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Creatinine versus specific gravity-adjusted urinary cadmium concentrations

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Abstract

The aim was to assess how urinary creatinine is affected by age, gender, body size and meat intake, and to determine to what extent such factors might affect the creatinine adjustment of urinary cadmium. The study was based on three Swedish studies: (1) 67 non-smoking women aged 20–50 years (24-h urine samples); (2) 289 men and 434 women aged 16–81 years (spot urine samples); and (3) 98 men and 105 women aged 19–72 years (spot urine samples). The effects of age, body surface area (as an indicator of muscle mass), and meat intake on urinary creatinine and cadmium were analysed using multiple regression analyses. Gender- and age-related variations in urinary creatinine and cadmium adjusted for creatinine or specific gravity were compared by ANOVA or ANCOVA. In the multiple regression analyses, body surface area, gender, age and meat intake were the major determinants of urinary creatinine. Urinary cadmium adjusted for creatinine and specific gravity were also dependent on body size, gender and age. Urinary cadmium adjusted for creatinine was 15–92% higher in women or older individuals than in men or younger individuals. Women or older individuals had –3 to 79% higher urinary cadmium adjusted for specific gravity than men or younger individuals had, and such a difference between gender or age group was less obvious in specific gravity adjustment than in creatinine adjustment. Thus, urinary cadmium adjusted for creatinine is more affected by age, gender, body size and meat intake than is specific gravity adjustment. When comparing individuals or populations with large differences in muscle mass or meat intake, such effects can be especially important. In such studies, specific gravity adjustment seems to be more appropriate.

Keywords: *Creatinine, specific gravity, cadmium, adjustment for dilution, urine analysis.*

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Introduction

Many clinical biomarkers are based on analysis of urine. The concentrations of markers in spot urine samples are highly influenced by variation in the dilution caused by variation in the intake of fluids, physical activity, temperature, etc. This may cause a bias in the results for spot urine sample measurements. For example, in studies of

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associations between urinary cadmium and markers of tubular damage, less fluid intake will cause concentrated urine and higher concentrations of both cadmium and the tubular marker. Therefore, even if there is a significant correlation between cadmium and a tubular marker, it is impossible to distinguish whether that is due to the harmful effect of cadmium or just due to the variation in dilution. The common way of compensating for such variation in dilution is to adjust for the urinary creatinine concentration (U-Cre). Timed collection, such as 24-h urine sampling, is the ideal way to measure excretion of different solutes in urine, but is often not feasible to obtain in large epidemiological studies. Furthermore, it has been shown that 24-h sampling often is incomplete (Johansson et al. 1998), which may bias the result.

The basis for creatinine adjustment of spot urine concentrations is the fairly constant rate of creatinine excretion in human urine. However, creatinine is formed by creatine, and hence excretion is related to muscle mass and meat intake (Worsfold et al. 1999, Hall Moran et al. 2001, Davies et al. 2002). Thus, U-Cre varies by age, gender, body size and diet (Boeniger et al. 1993). When adjusting different solutes in urine for U-Cre, those factors will affect the obtained concentrations. This is often neglected in epidemiological studies using urinary biomarkers of exposure. In particular, data from women and men are often combined without taking differences in muscle mass into consideration. Even if data are stratified by gender, evaluation of gender differences or difference between population groups may be hampered due to differences in creatinine excretion. Also, a measured increase in urinary concentration of a solute with age may be due to a decrease in U-Cre, as a result of decreasing muscle mass with increasing age (Davies et al. 2002).

A few studies have suggested adjustment by specific gravity (SG) instead of creatinine because of a strong correlation between SG and U-Cre (Moore et al. 1997, Parikh et al. 2002). However, those studies did not evaluate the possible variation in the SG adjusted and U-Cre adjusted values due to gender, age or body size. The aim of the present study was to assess how U-Cre and SG are affected by factors such as gender, age, body size and meat intake, and to assess to what extent these factor influence creatinine adjusted estimates of urinary cadmium (U-Cd), which is a widely used biomarkers for long-term exposure and body burden of the nephrotoxic metal cadmium.

Materials and methods

Factors affecting urinary excretion of creatinine and cadmium were evaluated based on data from three of our previous studies on cadmium exposure in Sweden (Table I). The Varberg Study includes Swedish women ($n=67$), aged 20–50 years, who completed a 4-day dietary record and 24-h urine collection (Berglund et al. 1994, Vahter et al. 1996, Johansson et al. 1998). The completeness of the 24-h urine sampling was evaluated using *para*-aminobenzoic acid (PABA) (Johansson et al. 1998). U-Cd was determined using graphite furnace atomic absorption spectrophotometry (method of standard addition) after acidification of the urine (Herber et al. 1990). U-Cre was determined by the Jaffe method (Hare 1950). SG was measured by a Goldberg refractometer.

The OSCAR study was performed in an area with previous environmental cadmium pollution in south-east Sweden (Alfven et al. 2000, 2002, Jarup et al. 2000). The present study only considered environmentally exposed men ($n=289$) and women

Table I. Characteristics of individuals in the various studies.

		Morning urine			Spot urine		
		OSCAR			Stockholm		
Type of urine collection	24-h urine Varberg Women ($n=67$)	Men ($n=289$)	Women ($n=434$)	p	Men ($n=98$)	Women ($n=105$)	p
Age (years)	37 (8)	53 (16)	52 (16)	0.410	44 (16)	47 (16)	0.251
Weight (kg)	63 (9)	82 (12)	68 (12)	<0.001	n.a.	n.a.	
Height (m)	1.66 (0.06)	1.78 (0.07)	1.64 (0.06)	<0.001	n.a.	n.a.	
Body surface area (BSA, m^2, DuBois)	1.70 (0.13)	2.00 (0.15)	1.74 (0.15)	<0.001	n.a.	n.a.	
Body mass index (kg m^{-2})	22.8 (2.7)	26.0 (3.3)	25.4 (4.5)	0.036	n.a.	n.a.	
Meat intake (g day^{-1})	58 (56)	n.a.	n.a.		n.a.	n.a.	
24-h solute excretion (g/24 h)	20 (5)	n.a.	n.a.		n.a.	n.a.	
Specific gravity (SG, g ml^{-1})	n.a.	1.023 (0.007)	1.020 (0.008)	<0.001	1.018 (0.006)	1.015 (0.006)	0.005
U-Cre (g/24 h)	1.13 (0.21)	n.a.	n.a.		n.a.	n.a.	
U-Cre (g l^{-1}, adjusted for SG)	n.a.	0.93 (0.24)	0.83 (0.25)	<0.001	1.13 (0.28)	0.91 (0.22)	<0.001
U-Cd (μg l^{-1})	n.a.	0.52 (0.34)	0.53 (0.44)	0.627	0.56 (0.43)	0.46 (0.34)	0.069
U-Cd (μg g^{-1} Cre)	n.a.	0.38 (0.23)	0.55 (0.38)	<0.001	0.47 (0.34)	0.55 (0.35)	0.097
U-Cd (μg l^{-1}, adjusted for SG)	n.a.	0.34 (0.20)	0.42 (0.29)	<0.001	0.51 (0.37)	0.49 (0.32)	0.685
Smoker (%)	0	49	43	0.148	66	56	0.410
Pearson correlation coefficient between age and BSA	0.11 ($p=0.375$)	0.073	0.049	n.a.			

Data are mean and standard deviation (SD), per cent or correlation coefficient.
n, Number of sample; p, p value; n.a., not available.

($n = 434$), aged 16–81 years. U-Cd was measured by inductively coupled plasma mass spectrometry (ICP-MS) (Barany et al. 1997). U-Cre was measured using an enzymatic colourimetric method using a Hitachi Modular-P (Roche Diagnostics, Mannheim, Germany) and SG by RD 712 EUROMEX digital hand refractometer.

The Stockholm study included randomly selected men ($n = 98$) and women ($n = 105$) aged 19–72 years in Stockholm and Västerås (Elinder et al. 1983, Jawaid et al. 1983). U-Cd in spot urine samples was determined using graphite furnace atomic absorption spectrophotometry (Jawaid et al. 1983). U-Cre was determined by the Jaffe method. Specific gravity was measured by a Goldberg refractometer. Weight and height were not measured in this study.

In all studies, the accuracy of measurements was checked using commercial reference samples.

For morning and spot urine samples, U-Cd was adjusted for U-Cre (U-Cd/U-Cre). Dividing by U-Cre ($g\,l^{-1}$) means that the U-Cd is adjusted to an amount of cadmium per 1 g U-Cre. U-Cd was also adjusted for SG to the overall mean value of 1.015 g ml^{-1} according to U-Cd $\times$ (1.015–1)/(SG-1)]. In addition, U-Cre in spot urine samples was adjusted for SG 1.015 [U-Cre $\times$ (1.015–1)/(SG-1)]. The U-Cre/(SG-1) ratio was considered a simple and suitable indicator for evaluation of potential factors influencing urinary creatinine excretion. Both U-Cre and SG are influenced by urinary dilution. A higher U-Cre/(SG-1) ratio in individuals with concentrated urine than in those with more diluted urine would suggest that U-Cre fluctuates more than SG, indicating additional variation in the U-Cre excretion.

The 24-h total solute excretion (g day^{-1}) was calculated by (SG-1) $\times$ urinary volume (ml/24 h) in the Varberg study. Body surface area (BSA, m^2), calculated by weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 0.007184$ (DuBois & DuBois 1916), was used as an indicator of muscle mass, based on the assumption that taller and heavier people have a higher BSA, whereas body mass index (BMI), to a large extent, is affected by the body fat percentage. Differences between gender were calculated using *t*-test and chi-square test. Pearson correlation coefficients were calculated for univariate comparisons. Then, multiple regression analyses were performed to evaluate the effect of each factor on U-Cre and U-Cd. As BSA and gender showed strong relationship, either one of the two, not both together, were included in the regression model to avoid errors due to collinearity (Michels et al. 2004). Because BSA was significantly higher for men than for women, it was assumed that the gender difference in U-Cre is explained mainly by difference in body size (muscle mass). Differences in U-Cd, adjusted for creatinine or SG, between gender or age groups were evaluated using analysis of variance/covariance (ANOVA/ANCOVA) to assess to what extent these factors influence creatinine adjusted estimates. Smoking status was categorized into smokers and non-smokers and included in the model. Smokers have higher levels of U-Cd (Jawaid et al. 1983) and blood cadmium (Jarup et al. 1998) than non-smokers. The cut-off values for age (OSCAR: 50 years, Stockholm: 45 years) were the medians. The analyses were performed with SPSS 12.0.1 for Windows (SPSS, Inc., Chicago, IL, USA). A $p < 0.05$ was considered as being statistically significant.

Results

Table I shows the characteristics of each study. In the OSCAR study, weight, height, BSA, SG and U-Cre (adjusted for SG) were significantly higher in men than in

women. U-Cd adjusted for both U-Cre and SG were significantly lower in men than in women. In the Stockholm study, SG and U-Cre were significantly higher in men than in women.

Table II shows the results of multiple regression analyses to test whether U-Cre and SG (24-h solute excretion) were dependent on age, body size and meat intake. Target variables were 24-h U-Cre (g/24 h, Varberg), 24-h solute excretion (g/24 h Varberg), or U-Cre (g l^{-1} adjusted for SG, OSCAR and Stockholm). Descriptive variables were age, BSA (Varberg, OSCAR) or gender (OSCAR, Stockholm) and meat intake (only in the Varberg). The 24-h U-Cre was determined by BSA, meat intake and age (in decreasing order of standardized regression coefficient) in the Varberg study. In addition, the 24-h solute excretion was determined by BSA and meat intake, but the standardized regression coefficients were lower than for 24-h U-Cre. Spot U-Cre was affected by age, gender and BSA in the OSCAR study, and by age and gender in the Stockholm study. The influence by gender was larger than that of BSA.

Table III shows the results of multiple regression analyses for U-Cd. Target variable was spot U-Cd adjusted for creatinine or to SG. Descriptive variables were age, smoking and BSA (OSCAR) or gender (OSCAR, Stockholm). U-Cd, adjusted for both U-Cre and SG, was determined by age, smoking and BSA in decreasing order in the OSCAR study, and by age and smoking in the Stockholm study. The influence of most factors was higher for U-Cd adjusted for U-Cre than for U-Cd adjusted for SG. Only the influence of smoking was similar for the two adjustments. The influence of gender was higher than that of BSA in either adjustment. Therefore, it was decided to conduct further analyses of gender and age group.

Gender differences in adjusted U-Cd in the OSCAR and Stockholm studies were evaluated by two-way ANCOVA, with smoking and age as covariates, and differences in U-Cre by ANCOVA with age as covariate. As shown in Figure 1, U-Cre adjusted for SG was higher in men than in women, and U-Cd, adjusted for both U-Cre and SG was higher in women than in men (statistically significant only in the OSCAR study). However, the ratio of U-Cd in women to that in men was higher for U-Cre adjustment

Table II. Multiple regression analyses to test whether U-Cre and 24-h solute excretion are dependent on age, body size and meat intake.

		Age (years)	BSA (m^2)	Meat intake (g day^{-1})	Gender[a]
Varberg, 24-h U-Cre (g/24 h)	B	−0.006⋆	0.70⋆	0.0012⋆	
$n=67$, $R^2=0.28$	Beta	−0.23⋆	0.43⋆	0.32⋆	
Varberg, 24-h solute excretion (g/24 h)	B	0.06	13.47⋆	0.02⋆	
$n=67$, $R^2=0.23$	Beta	0.09	0.35⋆	0.26⋆	
OSCAR, morning U-Cre (g l^{-1}, adjusted for SG)	B	−0.005⋆	0.19⋆		
$n=723$, $R^2=0.11$	Beta	−0.32⋆	0.15⋆		
OSCAR, morning U-Cre (g l^{-1}, adjusted for SG)	B	−0.005⋆			0.10⋆
$n=723$, $R^2=0.13$	Beta	−0.31⋆			0.20⋆
Stockholm, spot U-Cre (g l^{-1}, adjusted for SG)	B	−0.003⋆			0.21⋆
$n=203$, $R^2=0.17$	Beta	−0.16⋆			0.38⋆

B, Unstandardized regression coefficients; Beta, standardized regression coefficients; ⋆$p<0.05$.
[a]Men = 1, women = 0.

Table III. Multiple regression analyses for U-Cd.

	B		Beta	
Target variable	U-Cd adjusted for U-Cre	U-Cd adjusted for SG	U-Cd adjusted for U-Cre	U-Cd adjusted for SG
OSCAR				
Age	0.008*	0.005*	0.39*	0.29*
Smoking[a]	0.15*	0.14*	0.22*	0.26*
BSA	−0.30*	−0.15*	−0.18*	−0.12*
OSCAR				
Age	0.008*	0.005*	0.39*	0.29*
Smoking[a]	0.15*	0.14*	0.22*	0.26*
Gender[b]	−0.18*	−0.09*	−0.26*	−0.18*
Stockholm study				
Age	0.012*	0.010*	0.54*	0.49*
Smoking[a]	0.20*	0.23*	0.29*	0.33*
Gender[b]	−0.07	0.02	−0.10	0.03

B, Unstandardized regression coefficients; Beta, standardized regression coefficients. *$p < 0.05$.
[a]Smoker = 1, non-smoker = 0.
[b]Men = 1, women = 0.

than for SG adjustment: 148%(U-Cre) − 128%(SG) = 20% in the OSCAR study and 115% − 97% = 18% in the Stockholm study.

Age-related variation in U-Cd was evaluated by three-way ANOVA with gender and smoking as factors, and age differences in U-Cre by two-way ANOVA with gender as covariate. As shown in Figure 2, U-Cre adjusted for SG was higher in younger than older individuals (significant only in the OSCAR study) while U-Cd, adjusted for both U-Cre and SG (both studies), was higher in older than younger individuals. However, the ratio of U-Cd in older groups to that in younger groups was higher for U-Cre

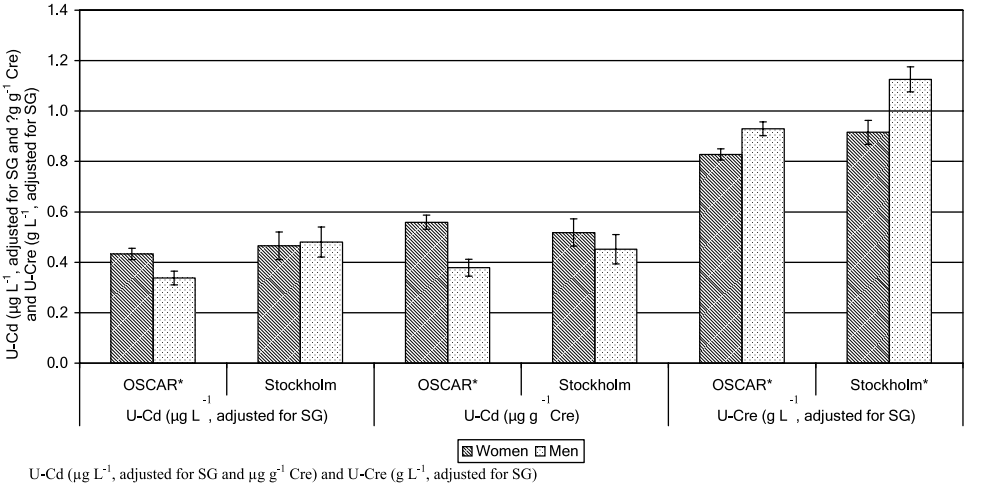

Figure 1. Gender differences in U-Cd and U-Cre (mean and 95% confidence interval). Bars show 95% confidence intervals. *$p < 0.05$.

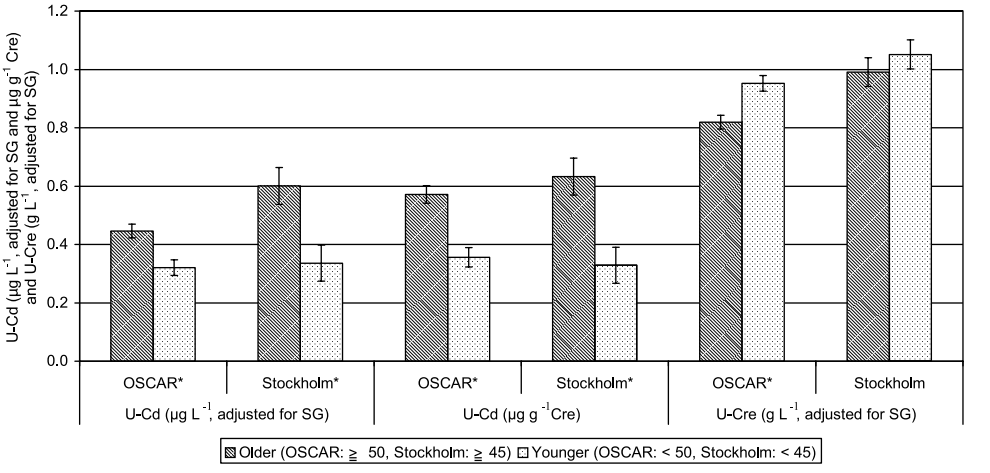

Figure 2. Age-related variation in U-Cd and U-Cre (mean and 95% confidence interval). Bars show 95% confidence intervals. $^{\star}p < 0.05$.

adjustment than for SG adjustment: 161% – 139% = 22% in the OSCAR study and 192% – 179% = 13% in the Stockholm study.

Discussion

As expected, the creatinine in urine was significantly influenced by age, gender and body size, most likely, related to differences in muscle mass. In addition, meat intake influenced urinary creatinine excretion. Consequently, U-Cd adjusted for creatinine was influenced by those factors. Although, also SG adjusted U-Cd was influenced by age, gender and body size, it was consistently less so than creatinine adjusted U-Cd. Only smoking, which was not associated with urinary creatinine, influenced U-Cd independent of adjustment. The results were consistent in two 'spot urine collection' studies and one study with 24-h urine. Thus, our results strongly indicate that SG adjustment has several advantages over creatinine adjustment.

Two previous studies reported that the creatinine adjusted concentration of a substance in spot urine collections was slightly better correlated to 12- or 24-h excretion of a target substance than was SG adjusted concentration (Barber & Wallis 1986, Trevisan et al. 1994). Another study showed no difference between creatinine and SG adjustments (Berlin et al. 1985). The present study does not necessarily contradict those previous studies, which indicate that U-Cre adjusted spot urine sample is a better indicator of 24-h excretion of a substance. This may reflect that U-Cre adjustment of spot samples displays less intra-individual variation in comparison with using SG adjustment, e.g. the uncertainty in a single spot urine sample to reflect the true excretion rate of substance in that individual being less using U-Cre adjustment rather than SG adjustment. However those studies did not consider differences among population groups, gender or age, which all are important in practical epidemiological studies.

On the other hand, in a study involving spot urine samples from 385 men and 149 women, 18–68 years of age, the ratio of U-Cre in men to that in women (134%) was higher than the ratio of solute excretion in men to that in women (115%) (Carrieri

et al. 2001). Also, U-Cre, but not SG, was significantly lower in older (>50 years) than in younger (<40 years) subjects. Furthermore, a group of 13 Bangladeshi women had significantly lower and more variable U-Cre than a group of 30 Americans, while the SGs were similar (Miller et al. 2004). Similarly, Barr et al. (2005) reported that US men had significantly higher U-Cre than women (total 22 245 individuals), and that individuals between 20 and 30 years of age had significantly higher U-Cre than those <12 or >30 years of age. However, the effect of variation in the dilution of urine was not considered.

In the further evaluation of the different adjustment methods, it was noted that U-Cre (not adjusted) and SG tend to fluctuate in the same way, as both are highly dependent on the dilution in urine. If, for example, U-Cre (not adjusted) and SG for two study groups, e.g. men and women, vary only because of dilution, the ratio of U-Cre to total solute excretion [U-Cre/(SG-1)] and U-Cre adjusted for SG [U-Cre × (1.015 – 1)/(SG-1)] would be exactly the same for the two groups. In contrast, if U-Cre adjusted for SG is higher in one group than another, as in the case of gender and age in the present study, the difference in U-Cre between the two groups is larger than the difference in SG. Thus, the observed significant difference in U-Cre adjusted for SG between age groups and gender suggests that U-Cre were more influenced by these factors than SG.

SG is simply a density measurement that, like creatinine, has certain limitations for adjustment purposes. SG may be elevated by glucosuria (often present in uncontrolled diabetes) or proteinuria. For example, urinary test strip can detect approximately 30–100 mg dl^{-1} (or 0.0003–0.001 g ml^{-1}) of proteinuria and glucosuria. Such amounts of glucose or protein would corresponds to 2–7% of solute excretion in urine at SG = 1.015 g ml^{-1}. However, such abnormal findings are rare in the general population and were only a few per cent in this study. The prevalence of diabetes is estimated to be 3–6% in Scandinavia (Andersson et al. 1991, Tuomilehto et al. 1991, Berger et al. 1999), of which only a smaller part is assumed to have glucosuria or proteinuria. Even so, the magnitude of the error that severe glucosuria or proteinuria might introduce in SG measurements is considerably lower than that caused by the gender effect on U-Cre. U-Cre (not adjusted) in men was about 1.4 times higher than in women's in the present study.

Due to the lack of data for meat intake in spot urine studies, the practical influence of meat intake in U-Cre and SG adjustment could not be definitely concluded. However, such a relationship is present, as indicated by the significant association between U-Cre and meat intake in our relatively small study involving 24-h urine sampling.

In conclusion, this study shows that U-Cre fluctuated more than SG by age and gender. Furthermore, by adjusting U-Cd (or any other solute in spot urine samples) for creatinine excretion, the concentrations in women or older age groups, compared with men or younger age groups, may be highly overestimated. When studying populations with large differences in muscle mass or meat intake, effects on U-Cd adjusted for U-Cre are particularly important. In such studies, U-Cd adjusted for SG would be more appropriate. A notable feature of present study is that one could construct a valid novel multivariate model for urinary excretion of creatinine and cadmium and determine how much each potential factor affects the creatinine adjustment compared with SG adjustment, taking other factors into consideration.

References

Alfven T, Elinder CG, Carlsson MD, Grubb A, Hellstrom L, Persson B, Pettersson C, Spang G, Shutz A, Jarup L. 2000. Low-level cadmium exposure and osteoporosis. J Bone Miner Res 15:1579–1586.

Alfven T, Jarup L, Elinder CG. 2002. Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. Environ Health Perspect 110:699–702.

Andersson DK, Svardsudd K, Tibblin G. 1991. Prevalence and incidence of diabetes in a Swedish community 1972–1987. Diabet Med 8:428–434.

Barany E, Bergdahl I, Schutz A, Skerfving S, Oskarsson A. 1997. Inductively coupled plasma mass spectrometry for direct multi-element analysis of diluted human blood and serum. J Anal Atomic Spectrometry 12:1005–1009.

Barber TE, Wallis G. 1986. Correction of urinary mercury concentration by specific gravity, osmolality, and creatinine. J Occup Med 28:354–359.

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ Health Perspect 113:192–200.

Berger B, Stenstrom G, Sundkvist G. 1999. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. Diabetes Care 22:773–778.

Berglund M, Akesson A, Nermell B, Vahter M. 1994. Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. Environ Health Perspect 102:1058–1066.

Berlin A, Alessio L, Sesana G, Dell'Orto A, Ghezzi I. 1985. Problems concerning the usefulness of adjustment of urinary cadmium for creatinine and specific gravity. Int Arch Occup Environ Health 55:107–111.

Boeniger MF, Lowry LK, Rosenberg J. 1993. Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: a review. Am Ind Hyg Assoc J 54:615–627.

Carrieri M, Trevisan A, Bartolucci GB. 2001. Adjustment to concentration-dilution of spot urine samples: correlation between specific gravity and creatinine. Int Arch Occup Environ Health 74:63–67.

Davies KM, Heaney RP, Rafferty K. 2002. Decline in muscle mass with age in women: a longitudinal study using an indirect measure. Metabolism 51:935–939.

DuBois D, DuBois EF. 1916. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871.

Elinder CG, Friberg L, Lind B, Jawaid M. 1983. Lead and cadmium levels in blood samples from the general population of Sweden. Environ Res 30:233–253.

Hall Moran V, Leathard HL, Coley J. 2001. Urinary hormone levels during the natural menstrual cycle: the effect of age. J Endocrinol 170:157–164.

Hare R. 1950. Endogenous creatinine serum and urine. Biol Med 74:148–151.

Herber RFM, Stoeppler M, Tonks DB. 1990. Cooperative interlaboratory surveys of cadmium analysis in urine. Fres J Anal Chem 338:279–286.

Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. 1998. Health effects of cadmium exposure — a review of the literature and a risk estimate. Scand J Work Environ Health 24 Suppl 1:1–51.

Jarup L, Hellstrom L, Alfven T, Carlsson MD, Grubb A, Persson B, Pettersson C, Spang G, Shutz A, Elinder CG. 2000. Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup Environ Med 57:668–672.

Jawaid M, Lind B, Elinder CG. 1983. Determination of cadmium in urine by extraction and flameless atomic absorption spectrophotometry. Talanta 30:509–513.

Johansson G, Akesson A, Berglund M, Nermell B, Vahter M. 1998. Validation with biological markers for food intake of a dietary assessment method used by Swedish women with three different dietary preferences. Public Health Nutr 1:199–206.

Michels KB, Bingham SA, Luben R, Welch AA, Day NE. 2004. The effect of correlated measurement error in multivariate models of diet. Am J Epidemiol 160:59–67.

Miller RC, Brindle E, Holman DJ, Shofer J, Klein NA, Soules MR, O'Connor KA. 2004. Comparison of specific gravity and creatinine for normalizing urinary reproductive hormone concentrations. Clin Chem 50:924–932.

Moore RR, Jr, Hirata-Dulas CA, Kasiske BL. 1997. Use of urine specific gravity to improve screening for albuminuria. Kidney Int 52:240–243.

Parikh CR, Gyamlani GG, Carvounis CP. 2002. Screening for microalbuminuria simplified by urine specific gravity. Am J Nephrol 22:315–319.

Trevisan A, Nicoletto G, Maso S, Grandesso G, Odynets A, Secondin L. 1994. Biological monitoring of cadmium exposure: reliability of spot urine samples. Int Arch Occup Environ Health 65:373–375.

Tuomilehto J, Korhonen HJ, Kartovaara L, Salomaa V, Stengard JH, Pitkanen M, Aro A, Javela K, Uusitupa M, Pitkaniemi J. 1991. Prevalence of diabetes mellitus and impaired glucose tolerance in the middle-aged population of three areas in Finland. Int J Epidemiol 20:1010–1017.

Vahter M, Berglund M, Nermell B, Akesson A. 1996. Bioavailability of cadmium from shellfish and mixed diet in women. Toxicol Appl Pharmacol 136:332–341.

Worsfold M, Davie MW, Haddaway MJ. 1999. Age-related changes in body composition, hydroxyproline, and creatinine excretion in normal women. Calcif Tissue Int 64:40–44.