Author’s response to reviews

Title: Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: A prospective cohort study

Authors:

Mary Díaz Santana (mary.diazsantana@nih.gov)

Susan Hankinson (shankinson@umass.edu)

Carol Bigelow (cbigelow@umass.edu)

Susan Sturgeon (ssturgeon@umass.edu)

R. Thomas Zoeller (tzoeller@umass.edu)

Lesley Tinker (ltinker@whi.org)

JoAnn Manson (jmanson@rics.bwh.harvard.edu)

Antonia Calafat (aic7@cdc.gov)

Jaymie Meliker (jaymie.melliker@stonybrookmedicine.edu)

Katherine Reeves (kwreeses@schoolph.umass.edu)

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Author’s response to reviews:

Dear Dr. Grandjean,

Thank you for your review of our revised manuscript, “Urinary concentrations of phthalate biomarkers and weight change among postmenopausal women: A prospective cohort study.” We appreciate the valuable comments of the reviewers, and we have addressed the identified concerns in the revised manuscript. All changes to the manuscript are tracked in the resubmitted version, and we also offer additional comments below.
Editor's comments:

1. We agree with the reviewers that the revision is close to being acceptable for publication. We do share the view of one reviewer that MI would have been useful and might have compensated in part for the large number of missing values. It would be appropriate if the issue of imprecision and the likely bias were expanded in the discussion (see the reviewer comments).

   We have incorporated discussion of these issues into the revised manuscript (pages 17-18).

2. There are certain expressions that need revision, e.g., "phthalate-free polypropylene urine collection containers, which are phthalate-free" (page 5). We discourage the use of non-SI units (e.g., dL and lbs).

   These changes have been made, as requested.

3. We also prefer the use of digital references, rather than repeated use of author names (e.g., Buser et al. should be substituted by the reference (4)).

   These changes have been made, as requested.

4. The acknowledgments are hard to understand, as institutions appear in parenthesis followed by a name - does that mean that the colleague mentioned has the affiliation in parenthesis?

   We have revised the acknowledgements to improve clarity, as requested.

Reviewer #1:

1. All comments were properly addressed either in the manuscript or response letter

   Thank you.
Reviewer #2:

1. The authors have done a reasonable job with the revisions, nevertheless, I am still concerned about some issues. The statement that multiple imputation leads to greater statistical imprecision does not seem correct. Multiple imputation is the gold standard for dealing with missing values in epidemiologic research. Based on the numbers given in the paper, slightly more than 20% of the total population were excluded due to missing values (997/1257)—not a trivial amount and slightly higher than the subset that they compared models for—997 vs 1187. Given all the other potential sources of error (primarily exposure measurement error), it might be a good idea to be as careful as possible with other aspects of the analysis. This is especially true because they state that there are differences between those with missing values and those without although they don't present data to allow the reader to determine how big a problem this might be for the results.

While we agree that multiple imputation is the gold standard for addressing missing data issues, we also remain concerned about the increased width of confidence intervals that results from utilizing imputed data (we referred to this as statistical imprecision in our earlier response, and we apologize if this term led to confusion regarding our concerns). We added the results we referenced in our earlier response showing comparison to a sample of N=1,187 as Supplementary Table 4 in the revised manuscript. Additionally, as noted above, we have provided a discussion of the potential impact of missing data to our revised Discussion section.

2. I find the numbers of participants and who is included/excluded quite confusing. A flow chart (also showing the three time points of the study) would help with greater clarity. The response mentions that 67 controls did not participate in the year 6 follow-up. Were these excluded from the cross-sectional baseline analyses as well?

We have added a flow chart to the revised manuscript as Figure 1. The controls lost to follow-up at year 6 were included in the cross-sectional analyses.
3. Also, I believe that phthalates are found at higher levels in certain foods such as meat and dairy, and it does seem possible that HEI would not fully control for these individual characteristics of diet. See Serrano SE et al, 2014 in your own journal: "DEHP exposure estimates based on typical diets were 5.7, 8.1, and 42.1 μg/kg-day for women of reproductive age, adolescents and infants, respectively, with dairy as the largest contributor to exposure. Diets high in meat and dairy consumption resulted in two-fold increases in exposure."

We agree that diet is an important contributor to phthalate exposure. While dietary factors might confound the association between phthalate exposure and weight change, it is also plausible that phthalate exposure is on the causal pathway between diet and obesity; in this latter case, adjustment for dietary factors would be inappropriate. We are exploring these questions in depth in an ongoing analysis, and thus prefer to keep our adjustment for HEI, but not intake of specific dietary categories, in this manuscript. This approach is consistent with our recent publications (Reeves Env Res 2019; Reeves JNCI 2019).

Thank you for your time and consideration. We look forward to hearing from you regarding our revised manuscript.

Sincerely,

Katherine W. Reeves, PhD, MPH

Associate Professor