Reviewer's report

Title: Associations between cadmium exposure and neurocognitive test scores in a cross-sectional study of US adults

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Reviewer: Sharon K. Sagiv

Reviewer's report:

This is a well-written paper that contributes to the sparse previous literature on the association of low-level cadmium exposure in the general U.S. population with neurocognitive function. Consideration of the following items would strengthen this manuscript.

Major Compulsory Revisions

1. The authors present a very thorough statistical analysis, including 3 models with varying levels of covariate adjustment: 1) unadjusted (except for urine dilution), 2) fully adjusted, and 3) removing smoking status and serum cotinine, to examine the impact of adjusting for smoking in the analysis. Since smoking is such an important confounder in this analysis (common cause of both cadmium and cognitive function), an analysis of cadmium-cognitive function associations independent of smoking (by restricting to non-smokers) would better address the independent role of cadmium. This would seem feasible given the large sample size (a particular strength of this study) and the large number of non-smokers in this sample (n=2,851; 51%).

2. It would be useful to many readers if the authors could describe how they decided on the list of covariates in model 2. For example, were they included a priori based on their associations with exposure/outcomes? Did they use some statistical criterion (e.g., change in estimate)?

3. Log-transformation of the outcome measures makes the estimates presented in Table 3 harder to interpret for most readers. Is a 0.0095 increase in the log-transformed Symbol Digit Substitution Test an important change in score? Perhaps there’s another way to present these data – for example, back-transforming to the original scale of these scores. Or perhaps some discussion of the magnitude of these changes in relation to other exposures measured in NHANES would help. The inclusion of the section on Implications for Cadmium Risk Assessment in the discussion is a strength of this paper.

4. I found the outcome acronyms difficult to follow. Perhaps a different naming convention would help? Maybe refer to the domain itself? E.g., visual motor speed (rather than SRTT), attention and perception (rather than SDST) and learning and memory (rather than SDLT). Also, did the 2 subtests for this last test correspond to specific domains (trials to criterion=learning, total-error-score=memory?)
5. The observation that age was correlated with cognitive function in this relatively young population (mean age=36) was surprising (as the authors point out). Can the authors offer any explanation for this or cite literature showing this in other studies? The concern that adjusting for age over-controls for cadmium exposure is common to studies of other environmental exposures (e.g., PCBs). Since this is similar to the concern raised about adjusting for smoking, I wonder if taking a similar approach to what was recommended in comment #1 would be helpful – stratifying on age group (5-10 year age groups perhaps)?

Minor Essential Revisions

6. Line 253: The authors may want to revise to say the “The results of previous work most similar to our own” since this other study is an occupational cohort and it’s really the results of this study that are comparable to the current study.

7. In Table 3 can the authors report confidence intervals for Simple Reaction Time Test and Symbol Digit Substitution Test measures, as they did for the Serial Digit Learning Test outcomes?

Discretionary Revisions

8. Did omitting the observation with a very high cadmium level influence the results?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.