Reviewer's report

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

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Reviewer: Elizabeth Hatch

Reviewer's report:

This paper analyzes data from a nested case-control study from the Women's Health Initiative to evaluate the association between phthalate metabolites and BMI, obesity, and weight change. Strengths of the study include the prospective component and the availability of many potential confounders. Limitations are the use of only one baseline measurement of exposure, potential residual confounding, and over-reliance on statistical significance testing (e.g. p-values in Table 1 are not helpful; and approach to assessing potential confounding seems a bit outdated).

Major questions and concerns are listed below:

This analysis includes only observations with complete data. How many participants were excluded because of missing data on one or more covariates? How many controls dropped out of the longitudinal follow-up after the 3 year visit? Did the authors examine whether there could be differential loss-to-follow-up? Some sensitivity analyses should be conducted to evaluate this type of bias since in practice loss to follow-up is often dependent on variables such as SES (which could be related to the exposures) and BMI.

Did the authors compare the characteristics of subjects who were excluded due to missing values with those in the final study population. Did the authors consider using multiple imputation to deal with missing values and if not, why not? Please see the 2008 article by MA Klebanoff and SR Cole in AJE.

Quartiles can obscure non-linear associations and many EDCs traditionally have low-dose effects. In addition to modeling quartiles, did the authors consider using other approaches to evaluate non-linear associations and/or to choose more meaningful cut-points for analysis?

The very strong positive associations between ∑DEHP and overweight/obesity in the cross-sectional analyses may indicate the presence of a strong confounder or reverse causality. Some studies have suggested that certain phthalates are lipophilic; perhaps that could partially explain this strong association. In addition, the strong inverse association between MEP and BMI cross-sectionally compared with the strong positive association prospectively is very puzzling and might indicate some sort of bias, especially considering that these are based on single measurement and therefore should be biased to the null in the extreme categories. Consider controlling for baseline BMI to address this possibility in the longitudinal analysis, and consider stratifying by baseline BMI to see if the associations between phthalates and weight gain are modified according to baseline BMI category.
The authors mention that underreporting of energy intake among obese women might have led to residual confounding by HEI. Consider conducting some bias analyses to determine how much this potential confounding might have affected your estimates.

Because diet is such a major source of many phthalates, consider exploring whether there could be confounding by individual dietary constituents...e.g. in addition to HEI, consider % saturated fat, fast food intake (if available) and other aspects of diet such as high fat dairy consumption that may be linked with both higher phthalate exposures and higher weight gain.

Minor points:

p. 10, lines 46-51; the statement that effects were often attenuated in controls (supplementary tables) does not appear to be strictly accurate based on a comparison with Supplementary table 2. Consider deleting.

p. 6, lines 36-41, The following sentence could be worded more simply to avoid confusion: We used as phthalate biomarkers the phthalate metabolite concentrations analyzed individually and, for certain metabolites, also grouped by their parent phthalate, by dividing each metabolite of a single parent by its molecular weight and then summing across metabolites;

Consider something like:

We analyzed concentrations of each phthalate metabolite individually. For phthalates with multiple measured metabolites, we also grouped the data by parent phthalate by dividing each metabolite of a single parent by its molecular weight and then summing across metabolites.

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