Reviewer’s report

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

Version: 1 Date: 07 Apr 2017

Reviewer: Virginia Weaver

Reviewer's report:

I am not sure that the models I recommended in my initial review were what has been added to the revised manuscript. My concern about what appears to have been added in Table 4 is that, as I noted in my initial review, I think the outcome needs to be adjusted. I am particularly unclear what was modeled in the paragraph at the end of on page 11 starting with the sentence "We also tested U-SG as an independent variable in the model of based on U-Creat adjustment and vice versa."

I have now explicitly written out the variables in the modeling approach I recommended in my initial review:

1. U-Cd (μg/g creatinine) as the outcome (dependent variable) with the following independent variables: age, BMI (kg/m²), U-Creat, U-Zn (ug/L), U-Pb (ug/L), U-RBP (ug/L), U-Alb (mg/L), U-A1M (mg/L), U-β2m (ug/L)

2. U-Cd (μg/g creatinine) as the outcome (dependent variable) with the following independent variables: age, BMI (kg/m²), U-SG, U-Zn (ug/L), U-Pb (ug/L), U-RBP (ug/L), U-Alb (mg/L), U-A1M (mg/L), U-β2m (ug/L)

As well as the U-Cd (ug/L adjusted for SG) models:

3. U-Cd (ug/L adjusted for SG) as the outcome (dependent variable) with the following independent variables: age, BMI (kg/m²), U-SG, U-Zn (ug/L), U-Pb (ug/L), U-RBP (ug/L), U-Alb (mg/L), U-A1M (mg/L), U-β2m (ug/L)

4. U-Cd (ug/L adjusted for SG) as the outcome (dependent variable) with the following independent variables: age, BMI (kg/m²), U-Creat, U-Zn (ug/L), U-Pb (ug/L), U-RBP (ug/L), U-Alb (mg/L), U-A1M (mg/L), U-β2m (ug/L)

(I understand that not all these variables would be retained in the backward stepwise regression approach the authors used and so would not be shown in the tables.)
I recommend that the model above labeled #1 be shown in Table 4 in the fourth column. This is the same model the authors have already written their statistical code for with the exception of changing the outcome. The text of the results could still include the fact that the model run without urine concentration adjustment of the outcome but with U-Creat added as an independent variable to the other urine biomarkers expressed per L was the same as the model with all urine measures adjusted for urine creatinine and urine creatinine also added as a separate independent variable. The results of model #2 above can be stated in the results section as they already did but with clarification of what was modeled. I recommend that the authors add model #3 to Table 5. Given the complexity of these models, a footnote in tables 4 & 5 showing the units of the variables would be useful.

Due to the complexity of the models and the importance of the urine concentration adjustment issue for urine biomarkers, I recommend that the authors explicitly state in the Statistical analyses section on page 7 line 44 "In the fourth method, the concentrations of urinary analytes were expressed per liter and adjusted with USG as a separate independent variable." Adding the words "separate independent variable" clarifies that this model is now the same as the approach in the third method for urine creatinine. They could also show the model here with units.

The new sentence on page 11 "Exactly the same associations were observed when running these models with U-Cd and other urinary analytes expressed per liter and with U-Creat added to independent variables (Table 4). " should have "although the urine creatinine associations were in opposite directions" added.

On page 10, lines 2-10, should the r values be negative reflecting the inverse correlation or are the authors showing r2? "By contrast for biomarkers with a strong inverse correlation with U-Creat, this beta coefficient was much lower: U-Cd, 0.71; U-A1M, 0.73; U-β2m, 0.43; UCC16, 0.36 (r = 0.67, 0.44, 0.44 and 0.14, respectively, all P<0.001 except for U-CC16, P=0.06).

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