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Implications for Urinary Biological Monitoring Measurements**

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Abbreviations:

10th = 10th percentile of weighted distribution

90th = 90th percentile of weighted distribution

50th = 50th percentile or median of weighted distribution

BMI = body mass index

C = Celsius

CDC = Centers for Disease Control and Prevention

dL = deciliter

FFM = fat free mass

g = gram

GFR = glomerular filtration rate

kg = kilogram

MA = Mexican American

μg = microgram

mg = milligram

mL = milliliter

N = sample size

N/A = not applicable

NCHS = National Center for Health Statistics

NE = could not be reliably estimated

NH = non-Hispanic

NHANES II = The Second National Health and Nutrition Examination Survey (1976-1980)

NHANES III = The Third National Health and Nutrition Examination Survey (1988-1994)

PE = population estimate

UER = urinary excretion rate

US = United States

WHO = World Health Organization

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Abstract

Biological monitoring (i.e., biomonitoring) is used to assess human exposures to environmental and workplace chemicals. Urinary biomonitoring data typically are adjusted to a constant creatinine concentration to correct for variable dilutions among spot samples. Traditionally, this approach has been used in population groups without much diversity. The inclusion of multiple demographic groups in studies using biomonitoring for exposure assessment has increased the variability in the urinary creatinine levels in these study populations. Our objectives were to document the normal range of urinary creatinine concentrations among various demographic groups, evaluate the impact that variations in creatinine concentrations can have on classifying exposure status of individuals in epidemiological studies, and recommend an approach using multiple regression to adjust for variations in creatinine in multivariate analyses.

We performed a weighted multivariate analysis of urinary creatinine concentrations in 22,245 participants of the Third National Health and Nutrition Examination Survey (1988-1994) and established reference ranges (10th to 90th percentiles) for each demographic and age category. Significant predictors of urinary creatinine concentration included age group, sex, race/ethnicity, body mass index, and fat free mass. Time-of-day that urine samples were collected made a small, but statistically significant difference, in creatinine concentrations. For an individual, the creatinine adjusted concentration of an analyte should be compared to a 'reference' range derived from persons in a similar demographic group (e.g., children with children, adults with adults). For multiple regression analysis of population groups, we recommend that the analyte concentration (unadjusted for creatinine) should be included in the analysis with urinary creatinine added as a separate independent variable. This approach allows the urinary analyte concentration to be appropriately adjusted for urinary creatinine and the statistical significance of other variables in the model to be independent of effects of creatinine concentration.

Introduction

Biological monitoring (i.e., biomonitoring) is used to assess human exposures to environmental and workplace chemicals. The most commonly used matrices for biomonitoring are blood (and its components, such as serum and plasma) and urine. The average blood volume of an individual changes an average of 80 mL per kg body weight (Guyton and Hall 2000), and remains relatively constant for a healthy individual who maintains a given body weight; thus, changes in blood concentrations of selected environmental and workplace chemicals in individuals or populations can be readily evaluated. For example, in the Third National Health and Nutrition Examination Survey (NHANES III) (Brody et al. 1994), blood lead concentrations demonstrated the decline in the concentrations of lead in the U.S. population between the Second NHANES (NHANES II), 1976-1980, and the first phase of NHANES III, 1988-1991 (Pirkle et al. 1994). Blood has also been used to evaluate exposures to lipophilic compounds, such as polychlorinated dibenzo-*p*-dioxins, polychlorinated biphenyls, and organochlorine insecticides. These chemicals are reported in blood and serum based on their lipid content, which varies among individuals and within an individual, especially after eating. Adjusting based upon lipid content allows direct comparisons of their concentrations within and among individuals, irrespective of the amount of lipid in the blood, and also comparisons among various biological matrices, such as blood and adipose tissue (Phillips et al. 1989).

Urine also is a widely used matrix for biomonitoring, especially for nonpersistent chemicals (i.e., chemicals that have short biological half-lives), such as some current-use pesticides, metals, and drugs. One of the major advantages of using urine in biomonitoring is its ease of collection for spot or grab (untimed) urine samples though not for 24-hour urine voids, because 24-hour collection can be cumbersome resulting often in improper or incomplete collection. Therefore, spot urine samples, whether first-morning voids or “convenience” samples, are generally used for biomonitoring. The major disadvantages of spot urine samples include the variability in the volume of urine and the concentrations of endogenous and exogenous chemicals from void to void. How to best adjust the urinary concentrations

of environmental chemicals in a manner analogous to the adjustment of the concentrations of lipophilic chemicals in blood samples remains a subject of research.

Variations in urinary analyte concentrations from changing water content in urine have been eliminated using urinary excretion rate (UER) calculations (Rigas et al. 2001). To calculate the UER, the metabolite concentration in urine is multiplied by the volume of the void, then divided by the duration of time the void was accumulating in the bladder. This model assumes that the entire bladder is emptied with each void and that the entire sampling void volume is known. Because this is based on the mass in the sample, variability in urine concentrations from urine dilution are removed, particularly for analytes where the rate of excretion varies with the urine flow (Boeniger et al. 1993). However, because the void volume and times of previous and current voids are required, this approach is often not practical for epidemiologic studies especially those studies involving young children or large population groups.

Urinary creatinine concentrations, specific gravity, and osmolality are common methods for dilution adjustment and for determining whether a spot urine sample is valid for assessing chemical exposures. The most widely used method is creatinine adjustment that involves dividing the analyte concentration (μg analyte/L urine) by the creatinine concentration (g creatinine/L urine). Analyte results are then reported as weight of analyte per gram of creatinine (μg of analyte/g creatinine).

Many studies have documented that creatinine adjusted urinary metabolite concentrations correlate better with blood, serum, or plasma concentrations of the parent chemical than the unadjusted concentrations suggesting that creatinine adjusted analyte concentrations may serve as good surrogates for size-related dose (Cline et al. 1989; Hill et al. 1995a; Shealy et al. 1996; To-Figueras et al. 1997). However, these studies typically self-correct for size variation because each data pair is from a single individual. Thus, children, who have blood volumes that are proportionately smaller (80 mL less per kg body weight lighter), would have higher blood concentrations of a chemical after the absorption of the same amount of chemical after an exposure as compared to adults with an identical exposure. Similarly, their lower urinary creatinine concentrations would increase the creatinine adjusted urine concentration of

the metabolite as compared to an adult with an identical exposure. Therefore, the paired urine and blood values from children and adults can be easily used to determine the relationship between matrices within an individual, but do not necessarily mean the creatinine adjusted metabolite concentrations can be used to accurately compare exposures among the study participants.

Creatinine concentrations also are used to determine whether the spot urinary sample is valid. The guidelines of the World Health Organization (WHO) for valid urine samples for occupational monitoring often are used. The WHO recommends that if a sample is too dilute (creatinine concentration less than 30 mg/dL) or too concentrated (creatinine concentration greater than 300 mg/dL), another urine void should be collected (WHO 1996) and analyzed for creatinine and the target chemical. These guidelines have been adopted for biomonitoring in the U.S. workplace (ACGIH 2002; Lauwerys and Hoet 1993). The U.S. Department of Transportation defines an acceptable urine specimen for the screening of selected drugs of abuse as one which has a creatinine concentration of 5 mg/dL or greater and a specific gravity of 1.001-1.020. Urine of “normal” persons would be unlikely to be excluded using these criteria (Barbanel et al. 2002).

Urine creatinine concentrations were used to adjust the urinary concentrations of pesticides and metabolites of pesticides and phthalates in subsets of adults participating in NHANES III. These “creatinine-corrected” concentrations ($\mu\text{g analyte/g creatinine}$) were reported in addition to the unadjusted concentrations in $\mu\text{g analyte/L urine}$ (Blount et al. 2000; Hill et al. 1995b). These reports also used WHO’s recommendation for exclusion of samples, regardless of age (these were all adults), sex, or race/ethnicity.

Because urinary creatinine concentrations are so widely used to adjust or correct urinary concentrations of environmental and workplace chemicals or their metabolites, the formation of urinary creatinine and the ways in which various factors may affect its concentration are important to review. Creatinine is a waste product formed by the spontaneous, essentially irreversible dehydration of body creatine and creatine phosphate from muscle metabolism. A total of 94%-98% of total creatine is

accumulated within skeletal muscle. The rate of creatinine formation is fairly constant, with about 2% of body creatine converted to creatinine every 24 hours; this rate decreases with age in adults.

Creatinine is cleared from the body through the kidney primarily by glomerular filtration. However, 15%-20% of the creatinine in urine can occur by active secretion from the blood through the renal tubules (Boeniger et al. 1993). The rate of secretion can vary substantially among persons due to various genetic and biological factors. Researchers have found a high correlation between urinary creatinine concentrations and muscle mass (Edwards and Whyte 1959; Fuller and Rich 1982); higher urinary creatinine concentrations in men than women (Bjornsson 1979; Turner and Cohn 1975); decreased urinary creatinine concentrations in adults with increasing age, probably because of a general decline in muscularity and glomerular filtration rate (Alesio et al. 1985; Drive and McAlevy 1980); and seasonal variation in creatinine concentrations in children (Freeman et al. 1995; O'Rourke et al. 2000). In addition, persons with a high red meat intake have a higher urinary creatinine concentration than those on a low red meat diet (Lykken et al. 1980). The effect of these factors and others on urinary creatinine concentrations has been reviewed (Boeniger et al. 1993).

Because of the relatively constant excretion rate of creatinine into the urine (which makes urinary creatinine concentration inversely proportional to urine flow rate), creatinine adjustment has been used to normalize analyte concentrations in spot samples for occupational and environmental exposure monitoring. This approach reportedly works well for individual occupational exposure analysis (e.g., preshift and postshift samples from the same person) if the analyte measured behaves similarly to creatinine in the kidney (Boeniger et al. 1993). However, if the analyte is excreted predominantly through passive secretion in the kidney, the analyte secretion will vary with urine flow rate and creatinine adjustment would not correct for urine concentration/dilution.

Urinary creatinine concentration data have been used to adjust urinary concentrations of environmental and workplace chemicals, primarily in adults. Thus, most of the published urinary creatinine concentration data are for adults. However, as more emphasis is placed on children's health

issues and assessment of their exposures to environmental contaminants, biomonitoring of younger populations is also increasing (Needham and Sexton 2000; O'Fallon et al. 2000).

Our study objectives were to document the normal range of urinary creatinine concentrations among various demographic groups, evaluate the influence demographic variations in creatinine concentrations can have on biological monitoring measurements, and explore methods to appropriately adjust urinary analytes using creatinine that take into account demographic differences in urinary creatinine levels. In this article, we present urinary creatinine concentrations in samples collected during 1988-1994 throughout the United States from NHANES III participants. We describe the distribution of urinary creatinine concentrations within this population by age, sex, and race/ethnicity for persons aged 6 years and older. We also examine other factors that can affect urinary creatinine concentrations, such as body mass index (BMI), fat free mass (FFM) and health status: kidney function, hyperthyroidism, hypertension, and diabetes (Boeniger et al. 1993). In addition, we compare urinary creatinine concentrations in urine samples collected at three different times throughout the day (morning, afternoon, and early evening). Finally, we propose a multiple regression approach to adjusting urinary analytes for differences in creatinine concentration. This information will greatly assist researchers, occupational health physicians, risk assessors, public health officials, and other users of urinary biomonitoring data better analyze and interpret urinary biomonitoring measurements.

Methods

NHANES III, which was conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), was a 6-year survey over the time period 1988-1994 designed to measure the health and nutrition status of the civilian, non-institutionalized U.S. population aged 2 months and older. National population estimates and estimates for the three largest racial/ethnic subgroups in the U.S. population (non-Hispanic white, non-Hispanic black, and Mexican American) can

be derived from each of the two individual 3-year phases (1988-1991 and 1992-1994) and from the full 6-year survey.

Sampling selection for NHANES III was based on a complex multistage area probability design. Children younger than 5 years, adults aged 60 years and older, non-Hispanic blacks, and Mexican Americans were oversampled to allow an adequate number of sample persons in these demographic groups from which population-based estimates could be derived. However, urine samples were not collected for children under the age of 6 years. Data were collected through a household interview and a standardized physical examination conducted in a mobile examination center. Urine specimens for analyses, including those for measuring creatinine concentrations, were collected during this examination throughout the day. Pre-examination procedures depended on the age and health status of the individual. For example, persons over age 12 years were asked to fast for 2-12 hours, depending on appointment times, and persons with known diabetes or under age 12 years were asked to eat a normal diet before the examination. Sociodemographic information and medical histories of the survey participants and their families were collected during the household interviews. Details of the sample design have been published (NCHS 1992). The data set used in our analysis is a part of the public release data set for NHANES III (NCHS 2004).

Laboratory Methods

During the physical examinations, urine specimens were collected, stored cold (2-4°C) or frozen, and sent to the Fairview University Medical Center (Minneapolis, MN) where they were analyzed for creatinine using an automated colorimetric determination based on a modified Jaffe reaction using a Beckman Synchron AS/ASTRA clinical analyzer (Beckman Instruments, Brea, CA) (Jaffe 1886). The laboratory and method were certified according to guidelines set forth in the Clinical Laboratory Improvement Amendment of 1988.

Demographic Covariates

Age was reported at the time of the household interview as the age in years at the last birthday. Age categories used in our statistical analyses were 6-11 years, 12-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, and 70 years and older. A composite racial/ethnic variable based on reported race and ethnicity was created to define three major racial/ethnic groups: non-Hispanic black, non-Hispanic white, and Mexican American. Persons who self-reported race as none of the three major racial/ethnic groups were included in the overall estimates but excluded from analyses in which race/ethnicity was the stratification variable.

Health Status Definitions

The health status of participants was considered in the data analysis. All participants were tested for a variety of physical conditions that have been reported to potentially affect urinary creatinine concentrations. Participants were not screened for a given condition if they reported having been previously informed by a physician as having one of the conditions. Clinical parameters for determining the health status of individuals are summarized in Table 1.

The glomerular filtration rate (GFR) used for kidney function analysis was calculated using the equation derived from the Modification of Diet in Renal Disease (MDRD) study (Coresh et al 2002; Coresh et al. 2003; Levey et al. 2003) in which serum creatinine, age, sex, and race were used. Serum creatinine measurements for the MDRD study and the NHANES III study were performed in different laboratories and a laboratory bias was observed (Coresh et al. 2002). Thus, serum creatinine values in the NHANES III dataset were calibrated to be more comparable to the laboratory data obtained in the MDRD study by subtracting 0.23 mg/dL from each value (Coresh et al. 2002; Coresh et al. 2003). For our analysis, we considered persons to have kidney dysfunction if their GFR was less than 60 mL/min/1.73 m², which corresponds to those GFRs indicative of moderately or severely decreased kidney function (Levey et al. 2003).

Statistical Analysis

Data were analyzed using the NHANES III Analytic Guidelines for sample size and coefficient of variation to ensure reliability of estimates. Survey-specific sample weights were used in statistical analyses. Arithmetic means, selected percentiles of urinary creatinine concentrations and their respective confidence intervals were calculated using SAS release 8 (SAS Institute, Cary, NC), and the SUDAAN (release 7.5.6.) Proc Descript procedure. SUDAAN incorporates the NHANES III sampling weights and adjusts for the complex sample design of NHANES III. Sample weights account for the unequal probabilities of selection resulting from the cluster design and the planned oversampling of certain subgroups. Oversampling of children, the elderly, non-Hispanic blacks, and Mexican Americans necessitated the use of sampling weights in all analyses to produce national estimates of prevalence and associated variances. Because Proc Descript does not provide design effect estimates for distribution percentiles, we multiplied the design effect associated with a mean by 30 or 80 (i.e., the NCHS recommended sample size for estimating a proportion of 0.50 (N=30) or a proportion of 0.10 or 0.90 (N=80) when the design effect is 1.0). If this product was larger than the actual sample size, we determined that the percentile estimate should not be reported. All distribution percentiles reported met this criterion.

The collective data set of urinary creatinine values were slightly skewed toward higher values; however, logarithmic transformation did not improve the shape of the distribution. Because the results were only slightly skewed and variance estimates obtained using SUDAAN software were robust, we chose not to transform the urinary creatinine results for the analysis.

An analysis of covariance was used correct for demographic covariates before comparing concentrations among demographic groups and daily collection times. Statistical significance was set at $p < 0.05$.

Similar to the approach used by Wilder et al. (2001), we used multiple linear regression models to study the influence of standard demographic variables on urinary creatinine concentration and additional factors previously reported to affect urinary creatinine concentrations. Nine variables were evaluated, though all variables were not used in the final model: race/ethnicity, sex, age, BMI, FFM, diabetes status, hypertension status, hyperthyroid disease status, and kidney disease status. FFM was calculated using a sex- and age-specific bioelectrical impedance analysis equation reported by Deurenberg et al. (1991). Height, weight, age, sex and reactance measurements (ohms, at 50kHz) were used in the equation to derive individual estimates of FFM. Reactance measurements were available only for persons 12 years and older.

Our analysis comprised 22,245 valid creatinine values in urine samples collected during 1988-1994. Though we did not perform a thorough analysis of the rate of non-response and its possible effects on our analyses, we did evaluate the potential effects of differential non-response using the method of Flegal (1991). We analyzed major demographic variables obtained from the interview data for persons with urinary creatinine values and persons without urinary creatinine values. For each variable, we compared the observed mean urinary creatinine level with the expected mean value for persons in the interviewed sample after we adjusted for that variable. The comparison assumed no statistical significance from differential non-response if the estimates were within 10% of the expected means (Flegal 1991). We did not detect bias resulting from differential non-response for any of the previously listed variables.

Results

The weighted urinary creatinine arithmetic means, medians, 10th and 90th percentiles, and their respective upper and lower 95th confidence intervals are shown in Table 2. The data are shown both collectively and divided into age, race/ethnicity, and sex categories. No data were excluded from the distribution analysis. Non-Hispanic blacks had significantly greater concentrations of urinary creatinine than all other racial/ethnic groups, across all age groups ($p < 0.0006$; Figure 1). On average, blacks had

33.43 and 34.25 mg more creatinine per dL urine than did Mexican Americans and non-Hispanic whites, respectively. Adult (i.e., 20 years and older) males had significantly greater urinary creatinine than adult females ($p < 0.0001$).

The percentage of individuals in each demographic group that had urinary creatinine concentrations outside the WHO exclusionary guidelines is shown in Table 3. Recently, Wilder et al. (2001) reported that these exclusionary criteria should be re-evaluated for urine samples taken from children. In that study (410 children aged 1-8 years), 12% of all children fell below the guideline value and 0% were too concentrated. Up to 8% of the NHANES samples examined had urinary creatinine concentrations less than 30 mg/dL, whereas fewer than 3% had concentrations greater than 300 mg/dL. Although these percentages differed for each demographic category, more samples were considered “too dilute” than “too concentrated.”

The mean concentrations of urinary creatinine stratified by collection time are shown in Table 4. Creatinine concentrations were statistically different for some of the collection periods though the differences were less than 6%. Morning voids typically yielded higher urinary creatinine concentrations than did urine samples at other collection times. Urinary creatinine differed significantly between morning and evening collections ($p = 0.001$); the difference was marginally significant between morning and afternoon ($p = 0.058$) collections. Afternoon and evening creatinine concentrations did not differ significantly from one another ($p = 0.272$).

We did not have the information to classify the diabetic status or kidney function of persons aged 6 to 19; thus, we first limited our multiple linear regression analysis to subjects 20 years and older to determine the effects of diabetes and kidney function on urinary creatinine. For subjects 20 years and older, statistically significant categorical independent variables in the model included race/ethnicity, sex, diabetic status, kidney function status, and age group. The continuous independent variable, BMI, was also a statistically significant factor. There were statistically significant interactions between race and diabetic status ($p = 0.0022$), between race and kidney function status ($p = 0.0073$), between race and age

group ($p=0.0028$), between sex and age group ($p=0.0260$), and between diabetic status and age group ($p=0.0133$). Hyperthyroidism, hypertension, and FFM were not significant factors in the model, thus, were not included in the final model.

Participants with diabetes tended to have lower urinary creatinine levels than did those without diabetes, and the magnitude of the decrease varied significantly among the three racial/ethnic groups studied and among the age categories. For example, non-Hispanic black participants with diabetes had urinary creatinine levels 34.2 mg/dL lower ($p<0.0001$) than those without diabetes, whereas no significant differences were observed in the other racial/ethnic groups. Similar variation was observed for persons with diabetes in different age group categories. For example, urinary creatinine levels for persons with diabetes aged 30-39 years were 40.6 mg/dL lower ($p=0.011$) than those without diabetes in the same age group.

The effect of kidney dysfunction on urinary creatinine concentration was not the same across racial/ethnic groups. Non-Hispanic whites with kidney dysfunction had urinary creatinine levels 10.7 mg/dL ($p=0.0047$) higher than those without kidney disease, whereas the levels for Mexican Americans with kidney disease were 15.5 mg/dL ($p=0.0329$) lower than those without.

So that we could include children and adolescents in our analyses, we next performed multiple linear regression analyses which included all ages. Subjects 20 years and older were only included if they could be classified as not having diabetes and as not having moderately or severely decreased kidney function.

Coefficients from the multiple linear regression model are presented in Table 5. The R^2 of the model was 0.175. Statistically significant categorical independent variables in the model included race/ethnicity, sex, and age group. Neither hyperthyroidism nor hypertension was a significant factor in the model. The continuous independent variable, BMI, was also a statistically significant factor. Statistically significant interactions were observed between race and age group ($p = 0.0002$) and between gender and age group ($p < 0.0001$).

According to the model results, the effect of age category on urinary creatinine concentrations differed among each racial/ethnic group. Among Mexican Americans, urinary creatinine levels for 20-29 year olds were 44.3 mg/dL higher ($p < 0.0001$) than those for 50-59 year olds. Among non-Hispanic whites, this difference was 55.8 mg/dL ($p < 0.0001$), and among non-Hispanic blacks, 57.5 mg/dL ($p < 0.0001$).

BMI also was significantly related ($p < 0.0001$) to urinary creatinine concentrations. According to the model results, every unit increase in BMI was associated with a 1.30 mg/dL increase in urinary creatinine. Thus, persons with a BMI at the 90th percentile (31.37 kg/m^2) would be expected to have urinary creatinine levels about 8.6 mg/dL higher than persons of the same demographic group but with a BMI at the median (24.75 kg/m^2). However, when FFM is included in the model, it interacts strongly with BMI. For example, at the median FFM (2574.97 units), a one-unit increase in BMI results in a 0.92 mg/dL increase in urinary creatinine. At the 75th percentile FFM (2692.15 units), a one-unit increase in BMI is associated with a 0.5 mg/dL increase in urinary creatinine. At the 25th percentile FFM (2462.47 units), a one-unit increase in BMI is associated with a 1.33 mg/dL increase in urinary creatinine. Thus, at higher FFM, BMI has a smaller effect on urinary creatinine.

Discussion

Biomonitoring of exposure is used in the workplace to evaluate a person's chemical exposure during the workday and to provide some standard measure for allowable individual workplace exposures. When timed urine excretion (to determine UER) or 24-hour samples are not collected, the chemical measurement is routinely adjusted using creatinine to correct for urine concentration/dilution in spot samples.

For occupational monitoring, the WHO has recommended exclusionary guidelines for urinary creatinine concentrations to identify individual samples that are invalid for chemical analysis. The rationale behind these guidelines is that urine samples with extremely low creatinine concentrations are

too dilute and may impair detection of low levels of toxicants, while samples with extremely high creatinine concentrations indicate dehydration, which could have changed the kidney's secretion, excretion, and/or reabsorption of the target chemical. Therefore, analysis of either dilute or concentrated spot samples would not result in an analyte concentration representative of actual exposures. Typical statistical rules of exclusion of outliers would exclude the upper and lower 1% or 5% of the population. However, our data indicate that in some demographic categories, almost no one would be excluded using these criteria. In other demographic categories, as many as 20% of the participants would be excluded. These data support the findings recently reported by Wilder et al. (2001). For example, essentially no Mexican-American female adults 70 years or older had urinary creatinine greater than 300 mg/dL. However, in the same demographic group, about 19% of the samples would be excluded because their urinary creatinine concentrations were less than 30 mg/dL.

The WHO guidelines may have been established for occupational monitoring using a workforce with less diversity than the U.S. workforce. If only non-Hispanic white males aged 20-60 years are considered, approximately 10% of the samples would have been excluded, 5% for each exclusionary criterion. Among both sexes in this age range or women alone, approximately 15% of samples would have been excluded, with the majority (9%-13%) excluded for being too dilute. In the U.S. population as a whole, samples from nearly 10 million women could be excluded using criteria that were likely not established using data from women. Clearly, with the change in the composition of the modern U.S. workforce to include women, multiple racial/ethnic groups, and older workers because of the increasing retirement age, the guidelines for sample exclusion should be reevaluated to reflect the results shown in Table 2. In addition, a special reconsideration, or perhaps elimination, of the lower limit of acceptable creatinine concentration should be given. As analytical technology for measuring environmental toxicants or their metabolites in urine samples has dramatically improved over the last several decades driving the limits of detection very low, detection of chemicals in urine samples considered "dilute" is much less likely to be an issue of concern. Rather, intermittent or low level exposures will likely have a

greater effect on the ability for a given marker of exposure to be measured with current analytical technology.

We observed a small, but statistically significant, increases in creatinine concentrations in the morning, compared to the afternoon and evening. Although we have no information suggesting the morning urine collections in NHANES III were first morning voids, our analyses appear consistent with the general thought that urine from a first morning void is more concentrated.

In the early 1980s, biomonitoring for nonoccupational, environmental exposures became an important exposure assessment tool in epidemiologic studies evaluating environmental exposure risks. In these studies, 24-hour samples were costly and logistically impractical to collect. Therefore, in keeping with the most common approach in workplace monitoring, spot urine samples were collected and chemical measurements were adjusted using creatinine. This approach was generally considered the only valid way to adjust spot urine samples for comparison across groups, even though limited data was available to evaluate the validity of this adjustment. With the increase in the number of child health studies in the 1990s, including assessing *in utero* exposures by analyzing the urine of pregnant women, the variation in creatinine concentrations among different age groups has become increasingly apparent. Several researchers have noted significant differences in chemical exposures among children and adults (Aprea et al. 2000; Heudorf and Angerer 2001; Mills and Zahm 2001; Wilder et al. 2001), and most have recognized and reported that creatinine adjustment elevates the urinary chemical concentrations in children compared to adults.

The differences between children and adults are due, in part, to differences in lean muscle mass. Children and the elderly tend to have less muscle than active adults. Accordingly, children have lower FFM than adults. Because lean muscle produces the vast majority of creatinine in the body, we evaluated the relation between FFM and urinary creatinine. Indeed, FFM and urinary creatinine were significantly associated ($r=0.222$; $p<0.0001$); however, the magnitude of their correlation was much lower than expected. When FFM is considered in the linear regression model, it accounts for much, but not all, of the

significant associations with age, sex, and race. Because bioimpedance analysis is not performed in most studies collecting biomonitoring data for exposure assessments, age, sex, and race can be used in concert as a surrogate for FFM. Further, because the FFM accounts for a significant proportion of the variation of creatinine, creatinine adjusted measurements may serve as a useful surrogate for estimating the size-related dose of an individual (Barr et al. 2004).

Urinary biomonitoring measurements are used to assess exposures of individuals and population groups. For an individual, if the urinary chemical level is divided by the creatinine concentration to adjust for dilution, one must recognize that the urinary creatinine concentration varies by age, sex, and race/ethnicity (Mage et al. 2004). Therefore, it would be best for ‘normal’ or ‘reference’ ranges for creatinine adjusted urinary levels to be available for separate demographic groups, (e.g., children, adolescents, and adults), rather than just for the total population. *The Second National Report on Human Exposure to Environmental Chemicals* (CDC 2003) provides separate reference ranges for 116 chemicals by age, sex, and race/ethnicity. In addition, the *Report* provides reference ranges for non-creatinine adjusted levels.

For population groups, public health scientists use the creatinine-adjusted urinary chemical level in two types of models. In model 1, the creatinine adjusted urinary chemical level is a dependent variable and other variables are regressed against it to determine significant predictors of exposure to that chemical. In model 2, the creatinine adjusted urinary chemical level is an independent variable used to determine if that chemical exposure is a significant predictor of a disease outcome. In both models, the urinary chemical concentration is typically divided by the urinary creatinine level and the resulting concentration, expressed per weight of creatinine, is the variable used.

In model 1, where the creatinine-corrected urinary level is the dependent variable, independent variables may be unrelated to the chemical concentration itself but related to the urinary creatinine concentration. In such a case, the independent variable could potentially achieve statistical significance only because it is related to urinary creatinine. Since age, sex, and race/ethnicity all relate to urinary

creatinine, this possibility would have to be considered if they were significant predictors of creatinine-corrected urinary chemical levels.

In model 2, a similar problem could exist in which the creatinine-corrected urinary level may be a significant predictor of a health outcome only because the health outcome is related to urinary creatinine levels, not to the levels of the chemical. This would be a less likely scenario than model 1, but is possible because the urinary level is a ratio of a chemical concentration divided by urinary creatinine concentration.

A straightforward solution to both of these potential problems in interpreting multiple regression results is to separate the urinary chemical concentration from the urinary creatinine concentration in the regression models. For model 1, the dependent variable would be the urinary chemical concentration, unadjusted for creatinine. Urinary creatinine concentration would be included in the multiple regression as an independent variable. In this manner, the urinary chemical concentration is adjusted for urinary creatinine, since urinary creatinine is an independent variable, and other covariates in the model are also adjusted for urinary creatinine. Statistical significance of independent variables would therefore not be due to association with urinary creatinine concentration.

Similarly, in model 2, urinary chemical concentration (unadjusted for creatinine) would be included with urinary creatinine as independent variables to predict the health outcome. The health outcome and the urinary chemical concentration variables are adjusted for creatinine by the urinary creatinine independent variable, so any association of the health outcome with chemical concentration would not be influenced by a relationship with urinary creatinine levels.

The present study has several limitations. First, some of the variables used in our evaluation of the data such as the bioimpedance measurements and serum creatinine measurements were available only for persons older than 12 years. Second, fasting times may have differed among participants and no dietary variables were considered in the analysis. Third, children younger than 6 years were not evaluated. Fourth, first morning void samples were not targeted for collection so few were likely present in our

study, therefore, these findings may not be directly applicable to first morning void samples. Lastly, upper bound confidence intervals could not be established for seven of the 90th percentile estimates given for creatinine levels in different age, sex, and racial/ethnic demographic groups.

Conclusions

Generally, in epidemiological studies it is not practical to collect 24-hour urine samples or when young children are involved even first morning voids. Therefore, spot samples are generally the urine samples that are analyzed for assessing human exposures to many chemicals. The urinary concentrations of these chemicals are often reported on a weight/volume basis and a creatinine-adjusted basis. However, urinary creatinine concentrations differ dramatically among different demographic groups, thus biomonitoring studies using creatinine concentrations to adjust the concentrations of environmental and occupational chemical concentrations should seriously consider the impact these findings will have on the data. For an individual, the creatinine adjusted concentration of an analyte should be compared to a ‘reference’ range derived from persons in a similar demographic group (e.g., children with children, adults with adults). For multiple regression analysis of population groups, we recommend that the analyte concentration (unadjusted for creatinine) should be included in the multiple regression analysis with urinary creatinine added as a separate independent variable. This approach allows the urinary analyte concentration to be appropriately adjusted for urinary creatinine and the statistical significance of other variables in the model (e.g., age, sex, race/ethnicity) to be independent of effects of urinary creatinine concentration.

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Table 1. Clinical parameters for designation of health status of individuals in NHANES III (1988-1994) survey.

Health Status	Clinical Parameter
Diabetes [†]	Blood glucose > 126 mg/dL after 8 hour fast
Hypertension ^{††}	Systolic value > 140 mmHg or diastolic > 90 mm Hg
Hyperthyroidism	Serum thyroid stimulating hormone (TSH) > 5 μ U/mL
Kidney dysfunction	Glomerular filtration rate < 60 mL/min/1.73 m ²

† Also included individuals who were told by a physician that they had diabetes.

†† Also included individuals who were told by one physician two or more time or by two or more physicians that they were hypertensive. Systolic and diastolic measurements were the average of 3 measurements.

Table 2. Weighted quantiles of urinary creatinine concentrations (mg/dL) in the NHANES III (1988-1994) study population in persons aged 6 to 90 years.

Race/ Ethnicity	Age	All				Male				Female						
		N	10 th	50 th	90 th	Mean	N	10 th	50 th	90 th	Mean	N	10 th	50 th	90 th	Mean
All [†]	All	22245	33.54	118.6	237.2	130.4	10610	49.56	137.2	254.4	148.3	11635	27.36	99.49	217.7	113.5
			32.07-35.22	115.6-121.4	234.7-241.1	128.2-132.7		46.08-53.30	134.2-141.0	249.9-262.1	145.3-151.3		26.04-28.90	97.15-102.9	212.6-224.0	110.7-116.3
	6-11	3078	42.84	98.09	163.1	102.1	1590	49.91	97.84	164.7	104.4	1488	33.22	98.34	160.6	99.48
			38.77-46.55	93.81-102.2	157.9-173.4	98.91-105.2		43.18-55.95	92.79-103.7	158.1-179.6	100.3-108.5		29.54-40.47	91.40-104.0	153.4-171.7	95.27-103.7
	12-19	3095	62.14	150.2	271.2	161.5	1461	65.27	151.9	271.2	163.6	1634	56.04	149.5	271.6	159.3
			56.47-67.04	145.1-158.7	263.0-283.4	156.7-166.2		60.08-75.83	145.3-163.6	258.8-285.3	157.3-169.9		46.63-64.40	140.5-158.7	261.3-290.1	153.4-165.1
	20-29	3438	47.45	153.8	275.4	161.8	1608	71.64	172.8	297.2	183.0	1830	37.24	132.8	246.6	141.0
			42.53-53.42	147.1-160.7	266.4-294.4	156.6-166.9		61.62-79.74	161.6-185.3	283.5-324.2	175.4-190.6		31.64-44.04	126.1-141.6	236.4-264.6	135.0-146.9
	30-39	3259	31.15	128.8	245.7	138.0	1438	44.77	150.5	263.3	157.9	1821	27.36	106.9	227.7	118.8
			28.80-36.01	121.5-135.8	239.0-259.1	132.4-143.5		39.90-55.96	140.2-162.1	251.8-285.2	150.1-165.7		24.80-29.49	100.6-113.9	215.3-240.0	112.6-125.0
40-49	2542	26.32	119.0	226.2	124.6	1203	43.24	146.9	252.3	149.7	1339	20.49	89.62	195.1	100.6	
		23.20-30.79	112.3-124.6	216.4-238.8	120.1-129.1		33.38-54.56	140.5-154.0	235.8-265.8	143.0-156.4		17.75-24.31	80.26-96.92	185.0-207.8	95.91-105.3	
50-59	1823	26.80	98.43	206.0	108.1	838	39.06	123.5	227.7	131.8	985	22.54	73.09	165.5	86.06	
		25.02-29.92	92.63-102.9	195.2-217.1	103.8-112.5		33.30-47.73	114.4-136.4	216.9-243.5	123.6-139.9		20.73-25.22	65.66-81.02	155.0-178.2	80.66-91.46	
60-69	2243	30.01	94.22	193.6	105.5	1134	43.54	121.4	213.4	126.4	1109	23.64	75.37	167.4	87.91	
		27.67-32.95	89.12-98.97	187.0-200.7	101.8-109.2		39.06-52.11	114.0-127.0	206.3-231.8	121.2-131.6		21.53-28.25	69.29-82.09	159.3-179.3	82.50-93.32	
70+	2767	29.37	86.23	179.6	97.99	1338	43.77	107.4	199.2	117.5	1429	23.90	69.14	166.5	84.51	
		27.41-31.37	82.36-90.57	175.3-189.1	95.14-100.8		39.62-50.19	103.0-115.4	188.6-210.9	112.8-122.2		21.86-26.68	65.23-74.63	157.2-180.0	80.87-88.15	
NH White	All	8150	30.94	112.7	229.5	124.6	3820	45.91	133.0	249.2	144.0	4330	25.27	92.09	205.9	106.1
			29.31-33.10	109.7-115.9	224.7-236.1	122.0-127.2		41.88-50.56	129.6-137.2	242.3-259.3	140.3-147.8		24.03-26.63	87.71-96.48	200.5-212.9	103.2-109.0
	6-11	800	42.75	98.11	155.1	99.92	413	48.74	97.19	158.6	102.1	387	32.95	99.00	152.0	97.48
			38.08-47.69	92.57-103.8	149.0-166.7	95.85-104.0		42.61-59.12	90.56-103.9	149.1-169.9	96.98-107.3		28.89-40.18	90.86-107.6	145.5-169.4	92.80-102.16
	12-19	790	55.90	147.1	261.4	156.0	348	61.84	147.4	252.0	155.7	442	47.86	145.3	269.6	156.2
			50.31-63.98	139.2-156.0	248.8-278.3	149.8-162.1		55.72-74.85	138.3-159.2	237.8-275.1	147.8-163.6		39.55-61.86	135.6-156.6	252.1-301.7	147.5-164.9
	20-29	879	42.72	143.3	271.7	154.8	388	63.81	169.7	299.4	181.7	491	31.55	120.3	233.7	128.9
			36.40-50.15	137.1-155.0	258.8-296.4	148.2-161.4		53.31-79.41	159.6-185.2	281.2-333.8	171.4-192.1		26.10-40.42	110.2-132.1	214.7-246.5	121.9-136.0
	30-39	1025	30.03	123.3	237.0	133.3	437	42.21	146.3	252.5	153.7	588	25.83	103.3	221.3	113.2
			27.68-34.07	115.2-131.9	231.2-254.5	126.5-140.1		36.31-53.47	132.9-162.3	241.1-286.5	143.4-163.9		23.08-29.71	94.32-108.3	208.0-232.5	106.4-120.0
40-49	893	23.40	113.9	219.2	119.8	422	37.14	142.3	244.5	145.0	471	18.61	78.56	182.9	94.46	
		20.58-28.72	106.6-120.2	208.7-234.9	115.0-124.6		27.78-49.52	136.0-152.0	225.5-260.1	137.2-152.9		16.70-22.96	71.33-95.15	172.8-22.2	89.08-99.83	
50-59	884	26.06	93.95	203.3	104.3	409	37.74	117.6	226.0	129.0	475	22.64	70.44	154.8	81.36	
		23.96-28.89	87.35-100.4	186.8-218.4	98.83-109.8		32.01-46.84	107.5-133.7	213.8-244.7	118.3-139.6		20.46-25.30	60.83-77.02	144.1-170.3	75.52-87.20	
60-69	963	30.04	90.41	189.0	102.7	495	43.84	121.0	210.3	124.8	468	22.76	72.55	162.9	83.35	
		27.35-33.20	84.88-97.18	184.0-197.1	98.60-106.8		39.83-54.25	110.5-125.2	201.7-231.6	119.4-130.2		20.24-27.22	64.84-80.14	153.6-174.0	77.53-89.17	
70+	1916	28.69	84.89	176.9	96.03	908	42.90	107.0	196.4	116.2	1008	23.44	66.73	160.9	82.30	
		26.60-30.86	79.77-88.55	171.2-187.6	92.84-99.22		38.70-49.49	101.1-114.9	184.3-209.6	111.0-121.3		21.27-27.17	63.62-72.34	152.0-173.8	78.16-86.44	
NH Black	All	6664	57.24	153.3	282.6	165.4	3117	72.84	170.3	298.5	181.9	3547	49.64	140.1	265.1	151.3
			54.37-61.00	149.6-158.1	277.7-289.5	162.3-168.5		68.31-76.59	164.5-177.6	292.7-310.3	177.3-186.4		45.94-53.27	136.5-144.4	257.6-272.6	147.8-154.8
	6-11	1060	53.72	113.8	201.2	120.9	553	54.58	113.2	199.5	120.3	507	52.64	115.6	203.9	121.6
		47.81-58.87	110.1-120.9	192.5-211.3	116.3-125.6		47.09-60.66	107.4-120.6	188.2-209.9	114.8-125.8		44.80-59.58	108.8-122.1	192.5-215.0	115.7-127.5	

	Age	All					Male					Female				
		N	10 th	50 th	90 th	Mean	N	10 th	50 th	90 th	Mean	N	10 th	50 th	90 th	Mean
NH Black (cont)	12-19	1113	83.12	179.4	310.9	193.1	530	88.38	188.5	322.3	203.9	583	75.86	172.3	295.0	182.4
			74.04-92.62	172.1-187.3	302.2-325.6	185.4-200.8		76.57-102.1	179.9-200.5	313.1-343.1	193.8-214.0		65.30-87.54	163.0-182.3	279.4-317.6	173.6-191.2
	20-29	1098	82.04	193.4	315.0	200.1	484	90.23	207.0	339.9	214.7	614	77.77	185.2	292.9	188.0
			69.40-93.87	188.1-202.9	301.5-332.9	192.8-207.5		76.67-115.3	193.1-224.3	316.1-377.4	202.5-227.0		61.32-89.35	175.2-194.3	285.9-315.4	179.6-196.2
	30-39	1120	64.14	164.4	284.9	172.0	480	82.70	186.1	312.0	193.1	640	56.48	148.7	267.4	155.3
			59.23-68.77	155.0-173.6	272.8-299.6	165.7-178.3		72.56-97.43	176.9-197.6	290.2-326.5	184.2-202.1		48.35-63.58	140.9-157.0	252.3-283.1	146.8-163.9
	40-49	798	53.76	152.8	275.2	164.2	359	78.50	180.6	293.5	189.5	439	44.54	130.0	238.3	142.9
			47.98-65.24	140.8-169.3	260.6-288.1	155.8-172.6		68.15-92.70	171.0-192.2	279.4-321.4	181.2-197.7		36.66-53.85	119.9-146.6	226.1-267.4	132.2-153.7
50-59	475	35.78	134.6	245.3	164.2	210	67.50	165.3	269.7	169.0	265	26.01	111.0	217.8	117.2	
		28.68-48.23	118.0-150.0	228.4-264.5	155.8-172.6		57.98-81.14	151.2-174.7	242.4-NE	157.8-180.1		22.35-36.53	95.86-125.3	195.0-232.7	105.9-116.7	
60-69	557	47.22	115.9	224.5	140.0	279	62.87	150.1	270.2	158.6	278	41.38	96.15	186.4	108.8	
		41.17-54.59	107.1-126.2	210.3-242.4	130.7-149.3		49.25-75.93	139.9-162.2	245.7-288.8	149.3-167.9		36.32-50.60	90.57-103.2	171.7-207.9	100.8-116.7	
70+	443	38.79	110.9	209.8	129.3	222	49.05	130.0	220.8	136.0	221	34.58	104.1	203.4	112.2	
		34.55-46.27	105.6-120.3	203.8-224.2	122.4-136.3		40.90-56.87	111.2-145.9	204.7-NE	126.7-145.4		30.28-42.77	93.44-109.7	185.0-NE	103.5-120.9	
MA	All	6496	38.35	123.3	236.5	132.9	3253	50.52	138.2	252.5	147.2	3243	30.80	106.0	218.3	117.6
			35.69-42.13	120.2-126.4	231.6-243.7	129.7-136.1		45.74-55.94	133.2-144.5	245.1-264.9	142.4-151.9		28.08-34.80	102.7-110.1	211.2-224.9	114.3-120.9
	6-11	1083	31.92	87.99	154.4	92.24	548	32.22	89.53	160.3	94.76	535	30.10	85.55	152.2	89.57
			26.14-37.65	82.28-92.45	142.6-166.6	87.67-96.82		25.61-41.30	84.26-97.65	144.3-173.5	89.59-99.93		24.10-38.54	77.88-95.20	135.4-165.8	82.58-96.55
	12-19	1039	57.50	140.0	249.0	148.2	518	57.72	142.3	255.7	151.5	521	56.75	133.6	240.4	144.8
			50.37-35.25	134.9-145.8	236.3-265.6	142.1-154.3		47.04-70.12	133.6-152.3	237.5-275.7	141.3-161.6		46.27-65.77	127.5-145.7	226.5-262.8	138.4-151.3
	20-29	1311	50.96	148.9	261.9	155.4	664	65.14	166.9	276.3	168.9	647	38.47	126.9	246.5	138.5
			42.23-61.01	142.8-156.9	247.8-282.7	150.2-160.7		52.75-77.76	157.8-174.4	258.8-297.8	162.4-175.4		33.15-48.69	117.1-137.6	230.1-269.9	132.0-145.0
30-39	979	36.71	132.4	251.8	139.9	464	52.12	152.2	270.9	160.9	515	29.57	108.8	216.1	116.7	
		32.00-44.12	126.9-138.5	236.7-265.9	133.5-146.3		45.63-63.38	143.9-159.7	259.3-285.2	153.1-168.6		25.79-33.52	101.0-115.5	189.2-236.6	108.9-124.6	
40-49	738	36.33	126.5	227.7	133.0	376	53.58	146.3	244.7	153.6	362	30.05	105.3	202.8	111.2	
		31.16-45.31	118.7-136.6	217.3-240.6	126.6-139.3		45.62-66.69	138.0-157.9	231.8-263.5	146.1-161.1		23.07-40.38	90.92-120.9	190.3-216.5	101.6-120.7	
50-59	367	27.21	99.12	196.2	109.1	177	46.38	125.2	218.5	134.5	190	18.60	71.09	170.7	85.27	
		22.37-33.48	85.91-113.7	188.0-210.9	100.2-118.1		37.21-60.52	106.7-151.5	202.3-NE	122.6-146.4		15.41-26.66	58.38-91.33	153.9-183.6	76.36-94.18	
60-69	641	21.39	88.47	196.8	99.68	326	28.99	111.2	201.6	116.9	315	20.89	66.85	192.2	86.36	
		19.67-27.51	79.08-97.59	184.4-211.1	94.73-104.6		19.82-47.54	102.1-130.0	174.7-217.9	108.4-125.3		14.85-25.71	57.74-80.61	157.1-NE	77.82-94.90	
70+	338	27.77	94.66	174.8	99.46	180	59.55	116.8	190.8	123.8	158	20.84	67.79	145.7	76.47	
		21.93-35.03	87.62-104.8	160.4-201.0	91.72-107.2		50.02-70.02	101.7-135.7	175.7-NE	114.3-133.3		16.97-29.49	55.72-81.33	116.5-NE	66.0-86.94	

† All population data including those individuals not grouped into one of the three race/ethnicity categories presented. Upper and lower 95th confidence intervals of each quantile are shown in smaller text below the estimate.

NH= Non-Hispanic; MA = Mexican American; N = sample size; NE = could not be reliably estimated; 10th = 10th percentile of distribution; 50th = 50th percentile or median of distribution; 90th = 90th percentile of distribution.

Table 3. Percentage of each demographic group in NHANES III (1988-1994) whose urinary creatinine concentrations (mg/dL) fell outside of the WHO guideline range (i.e., less than 30 mg/dL or greater than 300 mg/dL).

Race/Ethnicity	Age	All	Male			Female				
		N	< 30 mg/dL	> 300 mg/dL	N	< 30 mg/dL	> 300 mg/dL	N	< 30 mg/dL	> 300 mg/dL
All	All	22245	7.7	3.3	10610	4.0	4.6	11635	11	2.2
	6-11	3078	4.7	0.1	1590	2.9	0.1	1488	6.7	0.1
	12-19	3095	2.3	6.5	1461	1.6	6.0	1634	3.1	7.0
	20-29	3438	5.2	6.9	1608	3.4	10	1830	7.0	4.2
	30-39	3259	8.4	4.2	1438	4.3	6.4	1821	12	2.0
	40-49	2542	11	2.5	1203	5.9	3.8	1339	16	1.3
	50-59	1823	12	0.9	838	6.0	1.5	985	17	0.3
	60-69	2243	9.3	0.6	1134	3.9	1.2	1109	14	0.1
	70+	2767	10	0.7	1338	3.5	1.1	1429	15	0.5
NH White	All	8150	8.8	3.0	3820	4.5	4.2	4330	13	1.8
	6-11	800	4.3	0.0	413	2.6	0.0	387	6.1	0.0
	12-19	790	3.0	6.1	348	2.0	4.6	442	3.9	7.6
	20-29	879	6.2	6.4	388	3.9	10	491	8.4	3.0
	30-39	1025	9.2	4.0	437	4.9	6.2	588	14	1.8
	40-49	893	13	2.3	422	7.0	3.5	471	19	1.1
	50-59	884	13	0.6	409	7.4	1.1	475	18	0.2
	60-69	963	9.3	0.4	495	3.0	0.8	468	15	0.0
	70+	1916	11	0.8	908	3.6	1.2	1008	15	0.5
NH Black	All	6664	2.8	7.1	3117	1.5	9.8	3547	3.8	4.8
	6-11	1060	3.4	0.6	553	2.7	0.4	507	4.2	0.8
	12-19	1113	0.6	12	530	0.2	15	583	1.1	8.5
	20-29	1098	1.7	13	484	1.6	17	614	1.7	9.5
	30-39	1120	2.8	7.6	480	1.8	12	640	3.5	4.5
	40-49	798	3.3	5.8	359	1.4	8.2	439	4.9	3.7
	50-59	475	6.9	3.5	210	1.1	5.8	265	12	1.6
	60-69	557	2.4	2.6	279	1.0	5.4	278	3.4	0.7
	70+	443	4.9	1.1	222	3.6	1.2	221	5.9	0.6
MA	All	6496	6.5	3.1	3253	4.4	4.3	3243	8.8	1.8
	6-11	1083	8.9	0	548	8.0	0.0	535	9.8	0.0
	12-19	1039	2.8	4.2	518	2.0	5.0	521	3.5	3.4
	20-29	1311	4.8	5.4	664	3.8	6.5	647	6.1	3.9
	30-39	979	6.7	3.5	464	3.9	5.4	515	9.7	1.4
	40-49	738	6.5	2.1	376	4.0	4.0	362	9.2	0.2

Race/Ethnicity	Age	All N	Male		Female		< 30 mg/dL	> 300 mg/dL		
			< 30 mg/dL	> 300 mg/dL	N	< 30 mg/dL			> 300 mg/dL	
	50-59	367	10	1.5	177	3.3	3.3	190	16	0.0
	60-69	641	15	0.3	326	10	0.8	315	19	0.0
	70+	338	11	0.0	180	2.8	0.0	158	19	0.0

NH= Non-Hispanic; MA = Mexican American; N = sample size.

Table 4. Weighted mean urinary creatinine concentration (mg/dL) for each collection timeframe during the day. The concentrations were corrected for age, race/ethnicity, gender, and body mass index. Each mean was contrasted to the means of other collection timeframes using an analysis of covariance test to determine if they were statistically different.

Collection Timeframe	N	Mean Creatinine (mg/dL)	Contrasted to Morning	Contrasted to Afternoon	Contrasted to Evening
Morning	10621	133.5	N/A	p = 0.058	p = 0.001
Afternoon	7190	128.6	p = 0.058	N/A	p = 0.27
Evening	4434	126.1	p = 0.001	p = 0.27	N/A

N/A = not applicable

Table 5. Coefficients of the independent variables from the multiple linear regression model of urinary creatinine concentrations (dependent variable).

		Independent Variable Coefficient	Standard Error of Coefficient	P-value
Intercept		53.51	6.83	<0.0001
Race / Ethnicity				
Non-Hispanic White	(1)	- 7.33	5.00	0.1486
Non-Hispanic Black	(2)	20.82	5.68	0.0006
Mexican American	(3)	0.00	0.00	not applicable
Gender				
Male	(1)	34.59	4.14	<0.0001
Female	(2)	0.00	0.00	not applicable
Age Group				
6-11 years	(1)	12.55	5.24	0.0026
12-19 years	(2)	62.90	5.64	<0.0001
20-29 years	(3)	43.56	5.70	<0.0001
30-39 years	(4)	29.78	5.78	<0.0001
40-49 years	(5)	16.65	6.42	0.0125
50-59 years	(6)	- 1.17	6.24	0.8524
60-69 years	(7)	- 8.47	4.81	0.0847
70 + years	(8)	0.00	0.00	not applicable
BMI (continuous)		1.30	0.19	<0.0001
Race / Ethnicity*Age Group				
	(1)*(1)	16.19	6.09	0.0106
	(1)*(2)	16.14	6.67	0.0192
	(1)*(3)	10.74	6.68	0.1141
	(1)*(4)	4.34	5.66	0.4469
	(1)*(5)	-2.40	6.94	0.7308
	(1)*(6)	-0.82	5.73	0.8864
	(1)*(7)	6.99	4.86	0.1569
	(1)*(8)	0.00	0.00	not applicable
	(2)*(1)	8.64	6.48	0.1886
	(2)*(2)	24.28	6.48	0.0005
	(2)*(3)	28.19	6.50	0.0001
	(2)*(4)	15.01	7.12	0.0403
	(2)*(5)	14.69	7.77	0.0648
	(2)*(6)	14.98	8.27	0.0762
	(2)*(7)	8.58	6.35	0.1826

(2)*(8)	0.00	0.00	not applicable
(3)*(1)	0.00	0.00	not applicable
(3)*(2)	0.00	0.00	not applicable
(3)*(3)	0.00	0.00	not applicable
(3)*(4)	0.00	0.00	not applicable
(3)*(5)	0.00	0.00	not applicable
(3)*(6)	0.00	0.00	not applicable
(3)*(7)	0.00	0.00	not applicable
(3)*(8)	0.00	0.00	not applicable

Gender*Age Group

(1)*(1)	-30.64	4.26	< 0.0001
(1)*(2)	-30.44	5.86	< 0.0001
(1)*(3)	11.57	5.30	0.0339
(1)*(4)	6.01	7.16	0.4051
(1)*(5)	15.86	5.53	0.0061
(1)*(6)	12.53	7.57	0.1045
(1)*(7)	9.39	5.51	0.0944
(1)*(8)	0.00	0.00	not applicable
(2)*(1)	0.00	0.00	not applicable
(2)*(2)	0.00	0.00	not applicable
(2)*(3)	0.00	0.00	not applicable
(2)*(4)	0.00	0.00	not applicable
(2)*(5)	0.00	0.00	not applicable
(2)*(6)	0.00	0.00	not applicable
(2)*(7)	0.00	0.00	not applicable
(2)*(8)	0.00	0.00	not applicable

Figure Legend:

Figure 1. Mean urinary creatinine concentrations (mg/dL) for each sex and racial/ethnic group by age group. MA = Mexican Americans; NH = non-Hispanic.

Figure 1.

