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Response to discussion of 'Nutritional epidemiology methods and related statistical challenges and opportunities'

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We very much appreciate each of the three sets of comments on our manuscript. Our manuscript argued that the nutritional epidemiology research area, which is so important to worldwide public health, is burdened with challenges in estimating dietary intakes, both short-term intakes and intakes over the years or decades that may be relevant to chronic disease risk. The nutritional epidemiology literature having chronic disease outcomes mostly relies on dietary self-report data. For the few dietary variables having an established objective measure (biomarker), comparison with self-report data suggests that the data include not only a large 'noise' component, which available statistical methods can typically accommodate, but frequently also a large systematic bias component that, for example, may depend on such study subject body mass index (BMI), age and ethnicity, among other factors. It is the need to address this systematic bias component of dietary intake assessment that stimulates our call for additional reliance on biomarkers, for additional biomarker development, and for the development of novel and flexible statistical methods for use in disease association analyses.

In response to our perspectives, Drs Freedman and Shaw offer cautions concerning the use of biomarker-calibrated intake estimates, and they offer comments as to how the needed statistical methodology developments may depend on the nature of the biomarker, while contrasting biomarkers based on urinary recovery of pertinent nutrient metabolites, to those using blood concentrations and to those based on more extensive metabolite profiles in blood and/or urine. Dr Lin considers the important problem of case and control selection when biomarkers are expensive, but can be derived from stored bio-specimens. In comparison, Dr Spiegelman does not accept our premise concerning the state of nutritional epidemiology methodology. Rather, she provides arguments indicating that the needed information on dietary habits and chronic disease risk is being obtained with existing tools and that rather than statistical innovation, 'the greatest need is to foster the widespread application of existing methods in nutritional epidemiology'.

In response, and we have been asked to be brief, we agree with the points made by Drs Freedman and Shaw. The utility of biomarker-calibrated intake estimates, $\tilde{x}(t)$ in our notation, is only for disease association estimation, while making allowance for random and systematic bias in the self-reported intake estimates that are being calibrated. Specifically, the calibrated intakes are estimates of the conditional expectation of 'actual intake' given the corresponding self-report and pertinent study subject characteristics and, as such, cannot be regarded as providing corrected intake estimates for individual cohort members. Also, we agree that measurement error modelling and estimation procedures for novel biomarkers may need to differ from those used for established recovery biomarkers, such as the doubly labelled water (DLW) energy consumption biomarker if, instead, biomarkers are developed using blood concentrations or using metabolomic profiles. These types of biomarker developments, using specially designed human feeding studies, are crucial to strengthening the nutritional epidemiology knowledge base in our opinion, but the research enterprise to develop novel nutritional biomarkers is surprisingly small internationally. Also, the biomarkers that emerge may typically need to incorporate study subject characteristics, such as BMI or age, as a part of their specification. There are then related measurement error modelling complexities when these biomarkers are used to calibrate self-report data. Our research group is actively working on statistical modelling approaches to make use of these types of biomarker data. If the biomarkers in question can be evaluated from stored specimens (e.g., stored blood products), then an attractive alternative approach omits the self-report data from the analyses and directly associates the specimen-based biomarker values, with their Berkson error structure, to chronic disease risk, for example, using straightforward Cox model analyses. We have a submitted paper applying micronutrient biomarkers obtained from serum, identified in our

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Women's Health Initiative (WHI) feeding study (Lampe et al., 2017), to cancer, cardiovascular disease (CVD) and diabetes outcomes in WHI cohorts, that elaborates and applies this approach.

Dr Lin provides an update on case and control sampling procedures when there is an expensive biomarker that can be evaluated from stored specimens, along with inexpensive correlates such as self-reported intake and BMI, and possibly also other inexpensive covariates that can be assumed to be statistically independent of the expensive measurement. Dr Lin and his colleagues have developed semiparametric efficient estimation procedures for the regression coefficient of the expensive measurement under a broad class of statistical models under certain specified case and control sampling schemes. Furthermore, in yet unpublished work, they have developed a statistically optimal approach to case and control sample selection for this same purpose. The extensive cohort sampling literature, reviewed by Dr Lin, has not previously included sample selection optionality results of this type. As usual, these types of impressive advances spawn a host of additional questions, such as how does the preferred case and control sampling strategy change if the hazard ratio for the (expensive) exposure of interest is time-dependent; for example, close to one in the early part of the follow-up period, but well above one thereafter? Also, in the context of our paper, can these results, both for sample selection and for efficient data analysis, be extended to allow the expensive measurements, such as nutritional biomarker assessments, to include a substantial Berkson-type measurement error component? Furthermore, what sampling strategy can be recommended if some of the needed measurements cannot be obtained from stored specimens? This is the situation for the DLW energy intake biomarker. An energy biomarker is crucial since energy overconsumption is likely a key driver of the risk of many chronic diseases, and because none of the major approaches to dietary assessment via self-report can assess energy intake at all well (e.g., Prentice, Mossavar-Rahmani, et al., 2011). Research contributions to answer questions of this type, as well as questions posed in our paper concerning measurement error accommodation for exploratory and non-linear disease associations, will be valuable for the nutritional epidemiology research area.

In response to Dr Spiegelman, let us first agree that it is possible to hold very different views of the state of nutritional epidemiology knowledge, in spite of about 50 years of intensive analytic epidemiologic research. Dr Spiegelman's colleague, and our friend, Dr Willett, has been a central figure in the formulation and interpretation of nutritional epidemiology research over much of this time period. As Dr. Willett commented in a recent workshop, summarised in Mahabir et al. (2018), 'dietary assessment is a lot more difficult than many of us thought it would be'. It is a challenging research area, and those who have devoted their energies to it over a sustained period of time, including Dr Spiegelman, are to be commended. The major issue that distinguishes nutritional epidemiology research from readily interpreted epidemiologic research, for example, on cigarette smoking and mortality (see Carter et al., 2015, for a recent update) or HPV exposure and cervical cancer, is the severity of measurement challenges for assessing the primary exposure. The statistical challenges are exacerbated by the fact that there is limited variation within study populations for some dietary components (e.g., total energy intake), by the possibility that dietary exposures many years in the past may be relevant to chronic disease risk, and especially by societal sensitivity, and an associated dependence of self-report quality, on respondent body shape variations which are often attributed to dietary choices over the lifespan. Additionally, the diet, even in the short term, is a complex mixture of many foods and nutrients, with complicated correlational patterns and functional dependencies. The context for nutritional epidemiology research, especially in modern societies with their many food selection options and related industrial influences on the food supply, then demands that proposed procedures for dietary assessment be strongly supported by validation data. Biomarkers have potential to allow this type of validation assessment of self-report procedures and, importantly, also have potential to provide the needed dietary assessments, particularly for short-term intakes. Biomarkers used in this fashion provide a key approach to strengthening the nutritional epidemiologic knowledge base, and a concerted effort to develop nutritional biomarkers meeting suitable measurement criteria is sorely needed.

What can be said about the quality of current self-report assessment approaches when using the short list of established nutritional biomarkers in this fashion? Total energy intake is a recognised weak point of self-report assessments, but may be one of the most important drivers of obesity and chronic disease risk. Our analyses of WHI cohort data using DLW measurements to calibrate self-report data indicate that strong positive energy associations with cancer, CVD, and diabetes were evident when biomarker-calibrated energy was related to these outcomes, but few such associations were apparent when the self-report data were used without biomarker calibration (e.g., Prentice et al., 2009; Prentice, Huang, et al., 2011; Tinker et al., 2011; Zheng et al., 2014). Moreover, the role of energy consumption carries over to the absolute intake of macronutrients fat, carbohydrate and protein, as well as to absolute intakes of other nutritional variables. Studies using the urinary nitrogen biomarker of protein intake make clear that there is systematic bias with BMI in protein assessment also (e.g., Freedman et al., 2014; Prentice, Mossavar-Rahmani, et al., 2011). This bias is not as apparent for the density measure, per cent

of energy from protein. However, systematic bias with BMI is apparent for one of the few other ratio measures having an established biomarker; namely, the ratio of sodium intake to total energy, at least in WHI cohorts (Huang et al., 2014).

Dr Spiegelman excerpts a CVD table from a World Health Organization expert collaboration to support her thesis that many important nutritional associations are being identified at the 'highest possible level of evidence ranking'. Note the absence of energy intake from this list, which instead includes obesity, which in contrast to energy can be well measured, as a CVD risk factor. This table also indicates convincing evidence for sodium intake as a risk factor, and potassium intake as a protective factor, for CVD. Dr Spiegelman wrote that we have misinterpreted the conclusions from a National Academy of Science report on this topic and that evidence of the deleterious effects of high sodium intake in CVD has been 'clearly affirmed'. On the contrary, this important research topic, on which we have recently contributed using the biomarker calibration approach (Prentice, Huang, et al., 2017), is still under active debate and investigation, stimulated by reports from the international PURE study. In fact, the National Academy of Medicine has recently convened an expert group to evaluate the sodium and chronic disease data, and provide an updated report on this very topic.

Dr Spiegelman argues that the 'remarkable concordance' between observational epidemiology using self-reported diet and the results from randomised trials 'clearly demonstrates the validity of self-reported dietary measures'. While the comparisons excerpted from a forthcoming paper are interesting, these hardly provide a test of the validity of self-reported intake assessments. Several of the comparisons listed derive from our WHI Dietary Modification Trial of a low-fat dietary pattern. Dr Spiegelman refers to this long-term trial among 48,835 postmenopausal U.S. women as a 'failed' trial, presumably because significant risk reductions were not obtained for the breast and colorectal cancer primary outcomes, or for the coronary heart disease secondary outcome. However, much has been learned from this rare nutritional behavioural intervention trial with chronic disease outcomes, including recent reports showing risk reductions in the intervention group for breast cancer followed by mortality (Chlebowski et al., 2017), for coronary heart disease among women where there was no evidence of post-randomisation statin use confounding (Prentice, Aragaki, et al., 2017) and for diabetes requiring insulin injections (Howard et al., 2018).

Finally, Dr Spiegelman argues that powerful and flexible statistical tools have been developed for the analysis of nutritional epidemiology data. Unfortunately, for many nutritional variables, self-report dietary data alone have not been shown to provide intake estimates having the properties required by these methods: specifically, freedom from important systematic biases for at least one of the dietary measures to 'anchor' the assessment.

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References

Carter, B. D., Abnet, C. C., Feskanich, D., Freedman, N. D., Hartge, P., Lewis, C. E., ... Jacobs, E. J. (2015). Smoking and mortality – Beyond established causes. *New England Journal of Medicine*, *372*(7), 631–640.

Chlebowski, R. T., Aragaki, A. K., Anderson, G. L., Thomson, C. A., Manson, J. E., Simon, M. S., ... Prentice, R. L. (2017). Low-fat dietary pattern and breast cancer mortality in the Women's Health Initiative randomized controlled trial. *Journal of Clinical Oncology*, *35*(25), 2919–2926.

Freedman, L. S., Commins, J. M., Moler, J. E., Arab, L., Baer, D. J., Kipnis, V., ... Willett, W. (2014). Pooled results from five validation studies of dietary self-report instruments using recovery biomarkers for energy and protein intake. *American Journal of Epidemiology*, *180*(2), 172–188.

Howard, B. V., Aragaki, A. K., Tinker, L. F., Allison, M., Hingle, M. D., Johnson, K. C., ... Prentice, R. L. (2018). A low-fat dietary pattern and diabetes: A secondary analysis from the Women's Health Initiative Dietary Modification Trial. *Diabetes Care*, *41*(4), 680–687.

Huang, Y., Van Horn, L., Tinker, L. F., Neuhouser, M. L., Carbone, L., Mossavar-Rahmani, Y., ... Prentice, R. L. (2014). Measurement error corrected sodium and potassium intake estimation using 24-hour urinary excretion. *Hypertension*, *63*(2), 238–244.

Lampe, J. W., Huang, Y., Neuhouser, M. L., Tinker, L. F., Song, X., Schoeller, D. A., ... Prentice, R. L. (2017). Dietary biomarker evaluation in a controlled feeding study in women from the Women's Health Initiative cohort. *American Journal of Clinical Nutrition*, *105*(2), 466–475.

Mahabir, S., Willett, W. C., Friedenreich, C. M., Lai, G., Boushey, C., Matthews, C. E., ... Prentice, R. (2018). Research strategies for nutritional and physical activity epidemiology and cancer prevention. *Cancer Epidemiology Biomarkers & Prevention*, *27*(3), 233–244.

Prentice, R. L., Aragaki, A. K., Van Horn, L., Thomson, C. A., Beresford, S. A. A., Robinson, J., ... Howard, B. V. (2017). Low-fat dietary pattern and cardiovascular disease: Extended results from the Women's Health Initiative. *American Journal of Clinical Nutrition*, *106*(1), 35–43.

Prentice, R. L., Huang, Y., Kuller, L. H., Tinker, L. F., Van Horn, L., Stefanick, M. L., ... Johnson, K. J. (2011). Biomarker-calibrated energy and protein consumption and cardiovascular disease risk among postmenopausal women. *Epidemiology*, *22*(2), 170–179.

Prentice, R. L., Huang, Y., Neuhouser, M. L., Manson, J. E., Mossavar-Rahmani, Y., Thomas, F., ... Van Horn, L. (2017). Associations of biomarker-calibrated sodium and potassium intakes with cardiovascular disease risk among postmenopausal women. *American Journal of Epidemiology*, *186*(9), 1035–1043.

Prentice, R. L., Mossavar-Rahmani, Y., Huang, Y., Van Horn, L., Beresford, S. A., Caan, B., ... Neuhouser, M. L. (2011). Evaluation and comparison of food records, recalls and frequencies for energy and protein assessment using recovery biomarkers. *American Journal of Epidemiology*, *174*(5), 591–603.

Prentice, R. L., Shaw, P. A., Bingham, S. A., Beresford, S. A., Caan, B., Neuhouser, M. L., ... Tinker, L. F. (2009). Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. *American Journal of Epidemiology*, *169*(8), 977–989.

Tinker, L. F., Sarto, G. E., Howard, B. V., Huang, Y., Neuhouser, M. L., Mossavar-Rahmani, Y., ... Prentice, R. L. (2011). Biomarker-calibrated dietary energy and protein intake association with diabetes risk among postmenopausal women from the Women's Health Initiative. *American Journal of Clinical Nutrition*, *94*(6), 1600–1606.

Zheng, C., Beresford, S. A. A., Van Horn, L., Tinker, L. F., Thomson, C. A., Neuhouser, M. L., ... Prentice, R. L. (2014). Simultaneous association of total energy consumption and activity-related energy expenditure with cardiovascular disease, cancer, and diabetes risk among postmenopausal women. *American Journal of Epidemiology*, *180*(5), 526–535.