Reviewer’s report

Title: The physiological determinants of low-level urine cadmium: an assessment in a cross-sectional study among schoolchildren

Version: 0 Date: 18 Dec 2016

Reviewer: Virginia Weaver

Reviewer's report:

This study, in a sizable population of young schoolchildren, addresses the ongoing, recent concern regarding the optimal approach to adjustment of toxicant levels for urine concentration in studies of kidney outcomes. This is a particular problem when both the exposure and outcome measures are analyzed in urine. This is an important research challenge that has significant relevance for policy given levels of cadmium in food. Importantly, it also has relevance for any other biomarker measured in urine. Other strengths of this study include population size, focus on children, quality control of study measures, and use of traditional early biological effect markers for the kidney such that the work is relevant for past cadmium nephrotoxicity research which has relied heavily on such markers rather than on serum GFR measures.

Major

1. I recommend additional modeling in which concentrations of urinary analytes modeled as independent variables are expressed as per liter and urine creatinine and specific gravity are added as separate independent variables in separate models. This approach has been advocated for urine creatinine in the literature recently as well (e.g., Barr et al. EHP, 2005 which the authors mention as reference 29). Indeed, the authors note that this is the most recommended method. Unfortunately, the urine cadmium dependent variable would likely still have to be directly adjusted with either urine creatinine and specific gravity depending on model. However, the authors could model urine creatinine as an independent variable in the model of cadmium adjusted specific gravity and vice versa.

2. Given the potential for collinearity, please provide the highest variance inflation factor (VIF) in each creatinine-adjusted urinary biomarker models in which urine creatinine was also added.

3. Why isn't it possible, from a purely mathematical perspective, that associations of U-A1M, U-CC16 and U-β2m with U-Creat, initially positive, become negative when expressing the concentrations per g creatinine as opposed to indicating residual diuresis?
4. At the top of page 10, I recommend deleting the words "for the residual association" from the first sentence "of creatinine and further adjusted for the residual association with U-Creat. As I understand it from the methods, the authors used independent variables divided by U-Creat well as adding it to the model. Since they also discuss beta coefficients at the bottom of page 8 and top of page 9, the residual association phrase is confusing. This may seem like a minor comment but the modeling approach is complex and warrants as much clarity as possible.

Minor

1. The wording of in the abstract "When adding creatinine among predictors, urinary creatinine emerged as an additional strong predictor correlating negatively with U-Cd per g creatinine. This strong residual influence of diuresis, not seen when adding specific gravity among predictors, linked U-Cd to U-A1M or U-CC16 through secondary associations mimicking those induced by Cd nephrotoxicity." is confusing since it does not appear that the authors modeled specific gravity separately in the existing analysis.

2. Reference 18 (Interactions between domestic water hardness, infant swimming and atopy in the development of childhood eczema) appears to be an incorrect reference on page 5. The word cadmium is not in the article referenced. I think the authors meant ref 37 mentioned in the discussion.

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