Response to Letter to the Editor: Association of Maternal Iodine Status With Child IQ: A Meta-Analysis of Individual Participant Data

Deborah Levie,[1,2,3,4,5,6] Sarah C. Bath,[7] Mariana Dineva,[7] Henning Tiemeier,[3,8] Margaret P. Rayman,[7] Mònica Guxens,[3,4,5,6], Robin P. Peeters[2] and Tim I. M. Korevaar[1,2]

The authors have nothing to declare.

1 The Generation R Study Group, Erasmus University Medical Centre, 3000 CA Rotterdam, Netherlands; 2 Department of Internal Medicine, Academic Center For Thyroid Diseases, Erasmus University Medical Centre, 3000 CA Rotterdam, Netherlands; 3 Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children's Hospital, 3000 CB Rotterdam, Netherlands; 4 ISGlobal, 08003 Barcelona, Spain; 5 Pompeu Fabra University, 08003 Barcelona, Spain; 6 Spanish Consortium for Research on Epidemiology and Public Health, Instituto de Salud Carlos III, 28029 Madrid, Spain; 7 Department of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, United Kingdom; 8 Department of Social and Behavioral Science, Harvard TH Chan School of Public Health, Boston, Massachusetts 02115

Corresponding author: Email: r.peeters@erasmusmc.nl

We thank professor Boyages for his insightful comments. We certainly agree with his consideration that urinary iodine measurements currently have no place in clinical practice and his view on iodine supplementation. We also agree with the majority of the methodological concerns that were raised, however, we will explain why we believe it is unlikely that this leads to an overestimation of our findings.

On several occasions, the author refers to measurement error. First of all, it is well-recognized that the urinary iodine concentration (UIC) is not an appropriate marker for individual iodine status (as is mentioned as a limitation in our paper). However, the UIC is still a useful measurement for population studies because the median spot UIC is a valid reflection for a large group of individuals. This is mainly because differences iodine intake across a population would shift the UIC curve, and when the median is calculated, the outskirts of day-to-day variations are practically balanced-out against each other. In our study, we were able to estimate the population or group-iodine status with adequate precision (1). Second, we agree that correcting the UIC for creatinine (UI/Creat) is a valid alternative to the 24-hour urinary iodine excretion when used in homogenous population groups (2). Third, the author questioned whether aggregating IQ scores is a valid approach. IQ scores are, per definition, population-standardized scores (typically with a mean of 100 and a standard deviation of 15) and thus to a certain extent interchangeable between populations. We acknowledge that in our study especially verbal abilities was assessed using different methodologies (i.e., parental questionnaire versus interviews) and at different ages (i.e., pre-school versus school age). However, effect estimates across the different cohorts were similar and a sensitivity analysis in older children only (e.g., excluding the Dutch cohort), resulted in similar findings. In summary, we cannot deal with variations in the day-to-day iodine intake, but we dealt with the differences in measurement techniques (standardizing IQ scores, using certified reference materials, random effect models) as well as renal excretion and urine dilution (creatinine adjustment) to the best of our abilities. However, we believe that we do not overestimate our findings as actually the contrary can be expected. Measurement error of the exposure will bias effect estimates to the null while measurement error of a continuous outcome will widen effect estimate confidence intervals and decrease statistical significance (3).

For a large group of pregnant women, a median UIC <150 µg/L is classified as iodine deficiency (4), mild-to-moderate iodine deficiency is typically defined as a median UIC of 50-150 µg/L and iodine excess is typically defined as a UIC >500 µg/L (these cut-offs differ from those in school children)(4,5). Regardless of specific cut-offs, categorization of continuous data causes methodological issues (6). Therefore, the main analyses were performed using the UI/Creat as a continuous variable. Any effect estimates for UI/Creat values within the group of women with a UI/Creat <150 µg/g can be directly extrapolated from the graphs presented in the manuscript. The use of flexible modeling and various sensitivity analyses excludes that skewness of the data caused by values above 300 µg/g affected would affect our results. Although we had incomplete data on iodine supplement use in two of the three cohorts (7), high values of the UI/Creat in our study population do not necessarily reflect iodine supplement use. For example, it is unlikely that British pregnant women in the early 1990s would have taken iodine-containing supplements as there was, and still is, no legislation concerning iodine nutrition in the UK.

It should be noted that the TSH and FT4 concentrations displayed in Table 1 were measured using different assays and are therefore not comparable. Nonetheless, we are also intrigued by the paradoxical findings that in our study, and in the majority of studies in pregnant women, there is no association of UIC or iodine supplementation with TSH or FT4 concentrations (8). One possible reason for the lack of association could be the fact that a single measurement of UI/Creat does not reflect the duration of iodine deficiency. Since thyroidal iodine stores act as a

buffer and are expected to store enough iodine for roughly 3 months of thyroid hormone production, an association of UI/Creat with TSH or FT4 can perhaps only be expected to occur in women with a stable (low) iodine intake. In a similar fashion as described above, measurement error will occur in those with fluctuating iodine intake (i.e., the majority of women) and regression of the effect estimate to the null would cause false-negative results. A pathway that is much less affected by this physiology is that of fetal thyroid hormone production. The fetal thyroid incorporates iodine from 14 weeks onwards and provides at least 50-70% of fetal thyroid hormone concentrations. Therefore, even if maternal thyroid function is not affected by mild-to-moderate iodine deficiency during pregnancy, it is still very well possible that the link of low maternal iodine availability with child IQ is mediated through a thyroidal pathway.

References

1. Andersen S, Karmisholt J, Pedersen KM, Laurberg P. Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. Br J Nutr 2008; 99:813-818
2. Knudsen N, Christiansen E, Brandt-Christensen M, Nygaard B, Perrild H. Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values. Eur J Clin Nutr 2000; 54:361-363
3. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. BMJ 2010; 340:c2289
4. Secretariat WHO, Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr 2007; 10:1606-1611
5. Zimmermann MB. The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. Thyroid 2007; 17:829-835
6. Categorizing Continuous Variables. Wiley StatsRef: Statistics Reference Online.
7. Dineva M, Rayman MP, Levie D, Guxens M, Peeters RP, Vioque J, Gonzalez L, Espada M, Ibarluzea J, Sunyer J, Korevaar TIM, Bath SC. Similarities and differences of dietary and other determinants of iodine status in pregnant women from three European birth cohorts. Eur J Nutr 2020; 59:371-387
8. Dineva M, Fishpool H, Rayman MP, Mendis J, Bath SC. Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women. Am J Clin Nutr 2020;