CI) for sleep outcomes with urine antimony, 2009-2014 and 2015-2016, NHANES.

Obstructive sleep apnea symptoms 2015-2016			
	Model 1 (n = 1814)	Model 2 (n = 1436)	Model 3 (n = 1263)
Antimony Q1	1.00	1.00	1.00
Antimony Q2	0.96 (0.85, 1.11)	1.02 (0.89, 1.17)	1.06 (0.91, 1.23)
Antimony Q3	0.95 (0.83, 1.10)	1.08 (0.93, 1.25)	1.12 (0.95, 1.32)
Antimony Q4	1.09 (0.93, 1.27)	1.15 (0.96, 1.38)	**1.24 (1.03, 1.50)**
p-trend	0.63	0.16	**0.02**
LN antimony	0.99 (0.91,1.01)	1.00 (0.98, 1.01)	1.02 (1.00, 1.05)
Daytime sleepiness 2015-2016			
	Model 1 (n = 1974)	**Model 2 (n = 1568)**	**Model 3 (n = 1388)**
Antimony Q1	1.00	1.00	1.00
Antimony Q2	1.03 (0.95, 1.11)	1.04 (0.95, 1.13)	1.03 (0.97, 1.10)
Antimony Q3	1.08 (0.99, 1.17)	1.12 (1.02, 1.22)	1.07 (0.99, 1.15)
Antimony Q4	1.04 (0.94, 1.14)	1.05 (0.94, 1.17)	1.02 (0.93, 1.12)
p-trend	0.29	0.10	0.45
LN antimony	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	0.95 (0.89, 1.02)
Sleep problems (Told by a doctor) 2009-2014			
	Model 1 (n = 6168)	**Model 2 (n = 4870)**	**Model 3 (n = 4386)**
Antimony Q1	1.00	1.00	1.00
Antimony Q2	1.20 (0.93, 1.56)	1.13 (0.83, 1.53)	1.05 (0.77, 1.45)
Antimony Q3	1.24 (0.93, 1.66)	1.13 (0.79, 1.60)	0.98 (0.68, 1.41)
Antimony Q4	1.34 (0.97, 1.85)	1.22 (0.83, 1.80)	1.12 (0.74, 1.68)
p-trend	0.10	0.70	0.90
LN antimony	1.02 (0.98, 1.06)	1.00 (0.99, 1.00)	1.02 (0.90, 1.17)
Sleep problems (Self-Reported) 2009-2016			
	Model 1 (n = 8148)	**Model 2 (n = 6443)**	**Model 3 (n = 5779)**
Antimony Q1	1.00	1.00	1.00
Antimony Q2	1.00 (0.89, 1.12)	0.98 (0.88, 1.10)	0.97 (0.86, 1.08)
Antimony Q3	1.00 (0.89, 1.14)	0.98 (0.86, 1.12)	0.95 (0.83, 1.08)
Antimony Q4	1.03 (0.89, 1.18)	0.93 (0.80, 1.09)	0.92 (0.79, 1.07)
p-trend	0.77	0.50	0.35
LN antimony	1.00 (0.98, 1.02)	1.00 (1.00, 1.01)	0.99 (0.96, 1.03)

Model 1: adjusted for urinary creatinine.
Model 2: adjusted for model 1 covariates including BMI, gender, race/ethnicity, age, serum cotinine, smoking status, ratio of family to poverty income, education level, and alcohol intake.
Model 3: adjusted for model 1 and model 2 covariates including general health condition, CVD, diabetes, weak/failing kidneys.
Antimony quartiles: Q1: ≤ 0.028 μg/L; Q2: 0.029-0.046 μg/L; Q3: 0.047-0.081 μg/L; Q4: > 0.081 μg/L.
LN Antimony: Natural log-transformed urinary antimony; NHANES: The National Health and Nutrition Examination Survey

"Have you ever told a doctor or other health professional that you have trouble sleeping?"; "In the past month, how often did you have trouble falling asleep?"; "In the past month, how often did you wake up during the night and had trouble getting back to sleep?"; or, "In the past month, how often did you wake up too early in the morning and were unable to get back to sleep?". NHANES 2009-2016 only continued to use the question, "Have you ever told a doctor or other health professional that you have trouble sleeping?" regarding self-diagnosed sleep problems. A small association was observed between urine antimony and symptoms of OSA, somewhat consistent with Scinicariello et al.[30] reported strongest associations in the second quartile of urine antimony with OSA symptoms, whereas our strongest associations were in the fourth quartile. In addition, our association with OSA symptoms was only analyzed in the 2015-2016 cohort because questions were not asked in previous years; small sample size limits our interpretation of this finding. In addition, prevalence of sleep apnea symptoms is quite high in the NHANES 2015-2016 wave (54%). This high prevalence and the observed association with antimony deserve more research and comparison to other studies of self-reported and objectively measured symptoms.

Our paper extended the[30] study in a variety of ways. We used a measure of urine density, osmolality, in addition to creatinine. Results using osmolality or creatinine were consistent. Kidney disease was added as a potential confounding variable given that it can distort urine biomarker levels. We included a series of sensitivity analyses as well, including running analyses with and without sampling weights, with additional adjustment for urine metals, and changing the urine antimony quartiles so that the lowest quartile includes all of the values below detection limit. Finally, we used the most up to date NHANES datasets from 2009 to 2016, using four cohorts of years instead of the 2 used in[30] giving us a larger sample size.

Despite the improvements and strengths of this study, there are various limitations. The large national NHANES database has findings that are generalizable to the US adult population, but the questions asked per year change in quality and quantity and sleep questions are no different. OSA data was only available for 2015-2016 and sleep duration had to be run separately from 2009-2014 and 2015-2016 due to the difference in question phrasing. Potential covariates such

as “place of work” and “shift hours” were not included in NHANES for all 4 waves between 2009 and 2016; but we did adjust for urine metals as a proxy for potential occupational confounders in a sensitivity analysis. Further, certain questions that are “self-reported” should be noted for potential biases and inaccuracies such as those dealing with self-reported sleep problems, snoring, snorting (measures for OSA) and even hours of sleep. Clinical or autographic assessment of sleep outcomes would improve the measures of sleep. In addition, prospective studies represent a more powerful design, in comparison to cross-sectional studies, for clarifying associations between exposures and sleep outcomes.

In this study we found that urinary antimony is not associated with short sleep duration, or sleep problems, despite the findings from Scinicariello et al.[30] As a replication study, our study primarily found no consistently significant associations between urinary antimony and sleep outcomes, playing an important role in the scientific process by finding results in conflict with a published finding. Our finding covers more years of data from the prior analyses and raises questions about whether the observed association by Scinicariello et al.[30] is as robust as it appears. While we did find a small positive association between antimony and symptoms of OSA, our cross-sectional analysis also needs further investigation to confirm this finding is not spurious or a result of a confounding factor. In addition, OSA was only available for 2015-2016 waves, giving it a smaller sample size than some of the other sleep questions that had responses for all four years. Environmental exposures are typically understudied components of sleep health and may be an opportunity for developing interventions and treatment to reduce the burden of sleep disorders. While this study suggests antimony may not play a key role in sleep health outcomes, population-based studies such as NHANES should continue to be investigated for other potential linkages between environmental exposures and sleep health.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.sleh.2022.05.005.

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