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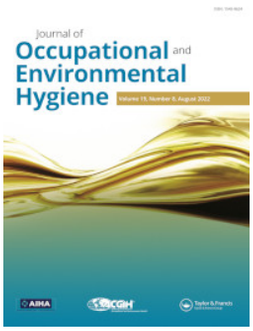

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Continuous NHANES survey data for environmental ambient and occupational hazard identification—feasibility and preliminary findings for osteoporosis and kidney disease

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ABSTRACT

The Continuous NHANES Survey provides detailed health and environmental chemical burden information on the U.S. population. As of 2012, there were data for 72,000 participants. Based on single biomarker determinations, cumulative burdens were estimated. Because age distributions would differ comparing ambient environmental and occupational exposures, a procedure to distinguish ambient from likely occupational exposures was applied. Associations are reported for osteoporosis and kidney disease-related outcomes with cadmium, lead, and other metals. Cumulative cadmium burden (from blood cadmium, ambient and occupational) was a strong predictor of bone fracture risk and ambient tungsten also had a positive association. Cumulative lead (ambient and occupational) had a *negative* ("protective") association with fractures as did mercury (occupational). Bone mineral density was statistically significant and similarly predicted by metal exposures. Kidney disease was significantly associated with cumulative lead burdens from both the estimated ambient and occupational sources and with ambient blood cadmium but was most strongly associated with cumulative occupational uranium burden. Systolic blood pressure statistically significantly increased with cumulative ambient and occupational lead (blood) burden and with ambient cadmium and cobalt. Diastolic blood pressure was significantly associated with several cadmium and cobalt metrics along with ambient and occupational cumulative burdens for lead. For environmental substances with burden half-lives measured in years, NHANES offers opportunities for hypothesis generation and confirmation.

KEYWORDS

Chemical body burden; lead; osteoporosis; renal insufficiency; surveillance; uranium

Introduction

The Continuous National Health and Nutrition Examination Survey (Continuous NHANES) is producing a large observational database with detailed risk factors for the U.S. population (National Center for Health Statistics: National Health and Nutrition Examination Survey. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm, accessed 03-03-2015). It conducts a stratified multistage probability survey of the civilian non-institutionalized population of the U.S. on a 2-year cycle beginning in 1999. Minor survey content revisions occur with each cycle. At the end of the seventh survey iteration (covering 1999–2012), 72,000 subjects had been surveyed. In addition to detailed basic demographics, areas of interest include self-report of medical history, physical exams, a variety of physiological and behavioral measurements, reproductive history, lifestyle history, a brief work history, and determinations for a comprehensive array of chemical species in blood or urine. Data in some areas of special focus are collected only in selected survey periods.

This dataset, while rich in some kinds of information but limited in others, nonetheless presents unique opportunities for research in public health. The uses of NHANES data have included determining population distributions of chemical burdens of concern and, also, the distributions of myriad medical conditions and associated metrics. Other opportunities include both hypothesis generation and testing in etiologic studies with an environmental etiological focus. For example, using NHANES data Gallagher et al. have investigated cadmium in relation to osteoporosis and breast cancer

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

(Gallagher et al. 2008, 2010), Patel et al. (2010) performed epigenome-wide association studies (EWAS) related to Type 2 diabetes, Xu et al. (2010) investigated organochlorine pesticide associations with prostate and breast cancer, and Patel et al. (2012) evaluated persistent pollutants and nutrition in relation to serum lipids.

Worker populations have been the basis for many studies supporting environmental risk assessments. For example, U.S. EPA used the occupational epidemiology literature in compiling the list of environmental pollutants (n = 553) in their Integrated Risk Information System (IRIS) database (http://www.epa.gov/IRIS/help_ques.htm #whatiris, accessed 2009). Some IRIS-listed chemical materials had insufficient experimental, toxicological, or epidemiological evidence to support any risk assessment (n = 103 or 19%). Of the remaining 450 chemicals, 404 (73% of total) had insufficient human epidemiological evidence for a quantitative risk assessment (QRA), depending entirely on experimental/toxicological data. But for the remaining 46 compounds with QRAs based on human epidemiology (8.3%), half came from occupational studies (25) and half came from non-occupational (25) studies (including four compounds with both types of studies).

While some studies have linked single biomarker chemical determinations in NHANES data to existing job-exposure matrices (JEM) (Allen et al. 2006; McHugh et al. 2010), the absence of a detailed work history and time-course of exposure limits such studies. In the present work, an attempt was made to distinguish ambient from occupational environmental sources and then estimate from single NHANES biomarker determinations relative past exposures which were then used to construct burden and cumulative burden measures taking into account the biological half-life of materials. This was a proof-of-concept investigation. The overall methodological approach is described and results are presented from investigating two initial outcome areas of interest: (1) osteoporosis and bone fractures and (2) kidney disease.

Methods

All Continuous NHANES subjects aged 20 and above were selected from the years 1999 to 2012, numbering 38,024. Using the common identifier (SEQN), files were aggregated across survey periods and merged across the following domains: demographic, anthropometric, medical questionnaire, occupational history, reproductive history, smoking history, physical examination, and laboratory findings (in some cases, variable name and coding changes across surveys required accommodation). New variables were derived for, e.g., body mass index (BMI) centered at 25, cumulative smoking exposure, education, and socioeconomic status (SES) scales and outcome measures. Education was coded as follows: 0 = <9 yr, 1 = 9–12 yr, 2 = high-school, 3 = some college, and 4 = college degree. Cumulative smoking, in pack-years, was estimated using several available related variables including *age starting continuous smoking*, and *cigarettes per day*; an indicator variable represented known smokers for whom pack-yr could not be estimated. SES, as *family annual income*, was coded as follows: 0 = <$20 K, 1 = $20–25 K, 2 = $25–34 K, 3 = $35–44 K, 4 = $45–54 K, 5 = $55–64 K, 6 = $65–74 K, 7 = $75 K (surveys 1999–2006), 7 = $75–99 K (surveys 2007–2012) 8 = $99 K or more (surveys 2007–2012). The education and SES variables were specified as continuous linear effects in statistical models.

Because a specific chemical determination may not have been included in every survey period or was missing for some subjects when included in a survey, a missing value variable was created (1 = missing, 0 = not missing) to permit including all records in analyses. The work history available was very limited (e.g., for some survey years: longest held job, in broad industrial categories). In the NHANES sampling scheme, samples are stratified across demographic and geographic groups to ensure representativeness and optimize statistical power, and thus exhibit distributions that do not describe the U.S. population. Generalization of the present findings to the full population would require a somewhat complex statistical adjustment (SAS, Cary, NC; SUDAAN procedure). In this etiologic investigation, generalizing to the full population making use of the sampling weights was not performed.

Exposures

Only one determination for a substance of interest (e.g., cadmium in blood) is available for an NHANES subject, current at the time of their survey and unrelated to occupational history. Using determinations for metals (lead, mercury, cadmium, cobalt, antimony, tungsten, manganese, uranium), both burden and cumulative burden at time of survey were calculated applying a whole-body half-life for each metal (Sugita 1978; Droz et al. 1991; Leggett 1994; Verma 2000; Suwazono et al. 2009) (see Supplementary Online Information, SOM 1). Because workplace exposures to specific process emissions tend to be far higher than ambient exposures to those agents, it was assumed that subjects with high reported determinations probably had a contributing occupational source which was

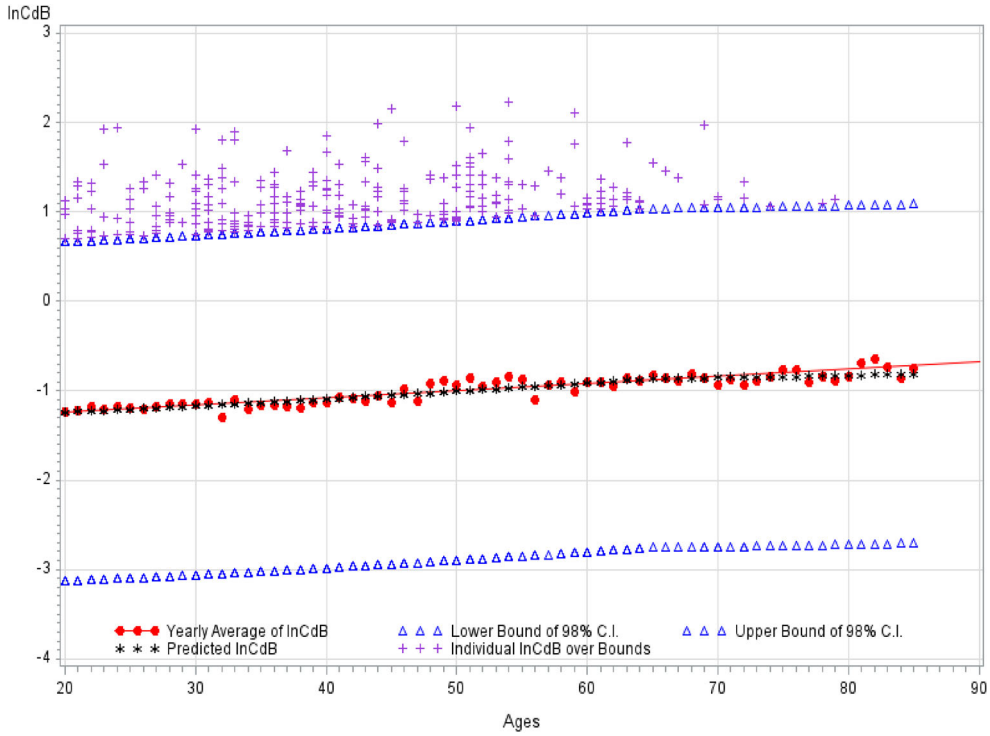

Figure 1. Identification of subjects with exposure burdens above the 98th percentile as likely occupationally exposed: (log) cadmium in blood.

quantified as follows: (1) regression models of the measured (log) concentration were fit to age, age-squared and age above 65, by sex; (2) the upper 98% confidence limit of the predicted concentration value was identified as a function of age and sex (Figure 1); (3) if a subject's concentration was below the 98% upper limit then their ambient burden (*BA*), was set equal to the observed burden concentration and their occupational burden (BO) was set equal to zero; and (4) if a subject's concentration was above the 98% upper limit, then their ambient burden, *BA*, was set equal to the predicted burden for that age and sex, and their occupational burden was set equal to their observed burden minus *BA*.

Without an occupational contribution, the lifetime constant environmental exposure (since age 20, from inhalation, dermal, or ingested sources) that would have produced the observed concentration (ambient burden), was calculated (as a multiplier of an unknown constant related to uptake), applying a whole-body half-life for the burden, from which the cumulative ambient burden was then calculated (SOM 1,2). If there was an occupational contribution, then a similar calculation using the *predicted* burden was the basis for the cumulative ambient burden, and the estimated occupational burden was used to calculate cumulative occupational burden using a sex- and age-specific ratio of burden to cumulative burden (Burden Factor, SOM 3), derived from a specified general propensity for employment in an exposed job, depending on age and sex (Figure 2; SOM 3), and expressed on an arbitrary scale.

The burden metric would be appropriate for examining reversible effects related to relatively recent exposures (in terms of half-lives). The cumulative burden metric would provide insight when health effects accumulate and are irreversible (because a cumulative burden can represent very different time courses of exposure which would determine degree of reversal). For cumulative but reversible health effects, the present analyses would be inappropriate, requiring either longitudinal biomarker determinations in individuals or prior knowledge of the reversibility kinetics of the health effects.

This was a new method for utilizing cross-sectional biomarker exposure information. Propensity of employment was based on general knowledge and, of course, would vary across employers and sectors of industry. For older subjects, this calculation estimates much higher putative exposures occurring earlier in life. Only biomarker exposure burdens were estimated here. Actual airborne, dermal, or ingested exposure history could not be estimated, although with linearity of uptake one can assume some degree of

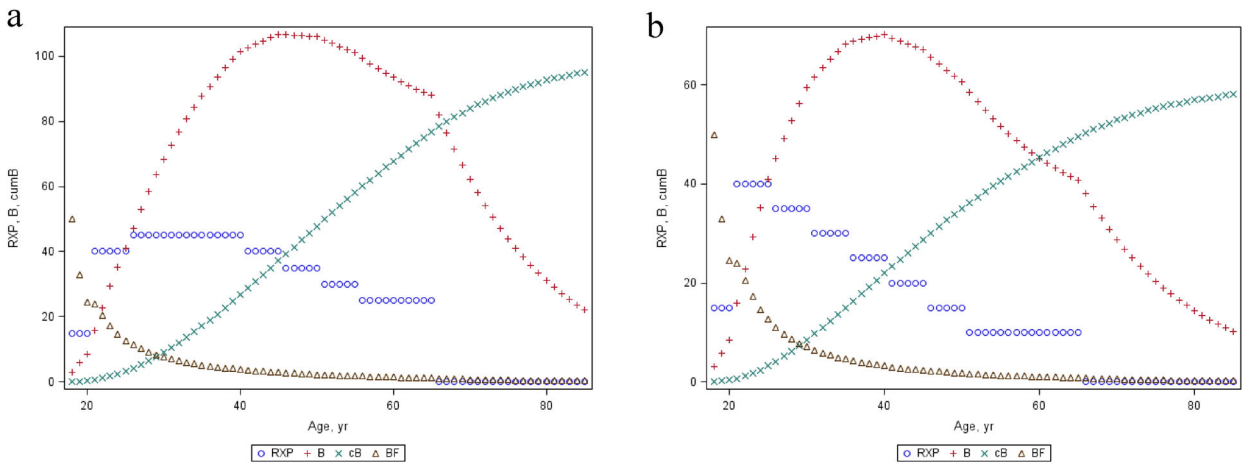

Figure 2. Hypothetical age profiles for employment in jobs likely to have industrial exposures to toxic metals (for half-life = 10 yr): a = men, b = women; RXP– relative exposure probability, B – burden, cB – cumulative burden, BF – burden factor to go from observed occupational burden to cumulative burden (as function of age). B and cB displayed with arbitrary scale.

proportionality between measured steady-state burdens and environmental exposures.

Non-detects for the NHANES biomarker samples were insignificant for lead in blood (less than 1% of samples), on the other hand, for cadmium in blood non-detects comprised about 30%. The limit of detection for Cd was 0.11–0.14 µg/L whereas the top 1% of samples ranged 2.6–10.8 µg/L or 20- to 80-fold higher than the limit of detection. The median cadmium in blood was about 0.33 µg/L, or three-fold above the limit of detection for the ambient exposures. For statistical models of exposure response, non-detects generally represent low levels and could be set to zero with minimal impact, unless the intent is to estimate a nonlinear exposure response at the low exposure end.

Outcomes

For osteoporosis/fractures, five questionnaire self-report items were used to construct a bone fracture score ranging 0–500 (Equation [1]). The score (OSQ) was largely a function of numbers (square root) of wrist, hip or spine fractures:

$$\begin{aligned}\mathrm{OSQ} = 100 \times \{&(\text{“ever told...brittle bones : ”}\ 0,1)\\ &+ (\text{“ever treated for osteoporosis : ”}\ 0,1)\\ &+ \mathrm{sqrt}(\text{no. of hip fractures})/5\\ &+ \mathrm{sqrt}(\text{no. of wrist fractures})/14\\ &+ \mathrm{sqrt}(\text{no. of spine fractures})/10\}/\\ &(\text{no. of non} - \text{missing answers})\end{aligned} \tag{1}$$

The score took into account the maximum number of fractures that could be reported (e.g., five for hip fracture) and was designed to give diminishing weight to each additional fracture at a specific site (e.g., hip) assuming that such fractures are not independent. In addition, bone mineral density (BMD, total femur) by dual-energy X-ray absorptiometry (DEXA) was analyzed both as an independent and dependent variable.

For kidney disease, the outcome (KIQ) was a composite of two questionnaire items (Equation [2]) with maximum value of 3, and heavily driven by self-report of dialysis. A small proportion of subjects answered “don’t know” to question “ever told weak or failing kidneys,” e.g., 0.2% during 2007–2008 survey; these responses were set to “no.” Related to kidney disease, other outcomes analyzed included systolic and diastolic blood pressures and blood urea nitrogen (BUN).

$$\begin{aligned}\mathrm{KIQ} = \{&(\text{“ever told...”}\ \text{kidney disease :}\ \ 0,1) + 5\\ &\times (\text{“had dialysis in last 12 mon : ”}\ 0,1)\}/2\end{aligned} \tag{2}$$

Onset information was not generally reported, e.g., for fractures or reported diagnoses (but available for most cancers). Two prior hypotheses were the well-known associations of (1) cadmium with bone and kidney disease and (2) lead with kidney disease. Other metals were examined for generating new hypotheses.

Analysis

For all tested outcome associations simple linear relations with the constructed burden variables were analyzed with multiple linear regression (SAS V.9.3, Cary, NC)). The regression estimates for the exposure metrics were interpreted as exposure-response relationships. BMD as a dependent variable was log-transformed for improved model fit. For the OSQ outcome

Table 1. Osteoporosis/fracture score (OSQ) predicted by demographic and biomarker exposure risk factors with multiple linear regression.

Parameter	Estimate ×100	SE ×100	t Value[a]	Pr > |t|[a]
Intercept	3.07	0.206	14.9	<0.0001
cum ambient burden, Cd_B	0.048	0.007	6.94	<0.0001
cum occup burden, Cd_B	0.022	0.005	4.89	<0.0001
cum ambient burden, Hg_B	−0.001	0.002	−0.77	0.44
cum occup burden, Hg_B	−0.003	0.001	−2.74	0.0061
cum ambient burden, Pb_B	−0.020	0.002	−10.9	<0.0001
cum occup burden, Pb_B	−0.003	0.001	−2.12	0.034
cum ambient burden, U_U	0.036	0.028	1.31	0.19
cum ambient burden, W_U	0.010	0.003	3.22	0.0013
Male	−2.00	0.104	−19.2	<0.0001
Non-Caucasian	−1.32	0.103	−12.8	<0.0001
Education (0,1,2,3,4)	0.110	0.042	2.64	0.0083
SES (0,1,2, … 8)	−0.099	0.017	−5.73	<0.0001
Age-40	0.079	0.005	16.6	<0.0001
(Age-40)^2	0.003	0.000	8.08	<0.0001
Age-65 if >65	−0.059	0.028	−2.13	0.033
BMI-25	−0.065	0.011	−5.81	<0.0001
(BMI-25)^2	0.001	0.001	2.45	0.014
Smoker, missing cum. smoking	0.194	0.240	0.81	0.42
cum. smoking, pk-yrs	0.002	0.002	0.77	0.44
Ever veteran (0,1)	−1.52	0.155	−9.80	<0.0001

Notes: Osteoporosis score (0–500): mean 2.77, range 0–76, n = 32,370; R^2 = 0.105.
Reference = white women, age: 40, education: <9th grade, SES: <$20k family income, BMI: 25, nonsmoking, non-veteran, SE – standard error Cd_B – cadmium in blood Hg_B – mercury in blood Pb_B – lead in blood, U_U – uranium in urine, W_U – tungsten in urine.
[a]Pr – probability of |t| by chance being as large as was observed; relative values due to the observed non-normal distribution of residuals.

score the residual distribution violated model assumptions and the t-scores produced were interpreted only as relative measures of association significance. For the more significant associations (generally for reported p-values less than 0.2), measures of excess effect were calculated as (1) Effect Ratio (ER): the ratio of the predicted outcomes to baseline values (from intercept), evaluated at the 50th and 90th percentiles of the predicting ambient burden metrics, or as (2) an absolute increase (e.g., blood pressure) at those burdens. For subjects with non-zero occupational exposures, the occupational burden percentiles were based on that subpopulation. Coding of demographic variables was such that the intercept represented the predicted outcome score for 40-yr-old white, non-veteran, non-smoking women with education of < 9 yr, SES (family income) < $20,000, BMI = 25 and zero exposure burdens.

The exposure response parameter estimates here for ambient vs. occupational burden metrics cannot be compared directly because the algorithm that distinguished ambient vs. occupational sources used an arbitrary scale for propensity of occupational exposure. To calculate ERs when there were both burden and cumulative burden contributions for a metal, the percentile of the combined (sum of) burden and cumulative burden metrics (with weights from regression coefficients) were calculated.

Table 2. Femur Bone Mineral Density (BMD, natural log) predicted by biomarker exposure risk factors (demographic risk factors not displayed) with multiple linear regression.

Parameter	Estimate ×100	SE ×100	t value	Pr > |t|[a]
Intercept	−12.7	0.466	−27.3	<0.0001
cum ambient burden, Cd_B	−0.089	0.015	−5.88	<0.0001
cum occup burden, Cd_B	−0.025	0.010	−2.52	0.012
cum ambient burden, Hg_B	0.020	0.004	5.39	<0.0001
cum occup burden, Hg_B	0.003	0.002	1.47	0.14
cum ambient burden, Pb_B	0.013	0.004	3.04	0.0024
cum ambient burden, U_U	−0.127	0.061	−2.09	0.037
cum occup burden, U_U	−0.009	0.004	−2.22	0.026

Notes: Adjusted for sex, race, age, education, SES, BMI, smoking, veteran status as in Table 1.
Intercept: total femur bone mineral density (BMD) = exp(0.01 × −12.7)=0.88 gm/cm^2, by dual-energy X-ray absorptiometry; BMD: mean 0.97, range 0.33–1.82, n = 13,255; R^2 = 0.424.
Reference = white women, age: 40, education: <9th grade, SES: <$20k family income, BMI: 25, nonsmoking, non-veteran, SE – standard error.
[a]Pr – probability of |t| by chance being as large as was observed.

Results

Over the period 1999 to 2012 the 38,024 NHANES participants age 20 and above consisted of 52% women, 53% non-Caucasian ethnic groups, primarily African-Americans (SOM 4, Table S1). The exposure metrics in the form of ambient burdens and cumulative burdens for the metals analyzed were available for between 8491 and 20,589 subjects depending on what surveys sampled a specific metal (SOM 4, Table S2).

Osteoporosis and bone fractures

The OSQ fracture score, available for 32,370 subjects from six surveys, ranged from 0 to 76 (maximum possible: 500), with mean 2.77. Male sex, non-Caucasian race, veteran status, and elevated BMI and SES were all protective risk factors, while age and education were adverse risk factors (Table 1). Cumulative cadmium burden (from blood cadmium) was a strong predictor of fracture risk, from both the estimated ambient (t = 6.9) and occupational sources (t = 4.9). Cumulative lead (ambient, t = –10.9, and occupational, t = –2.1), not hypothesized, had a *negative* (protective) association as did mercury (occupational, t = –2.7). Urinary uranium showed a weak association (t = 1.3), but cumulative ambient urinary tungsten had a stronger association with fracture score (t = 3.2). Although smoking was a statistically significant predictor of blood cadmium levels accounting for a 2.5% increase in the cumulative burden of ambient blood cadmium per pack-year (data not shown), in

Table 3. Predicted effect ratio (ER) for osteoporosis/fracture and bone mineral density at median and 90th percentile biomarker exposure metrics.

		Level of biomarker		Exposure in percentiles	
		50th percentile		90th percentile	
		Predicted		Predicted	
Osteoporosis/fracture[a]					
Parameter	n	OSQ	ER	OSQ	ER
cum ambient burden, Cd_B	20589	4.63	1.07	5.47	1.26
cum occup burden, Cd_B	457	5.24	1.21	7.15	1.65
cum ambient burden, Hg_B	20133	4.32	1.00	4.25	0.98
cum occup burden, Hg_B	272	3.66	0.84	2.26	0.52
cum ambient burden, Pb_B	20133	3.83	0.88	2.49	0.57
cum occup burden, Pb_B	413	4.05	0.93	2.92	0.67
cum ambient burden, U_U	8491	4.39	1.01	4.56	1.05
cum ambient burden, W_U	9809	4.49	1.03	4.92	1.13
Femur Bone mineral density[b]					
Parameter	n	logBMD	ER	logBMD	ER
cum ambient burden, Cd_B	12791	0.886	0.995	0.873	0.98
cum occup burden, Cd_B	285	0.882	0.990	0.867	0.97
cum ambient burden, Hg_B	12791	0.894	1.003	0.903	1.01
cum occup burden, Hg_B	183	0.897	1.007	0.909	1.02
cum ambient burden, Pb_B	12791	0.894	1.003	0.902	1.01
cum ambient burden, U_U	4436	0.890	0.998	0.885	0.99
cum occup burden, U_U	87	0.889	0.997	0.849	0.95

[a]Osteoporosis/fracture score (OSQ) observed range = 0–76.
Baseline OSQ = $3.070 - 2.0^{*}$male $- 1.32^{*}$non-Caucasian $+ 0.11^{*}$educ $- 0.099^{*}$SES $+ 0.079^{*}$(age-40) $+ 0.0025^{*}(\text{age-40})^2$ $= 3.070 - 2.0^{*}0.5 - 1.32^{*}0.10 + 0.11^{*}2 - 0.099^{*}4 + 0.079^{*}20 + 0.0025^{*}400 = 4.34$ for population: 50% men, 10% non-Caucasian, HS education, family income $50k, age 60, BMI 25, non-smoking, non-veteran.
For exposure X: predicted OSQ = baseline OSQ + $\beta_X{}^{*}X = 4.34 + \beta_X{}^{*}X$.
Effect Ratio, ER = predicted OSQ/baseline OSQ.
[b]Bone Mineral Density (BMD) observed range = 0.33–1.82 gm/cm^2.
Baseline BMD = $\exp(-.1273 + 0.118^{*}0.5 + 0.0272^{*}0.10 + 0.0046^{*}2 + 0.0021^{*}4 - 0.00311^{*}20 - 0.000013^{*}400) = \exp(-.1273 + 0.118^{*}\text{male} + 0.0272^{*}$ non-Caucasian $+ 0.0046^{*}\text{educ} + 0.0021^{*}\text{SES} - 0.00311^{*}(\text{age-40}) - 0.000013^{*}(\text{age-40})^2 = 0.891$, for population: 50% men, 10% non-Caucasian, HS education, family income $50k, age 60, BMI 25, non-smoking, non-veteran.
For exposure X: predicted BMD = exp(ln(baseline BMD)+$\beta_X{}^{*}X$)= 0.89 $^{*}\exp(\beta_X{}^{*}X)$.
Effect Ratio, ER = predicted BMD/baseline BMD = exp($\beta_X{}^{*}X$).

the osteoporosis prediction the smoking term itself was very small and insignificant (Table 1).

BMD was assessed by DEXA determinations in four of the NHANES surveys (covering 8 yr). The prediction of bone density by metals followed essentially the same pattern as for fractures, highly statistically significant in most cases (i.e., for Pb, Cd). Ambient (t = 2.1) and occupation (t = 2.2) cumulative exposures to uranium also predicted lower bone density; education was protective (higher bone density) (Table 2; SOM 4, Table S3). Bone density itself was a very strong predictor of (low) fracture risk (t = –14.7, R^2 = 0.10), eliminating the metal contributions, substantially reducing the effects of all other demographic risk factors, and reversing the BMI effect (SOM 4, Table S4).

The effects of metal burdens on the fracture score (for age 60) at the 50th percentiles of the burden metrics ranged from an Effect Ratio of 0.84 (protective) to 1.21 (adverse) and at the 90th percentile, from 0.52 to 1.65 (for occupational cadmium cumulative burden) (Table 3). For bone mineral density at the 90th percentiles, the ER ranged 1.02 (protective) to 0.95 (adverse). Thus, the 90th percentile of occupational cumulative burden for uranium was estimated to result in a 5% loss of BMD.

Table 4. Kidney Disease (KIQ) predicted by demographic and biomarker exposure risk factors with multiple linear regression.

Parameter	Estimate ×100	SE ×100	t Value[a]	Pr > |t|[a]
Intercept	−0.296	0.452	−0.65	0.51
cum ambient burden, Cd_B	0.089	0.015	6.15	<.0001
cum ambient burden, Cd_U	−0.013	0.002	−5.87	<.0001
cum ambient burden, Pb_B	0.028	0.004	6.95	<.0001
cum occup burden, Pb_B	0.027	0.003	9.39	<.0001
cum ambient burden, Sb_U	0.019	0.010	1.90	0.0571
cum ambient burden, U_U	−0.163	0.066	−2.47	0.0134
cum occup burden, U_U	0.062	0.004	17.5	<.0001
cum ambient burden, W_U	0.030	0.008	3.88	0.0001

Notes: Adjusted for sex, race, age, education, SES, BMI, smoking, veteran status as in Table 1.
Intercept = −0.296/100 = −0.003; Kidney disease score (0–3): mean 0.0231, range 0–3, n = 33,072; R^2 = 0.026. Reference = white women, age: 40, education: <9th grade, SES: <$20k family income, BMI: 25, nonsmoking, non-veteran.
SE – standard error, Cd_B – cadmium in blood, Pb_B – lead in blood, Sb_U – antimony in urine, U_U – uranium in urine, W_U – tungsten in urine.
[a]Pr – probability of |t| by chance being as large as was observed; relative values due to the observed non-normal distribution of residuals.

Table 5. Systolic BP (mm Hg) predicted by demographic and biomarker exposure risk factors with multiple linear regression.

Parameter	Estimate	Standard Error	t value[a]	Pr > |t|[a]
Intercept	112.6	0.504	223.	<.0001
ambient burden, Cd_B	1.32	0.292	4.51	<.0001
ambient burden, Co_U	−0.211	0.076	−2.77	0.0056
cum ambient burden, Co_U	0.011	0.002	4.74	<.0001
ambient burden, Pb_B	2.60	0.211	12.3	<.0001
cum ambient burden, Pb_B	−0.085	0.007	−12.7	<.0001
cum occup burden, Pb_B	0.012	0.003	4.51	<.0001
occup burden, Sb_U	0.368	0.162	2.27	0.0231
cum occup burden, Sb_U	−0.001	0.001	−2.24	0.0248
cum ambient burden, W_U	−0.012	0.007	−1.84	0.0653

Notes: Adjusted for sex, race, age, education, SES, BMI, smoking, veteran status as in Table 1.

Intercept: sysBP = 112.6 mm Hg; sysBP: mean 124, range 72–270, n = 34,212; R^2 = 0.268.

Reference = white women, age: 40, education: <9th grade, SES: <$20k family income, BMI: 25, nonsmoking, non-veteran, Cd_B – cadmium in blood Co_U – cobalt in urine Pb_B – lead in blood Sb_U – antimony in urine, W_U – tungsten in urine.

[a]Pr – probability of |t| by chance being as large as was observed; relative values due to the observed non-normal distribution of residuals.

Kidney disease

The kidney disease variable was available for all seven survey periods. The strongest association of any metals was with occupational cumulative exposure to uranium (t = 17.5) followed by cumulative lead (blood) exposures from both the estimated ambient (t = 6.9) and occupational (t = 9.4) sources and ambient cadmium (blood, t = 6.2) but negatively with ambient (urinary) cadmium (t = 5.9) (Table 4; SOM 4, Table S5). Tungsten had an association comparable to that of lead. Elevated BUN was predicted by both ambient (t = 6.6) and occupational (t = 2.7) cumulative cadmium but current cadmium burdens predicted a reduction in BUN (SOM 4, Table S6). Cumulative ambient tungsten increased BUN while cumulative ambient antimony predicted lowered BUN.

Systolic blood pressure (sysBP), with intercept = 112.6, was elevated with cumulative occupational lead burden (t = 4.5) and also was predicted by a contrary combination of ambient (adverse, t = 12.3) and cumulative ambient (protective, t = –12.7) lead burdens (Table 5; SOM 4, Table S7). Ambient cadmium predicted higher sysBP (t = 4.5) as did urinary cobalt but with contrary contributions of burden and cumulative burden (Table 5). Diastolic blood pressure (diaBP), with intercept = 70.1, was statistically significantly associated with several cadmium and cobalt metrics, along with ambient and occupational cumulative burdens for lead (SOM 4, Table S8).

The Effect Ratios (for age 60) for the kidney disease score at the 50th percentile of burden metrics ranged from 0.81 (protective with cumulative ambient uranium) to 3.96 (cumulative occupational lead) (Table 6). At the 90th percentile in those thought to have occupational exposure, the Effects Ratios for cumulative occupational lead and uranium, respectively, were 13.7 and 29.2. Systolic blood pressure was elevated at the 90th percentile of the predicting burdens by 1.3 to 5.8 mmHg (Table 7).

Discussion

This investigation supports the utility of Continuous NHANES for environmental exposure study distinguishing ambient and occupational sources, with a special focus on whether meaningful population biomarker cumulative exposure metrics, such as cumulative burden, can be constructed based on single chemical determinations in individuals. For many chronic disease outcomes, cumulative metrics would be much more appropriate physiological predictors than single current burden measurements. The importance of the ambient vs. occupational distinction arises in part from the different age distributions expected for ambient vs. occupational exposures, which would produce different cumulative burden estimates. The separation of ambient and occupational risk factors would be enhanced with more accurate information on propensity of industrial exposure by age and sex.

Among published studies estimating exposure response using NHANES biomarker chemical concentration determinations (through 2021) no examples were found where investigators attempted to construct *cumulative* exposure metrics given the absence of individual-level exposure histories in the public-use NHANES datasets. A number of published studies using NHANES data have reported exposure response in relation to cumulative exposure but by "cumulative exposure" these studies were referring to aggregated current exposures to *mixtures* such as heavy metals, groups of pesticides, or classes of chlorinated compounds or phthalates, in some cases combined using *a priori* potency weights (e.g., Varshavsky et al. 2016). Epidemiological exposure metrics representing exposure accumulation over time have not been reported using NHANES public-use data.

Osteoporosis

One concern in studying bone fractures is that metabolic mobilization of metals during bone remodeling after fracture could result in non-causal associations, such as with cadmium (Berlin et al. 1995). However,

Table 6. Predicted effect ratio for kidney disease (KIQ) at median and 90th percentile biomarker exposure metrics.

		Level of biomarker exposure in percentiles			
		50th percentile		90th percentile	
Parameter	n	KIQ	ER	KIQ	ER
cum ambient burden, Cd_B[a] cum ambient burden, Cd_U	9005	0.0104	0.99	0.0155	1.47
cum ambient burden, Pb_B	25161	0.0170	1.61	0.0348	3.31
cum occup burden, Pb_B	477	0.0416	3.96	0.1441	13.7
cum ambient burden, Sb_U	10759	0.0129	1.23	0.0195	1.86
cum ambient burden, U_U	10760	0.0085	0.81	0.0012	0.12
cum occup burden, U_U	221	0.0288	2.74	0.3062	29.2
cum ambient burden, W_U	10728	0.0145	1.38	0.0265	2.52

Notes: Kidney disease score (KIQ) observed range = 0–3; baseline KIQ: from regression model for population: 50% men, 10% non-Caucasian, HS education, family income $50k, age 60, BMI 25, non-smoking, non-veteran (Table 4) was small, negative value; sample average KIQ = 0.023; BL KIQ with logistic regression ("told have kidney disease") = 0.0105; (intercept = −3.848; BL prevalence = exp(−3.848) = 0.021; KIQ score for "told have kidney disease" = 0.50; BL KIQ = 0.021*0.50 = 0.0105).

For exposure X: predicted KIQ = baseline KIQ + β_X*X = 0.0105 + β_X*X.

Effect Ratio, ER = predicted KIQ/0.0105, Cd_B – cadmium in blood, Pb_B – lead in blood, Sb_U – antimony in urine, U_U – uranium in urine, W_U – tungsten in urine.

[a]Percentiles of {0.089 × Cd_B − 0.013 × Cd_U} from Table 4.

against this hypothesis was the observation of *diminishing* lead and Hg associated with fracture. A "protective" role for lead and mercury is a new hypothesis but may represent confounding in that occupations with those exposures could also have higher levels of protective physical activity than other occupations, for example, and other metabolic mechanisms may be occurring. Observing reduced fractures as well as increased BMD with lead argues against a mere artifact of lead deposition increasing bone density. Cadmium is a well-known toxic agent for bone health, an association that has been observed previously within the NHANES dataset (1999–2008) (Gallagher et al. 2008). The uptake of uranium in bone from drinking water has been reported as a possible toxic threat (Kurttio et al. 2005) for which there is support in the present findings with respect to bone mineral density. The association of fractures with tungsten is a new finding. Recent literature on environmental risk factors for osteoporosis includes several studies based on NHANES (Elonheimo et al. 2021; Lu et al. 2021). Evidence for a negative association between biomarkers of current lead exposure and BMD were reported without accounting for cumulative burden and were in contrast to the positive association found here which was based on cumulative burden.

In predicting fracture risk using BMD (SOM 4, Table S4), the BMI risk factor becomes positive, suggesting that injury risk (e.g., slips and falls) is playing a role. Up to 25% of NHANES surveys records for measuring bone mineral density by DEXA had missing values for some of the measurements. These missing values depended on age and other demographic classification but also on the successful scheduling of DEXA procedures. Although missing DEXA results could have been associated with osteoporosis morbidity (e.g., impairment) it can reasonably be assumed that this association was not jointly dependent on exposure status as well, and would have a minor effect on the regression results reported here

Kidney disease

The effects of lead and cadmium on kidney health have been studied extensively in the general and occupational populations. Antimony had a smaller effect than cadmium on kidney toxicity in the present study as has been observed in lead workers reflected in elevated N-acetyl-β-D-glucosaminidase (NAG) (Shelley et al. 2012). A study using NHANES data observed a positive association between adverse renal outcomes and current blood cadmium and lead levels, and a negative association with cadmium in urine (Buser et al. 2016), findings consistent with those reported here based on cumulative burden estimates. Uranium in drinking water was weakly associated with proximal tubular function but not glomerular function at low levels (Kurttio et al. 2002). The large estimated ER for cumulative occupational uranium burden but smaller, negative, and less significant effect for ambient cumulative uranium remains unexplained; most ambient uranium exposures may be quite small: the median ambient uranium urinary burden was 0.065 vs. 2.8 µg/g for cadmium (SOM 4, Table S2) and the mean ambient levels may have been diminished by samples below the limit of detection. Acute effects have been reported for tungsten exposures (not combined with

Table 7. Predicted and excess systolic blood pressure (mm Hg) at median and 90th percentile biomarker exposure metrics.

		Level of exposure in percentiles			
		50th percentile		90th percentile	
Parameter	N	Predicted	Excess	Predicted	Excess
ambient burden, Cd_B	24481	125.7	0.4	126.6	1.3
ambient burden, Co_U[a]	11628	125.5	0.2	126.7	1.4
cum ambient burden, Co_U					
ambient burden, Pb_B[B]	24028	126.5	1.2	128.6	3.3
cum ambient burden, Pb_B					
cum occup burden, Pb_B	451	126.7	1.4	131.1	5.8
occup burden, Sb_U[c]	219	126.7	1.4	129.3	4.0
cum occup burden, Sb_U					

Notes: Baseline sysBP = 112.6 + 3.22*male + 1.98*non-Caucasian − 0.37*educ − 0.167*SES + 0.447*(age-40) + 0.0084*(age-40)^2 = 112.6 + 3.22*0.5 + 1.98*0.10 − 0.37*2 − 0.167*4 + 0.447*20 + 0.0084*400 = 125.3 mm Hg, for population: 50% men, 10% non-Caucasian, HS education, family income $50k, age 60, BMI 25, non-smoking, non-veteran; for exposure X: predicted sysBP = baseline sysBP + β_X*X = 125.3+ β_X*X.
Excess sysBP = β_X*X, Cd_B – cadmium in blood, Co_U – cobalt in urine, Pb_B – lead in blood, Sb_U – antimony in urine.
[a]Percentiles of {-0.211 × Co_U + 0.011 × Co_U} from Table 5.
[b]Percentiles of {+2.60 × Pb_B − 0.085 × Pb_B} from Table 5.
[c]Percentiles of {+0.368 × Sb_U − 0.001 × Sb_U} from Table 5.

cobalt as in tungsten carbide tools) in humans (Gbaruko and Igwe 2007). A study of chronic kidney disease in a population with elevated tungsten concentrations in drinking water observed a positive association with incremental cumulative burden of tungsten (in urine, longitudinal samples) (Fox et al. 2021), a finding replicated in the present study.

Effects of toxic metals could impact blood pressure unrelated to kidney disease. Cobalt, observed here associated with increased *sysBP*, is a known cause of cardiomyopathy. No excess blood pressure was observed in a population of cobalt exposed workers (Linna et al. 2004) but those workers did have echocardiographic changes. BUN, a nonspecific measure of kidney function, showed several associations in both directions with the metals analyzed here.

As Weaver et al. (2016) pointed out, blood and urine biomarker associations with kidney dysfunction may be caused by the dysfunction rather than causing it, and conceivably causation is acting in both directions in some cases. If renal impairment is increasing blood levels of some metals such as cadmium (Table 4), it could be exacerbating risk of bone fracture for those metals, but it is difficult to hypothesize a mechanism for a protective effect for lead, for example.

The on-going debate on the direction of causality in these renal effects would perhaps benefit from studies with estimates of cumulative burdens. Findings from an NHANES-based study of metabolic syndrome (Noor et al. 2018) and many others also pose the question of the importance of cumulative exposures.

Inherent limitations and methodological issues

In addition to inherent limitations in NHANES data (self-report, unknown onset, single measurements, limited work history), in the present analyses there is additional uncertainty in (1) burden half-life, (2) estimation of burden metrics from biomarker determinations, (3) unknown time courses of individual ambient and occupational exposures, and (4) choices in constructing outcome scores. These would tend to diminish effect estimates and model fit. Half-life for a substance varies across tissue and depends on exposure history, including current intake, and deposition, so that blood (or urine) levels may be a poor measure of body burden. Nonetheless, there were clear findings representing well-known associations and possibly other new observations. For some findings both ambient and cumulative effects were observed, sometimes with opposite sign. This could be a consequence of misclassification arising from the algorithm employed in constructing the specific burden and cumulative burdens.

Treating chemical determinations below the limit of detection as zero exposure could lead to over-estimating regression model intercepts which would tend to underestimate the corresponding exposure-responses. In regression models with multiple exposure risk factors the effect of one exposure having a high proportion of non-detects would be small; there were no non-detects for the occupational estimates as they were based on NHANES records selected for high biomarker values. For metal exposures having relatively short half-lives, the occupational burden and cumulative burden estimates will necessarily have high variance, especially for subjects no longer working and those retired who would have small residual occupational burdens at survey. This could account for the extreme maximum values obtained for some occupational burdens, especially for cobalt with two-year half-life (SOM 3). Different age profiles were specified

by sex for participation in exposed jobs. This may have generated artifactual interactions between sex and burden metrics, and bias in the sex effect estimates. These were not investigated.

The OSQ and KIQ scores in multiple regressions exhibited residual distributions that were not consistent with estimation of parameter variance in linear models and therefore the t-values (and P-values) reported are not good estimates for parameter precision. However, their relative values are likely indicative of strength of association. In the case of OSQ, the BMD regression estimates had uniform, Gaussian residuals which supported the OSQ findings, as did the sysBP results in the analysis of kidney disease.

Failing to adjust for the sampling design would affect exposure-response estimates if there was effect modification, for example if the true exposure response depended on age, gender, smoking, or BMI. In this situation, of course, the SUDAAN adjustment would also be biased unless those effect modifications were addressed in modeling with interaction terms. The present analysis, as an exercise in hazard identification, did not attempt to examine effect modification. In general, etiologic generalization from NHANES data would be no less valid than generalization from well-executed case-control study designs which also sample the population at risk. The fundamental premise here and in the NHANES sampling design is that the underlying physiology is common to the full and sampled populations. A study utilizing Continuous NHANES Survey data that examined phthalate metabolites in relation to heart disease also justified analysis without the sampling weight adjustment (Sturgeon et al. 2016).

The construction of the four exposure metrics related to ambient and occupational burdens and cumulative burdens could lead to important multicollinearity. However, only about 2.5% of subjects were assigned non-zero occupational exposures so the collinearity between ambient and occupational metrics would be small. Between burdens and cumulative burdens there would be association; significant parameter estimates were observed for these pairs of variables, sometimes with opposite signs. But the construction of the burden variables, depending on half-life and age, would reduce the collinearity. A more important source of the conflicting parameter signs is probably the departure of the age dependence of environment exposures from that assumed: constant for ambient and following a plausible profile for occupational. The combinations of ambient and cumulative ambient metrics were apparently better predictors than either alone and were used to estimate excess blood pressure (Table 7). Similarly, prediction from cadmium blood and urine biomarkers was combined for kidney disease (Table 6).

Conclusion

As demonstrated for two outcomes and environmental exposures to toxic metals, continuous NHANES survey data provide opportunities for enhanced exploratory environmental epidemiology and hazard identification. Outcomes that may be amenable to the present approach are somewhat limited to investigating chronic diseases and exposures with irreversible effects that have body burden half-lives measured in years, or outcomes that have reversible effects associated with current burdens. Many organic compounds of interest, such as bis-phenol-A (BPA), have relatively very brief residence times in the body. For materials with low ambient exposures this method may be optimal and unique but subject to the limitation of single determinations of blood or urine concentrations for the agent of interest. The method could be applied for cancer outcomes in NHANES as well as for many other non-cancer end-points.

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Conflict of interest

The authors report no conflicts of interest in this work.

Data availability

All data were obtained as public-use files from National Center for Health Statistics, https://wwwn.cdc.gov/nchs/nhanes/. The data that support the findings of this study are available from the corresponding author, RMP, upon reasonable request.

References

Allen R, Mage DT, Gondy G, Kodali A, Christensen C, Coble J, Stewart P. 2006. Investigation of job-related pesticide exposure in the Third National Health and Nutrition Examination Survey. Arch Environ Occup Health. 61(2):75–86. doi:10.3200/AEOH.61.2.75-86

Berlin K, Gerhardsson L, Börjesson J, Lindh E, Lundström N, Schütz A, Skerfving S, Edling C. 1995. Lead intoxication caused by skeletal disease. Scand J Work Environ Health. 21(4):296–300. doi:10.5271/sjweh.42

Buser MC, Ingber SZ, Raines N, Fowler DA, Scinicariello F. 2016. Urinary and blood cadmium and lead and kidney function: NHANES 2007-2012. Int J Hyg Environ Health. 219(3):261–267. doi:10.1016/j.ijheh.2016.01.005

Droz PO, Berode M, Wu MM. 1991. Evaluation of concomitant biological and air monitoring results. Appl Occup Environ Hyg. 6(6):465–474. doi:10.1080/1047322X.1991.10387914

Elonheimo H, Lange R, Tolonen H, Kolossa-Gehring M. 2021. Environmental substances associated with osteoporosis—a scoping review. Int J Environ Res Public Health. 18(2):738–754. doi:10.3390/ijerph18020738

Fox J, Macaluso F, Moore C, Mesenbring E, Johnson RJ, Hamman RF, James KA. 2021. Urine tungsten and chronic kidney disease in rural Colorado. Environ Res. 195:110710. doi:10.1016/j.envres.2021.110710

Gallagher CM, Chen JJ, Kovach JS. 2010. Environmental cadmium and breast cancer risk. Aging. 2(11):804–814. doi:10.18632/aging.100226

Gallagher CM, Kovach JS, Meliker JR. 2008. Urinary cadmium and osteoporosis in US women $\geq$ 50 years of age: NHANES 1988-1994 and 1999-2004. Environ Health Perspect. 116(10):1338–1343. doi:10.1289/ehp.11452

Gbaruko BC, Igwe JC. 2007. Tungsten: occurrence, chemistry, environmental and health exposure issues. Global J Environ Res. 1(1):27–32.

Kurttio P, Auvinen A, Salonen L, Saha H, Pekkanen J, Mäkeläinen I, Väisänen SB, Penttilä IM, Komulainen H. 2002. Renal effects of uranium in drinking water. Environ Health Perspect. 110(4):337–342. doi:10.1289/ehp.02110337

Kurttio P, Komulainen H, Leino A, Salonen L, Auvinen A, Saha H. 2005. Bone as a possible target of chemical toxicity of natural uranium in drinking water. Environ Health Perspect. 113(1):68–72. doi:10.1289/ehp.7475

Leggett RW. 1994. Basis for the ICRP's age-specific biokinetic model for uranium. Health Phys. 67(6):589–610. doi:10.1097/00004032-199412000-00002

Linna A, Oksa P, Groundstroem K, Halkosaari M, Palmroos P, Huikko S, Uitti J. 2004. Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart. Occup Environ Med. 61(11):877–885. doi:10.1136/oem.2003.009605

Lu J, Lan J, Li X, Zhu Z. 2021. Blood lead and cadmium levels are negatively associated with bone mineral density in young female adults. Arch Public Health. 79(1):116. doi:10.1186/s13690-021-00636-x

McHugh M, Symanski E, Pompeii L, Delclos G. 2010. The feasibility of adapting a population-based asthma-specific job exposure matrix (JEM) to NHANES. Am J Ind Med. 53(12):1220–1224. doi:10.1002/ajim.20879

Noor N, Zong G, Seely EW, Weisskopf M, James-Todd T. 2018. Urinary cadmium concentrations and metabolic syndrome in U.S. adults: the National Health and Nutrition Examination Survey 2001-2014. Environ Int. 121(Pt 1):349–356. doi:10.1016/j.envint.2018.08.029

Patel C, Bhattacharya J, Butte A, Zhang B. 2010. An Environment-Wide Association Study (EWAS) on Type 2 diabetes mellitus. PLoS One. 5(5):e10746. doi:10.1371/journal.pone.0010746

Patel C, Cullen M, Ioannidis JPA, Butte A. 2012. Systematic evaluation of environmental factors: persistent pollutants and nutrients correlated with serum lipid levels. Int J Epidemiol. 41(3):828–843. doi:10.1093/ije/dys003

Shelley R, Kim N-S, Parsons P, Lee B-K, Jaar B, Fadrowski J, Agnew J, Matanoski GM, Schwartz BS, Steuerwald A, et al. 2012. Associations of multiple metals with kidney outcomes in lead workers. Occup Environ Med. 69(10):727–735. doi:10.1136/oemed-2012-100765

Sturgeon SR, Flynn D, Kaiser AB, Reeves KW. 2016. Urinary levels of phthalate metabolites and cardiovascular disease mortality (NHANES, 1999-2008). Int J Hyg Environ Health. 219(8):876–882. doi:10.1016/j.ijheh.2016.07.006

Sugita M. 1978. The biological half-time of heavy metals. The existence of a third, "slowest" component. Int Arch Occup Environ Health. 41(1):25–40. doi:10.1007/BF00377797

Suwazono Y, Kido T, Nakagawa H, Nishijo M, Honda R, Kobayashi E, Dochi M, Nogawa K. 2009. Biological half-life of cadmium in the urine of inhabitants after cessation of cadmium exposure. Biomarkers. 14(2):77–81. doi:10.1080/13547500902730698

Varshavsky JR, Zota AR, Woodruff TJ. 2016. A novel method for calculating potency-weighted cumulative phthalates exposure with implications for identifying racial/ethnic disparities among U.S. reproductive-aged women in NHANES 2001-2012. Environ Sci Technol. 50(19):10616–10624. doi:10.1021/acs.est.6b00522

Verma DK. 2000. Adjustment of occupational exposure limits for unusual work schedules. AIHAJ. 61(3):367–374. doi:10.1080/15298660008984545

Weaver VM, Kotchmar DJ, Fadrowski JJ, Silbergeld EK. 2016. Challenges for environmental epidemiology research: are biomarker concentrations altered by kidney function or urine concentration adjustment? J Expo Sci Environ Epidemiol. 26(1):1–8. doi:10.1038/jes.2015.8

Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. 2010. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect. 118(1):60–66. doi:10.1289/ehp.0900919