TWO AUTHORS REPLY

We thank Sugiyama (1) for the interest in our work (2). We agree that the finding of no association between serum 25-hydroxyvitamin D (25(OH)D) concentration and odds of fracture in young children (2) was consistent with a previous case-control study in older children (3) and prospective studies of 25(OH)D during pregnancy (4, 5) and the neonatal period (6).

As suggested by Sugiyama, it is possible that there is a compensatory mechanism whereby low vitamin D status leads to increased bone mineralization due to an increase in bone strain (7, 8). Unfortunately we were not able to evaluate this hypothesis in our study because bone mass and mechanical strain were not measured. Future studies with additional bone measures would be needed to evaluate this hypothesis.

As Sugiyama has indicated, the null finding for 25(OH)D conflicts with our results of an inverse association between vitamin D supplement use and odds of fracture. 25(OH)D is generally regarded as the preferred biomarker of current vitamin D status, but it is not without limitations (9). Further, serum 25(OH)D reflects only current vitamin D status, not long-term intake (10). It is possible that our measure of the use of vitamin D supplements reflects an earlier or prolonged period of exposure that may be more important for fracture risk than current vitamin D status. It is also possible that our finding for vitamin D supplement use was the result residual confounding despite our attempt to control for known confounders.

Acknowledgments

Funding for this study was received from the Canadian Institutes of Health Research.

Funding for this study was also received from the Dairy Farmers of Canada, Montreal, Quebec (2011–2012), and J.L.M. has received nonfinancial support (vitamin D supplements) from Ddrops, Toronto, Ontario, for an investigator-initiated study on vitamin D and respiratory tract infections (2011–2015).

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DOI: 10.1093/aje/kwy012; Advance Access publication: February 6, 2018

RE: "INVITED COMMENTARY: EXPOSURE BIOMARKERS INDICATE MORE THAN JUST EXPOSURE"

The commentary by Savitz and Wellenius (1) on the article by Sagiv et al. (2) illustrates the importance of understanding determinants of chemical exposure biomarkers and empirically testing how they influence relationships between chemical exposures and human health. A key point in this understanding is the relative contribution of physiological and nonphysiological factors to between-person variation in chemical exposure biomarkers. I believe that Savitz and Wellenius underestimate the nonphysiological variation of several chemical exposure biomarkers in their statement that "many toxicants, including PFAS, phthalates, and fire retardants, are ubiquitous in our environment, and levels are not likely to be notably different across homes,

product selection, or other factors" (1). I argue below that the relative contribution of nonphysiological sources to between-person variation in chemical exposure biomarkers is as great as or greater than physiological ones for some chemicals, especially phthalates. Moreover, the relative contributions of nonphysiological and physiological sources of between-person variation differ across the life span.

In the case of phthalates, there is considerable evidence that nonphysiological factors result in substantial between-person differences in urinary concentrations of phthalate metabolites. My colleagues and I previously reported that urinary monoethyl phthalate concentrations were 2.5-fold higher among women who used cologne than among those who did not (geometric mean = 111 ng/mL vs. 42 ng/mL) (3). In addition, Rudel et al. (4) found that urinary levels of di-2-ethylhexyl phthalate metabolites decreased by more than 50% during a dietary intervention that minimized the use of plastic packaging in food preparation and storage. Moreover, other nonpersistent chemicals, like parabens, also have substantial between-person variation related to the use of personal care products, and this has been demonstrated in both experimental and observational studies (3, 5). Between-person variation in phthalate exposure may also arise from the types or brands of products used. Koo et al. (6) previously reported that phthalate diester levels in different brands of perfume, nail polish, hair products, and deodorant could range from nondetectable to over 12 parts per thousand. The magnitude of these variations in phthalate exposure and phthalate biomarkers is quite large, especially compared with the relatively weak associations between physiological factors and chemical exposure biomarkers (2, 7).

A second important point to consider is that the relative contribution of physiological and nonphysiological factors to between-person variation in chemical exposure biomarkers depends on the timing of development when exposure assessment is conducted. For instance, breastfed infants have considerably higher levels of perfluoroalkyl substances (PFAS) than nonbreastfed infants (8, 9). In one study, duration of breastfeeding explained the largest amount of variation in children's serum PFAS concentrations, as compared with other exposure sources (9). Breastfeeding duration is also a predictor of levels of other persistent pollutants, including polybrominated diphenyl ether flame retardants (10). Thus, for persistent chemical exposure biomarkers, including PFAS, the proportion of between-person variation related to nonphysiological factors will be greater than the variation due to physiological factors during infancy or childhood.

Epidemiologists must carefully consider the multiple sources of between-person variation in chemical exposure biomarkers, while also appreciating that the relative contribution of these different sources varies by chemical exposures and across developmental life stages. Thus, broad and sweeping generalizations about how physiological factors influence biomarkers of chemical exposure need to be accompanied by appropriate caveats. Otherwise, such broad generalizations could diminish the potential value of chemical biomarkers, when in fact there are many cases where they can validly and reliably distinguish interindividual differences in true exposure.

Acknowledgments

This work was supported by grants from the National Institute of Environmental Health Sciences (grants ES024381 and ES025214).

Conflict of interest: none declared.

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DOI: 10.1093/aje/kwy009; Advance Access publication: January 17, 2018