ALINEA

NUTRITION

AUGUST 2021

www.alineanutrition.com

TABLE OF

CONTENTS

Levie D, Korevaar TIM, Bath SC, Murcia M, Dineva M, Llop S, Espada M, van Herwaarden AE, de Rijke YB, Ibarluzea JM, Sunyer J, Tiemeier H, Rayman MP, Guxens M, Peeters RP. Association of Maternal Iodine Status With Child IQ: A Meta-Analysis of Individual Participant Data. J Clin Endocrinol Metab. 2019 Dec 1;104(12):5957-5967.

What We Know, Think We Know, or Are Starting to Know

We know that iodine is a crucial trace mineral, required for the synthesis of the thyroid hormones thyroxine [T4] and triiodothyronine [T3], and the majority of iodine is stored in the thyroid gland. Iodine deficiency* was one of the first single-nutrient deficiencies to be identified during the early evolution of nutrition as a formal science, with the hypothesis that lack of iodine was the cause of goitre [an enlargement of the thyroid gland] first proposed in 1851 [(1)]. Early population interventions which targeted the fortification of salt with iodine were successful in reducing incidence of goitre [(1)].

However, it is important to stress that the consequences of iodine deficiency are not confined to an awkwardly large neck. It has long been known that iodine plays vital neurological roles, and in 2007 a World Health Organisation report declared that; *"On a worldwide basis, iodine deficiency is the single most preventable cause of brain damage"* [(2)]. Iodine Deficiency Disorders (IDD) represents a spectrum of disorders, including (but not limited to) goitre, low IQ, and congenital hypothyroidism [known as 'cretinism'] [(3)].

The adverse effects of iodine deficiency bring sharp focus on to pregnancy. The development of a foetal brain is dependant on maternal iodine status and maternal T4 production for the first 10-12 weeks gestation [(4)]. To cope with this increased demand, maternal iodine requirements increase by >50% during pregnancy [(4)]. Thus, in this life-stage with specific increased iodine requirements, there is a higher risk of mild-to-moderate iodine deficiency [(5)].

During pregnancy, mild-to-moderate iodine deficiency is considered the most common cause of maternal hypothyroid and hypothryroxinemia [low T4] [(6)]. However, the implications of maternal iodine insufficiency and low T4 for infant cognitive development have been unclear [(7)]. The present study investigated the effects of iodine deficiency on child IQ in three birth cohorts

*Geek Box: Measuring Iodine and Defining Deficiency

Biomarkers may be classified according to where they are measured in the body. For example, where levels of a nutrient are measured in adipose tissue or plasma, these are termed 'concentration biomarkers' because the concentration of the nutrient in these tissues is being measured. Biomarkers that are measured through excretion are known as 'recovery biomarkers', because it is the level of output in, for example, urine, that reflects intake. Recovery biomarkers are few and far between in nutrition, with sodium and potassium being the two commonly used examples: both are measured through urinary collections. Iodine status may also be measured by urinary sample collections, as the majority of iodine is excreted in urine. Further, iodine may have more reliable immediate measurements because a high proportion of intake appears very rapidly in urine. Generally, urinary iodine reflects intake in the immediate preceding 2-3 days. For iodine, urinary content practically equals intake, and thus urinary iodine is a highly accurate reflection of short-term intake. However, these spot urinary samples [i.e., where only a single sample is taken during the day, not a full 24hr of all urine collection] are not as accurate as a full 24hr collection. As a result, the 'next best thing' is to use the ratio of iodine to creatinine in urine. This is because creatinine excretion is relatively consistent throughout the day, thus the ratio of iodine may be used to estimate 24hr iodine levels from a single spot urinary sample. Currently, the WHO defines iodine urinary levels of <150µg/g as deficiency, 150 to <50 µg/g as adequate, and ≥500µg/g as excess.

The Study

The study population was derived from three birth cohorts [where children born in a particular year are followed over the course of their life]: the Generation R cohort in the Netherlands, the INfancia y Medio [INMA] cohort in Spain, and the Avon Longitudinal Study of Parents and Children [ALSPAC] in the UK. The present study included mother-child pairs if the mother had a measure of urinary iodine and creatinine concentrations during pregnancy, and the child had an Intelligence Quotient [IQ] score available. Iodine excretion was expressed as Urinary Iodine /Creatinine ratio [UI/C]. Thyroid-stimulating hormone [TSH] and T4 were also measured.

For the IQ tests, both non-verbal and verbal IQ were measured. In the Generation R cohort, non-verbal IQ was measured at an average of 5.9yrs old. In the INMA cohort, non-verbal and verbal IQ were measured at an average of 4.6yrs old. In ALSPAC, non-verbal and verbal IQ were measured at an average age of 8.6yrs old. Suboptimal IQ was defined as a score of <85.

Results: 6,180 mother-child pairs were included in the final analysis. Iodine status was determined on average at 12-13 weeks gestation in each cohort. The average urinary UIC differed by cohort:

- Generation R: 159ug/L [adequate]
- NMA: 128ug/L [mild deficiency]
- ALSPAC: 96ug/L [moderate deficiency]

- ***Verbal IQ*:** Using pooled data with all cohorts, there was a significant positive curvilinear association between UI/C and mean non-verbal IQ score. In the cohort-specific analysis, compared to women with UI/C of 150-500ug/g, neither <150ug/g or >500ug/g were associated with verbal IQ scores, or suboptimal verbal IQ.

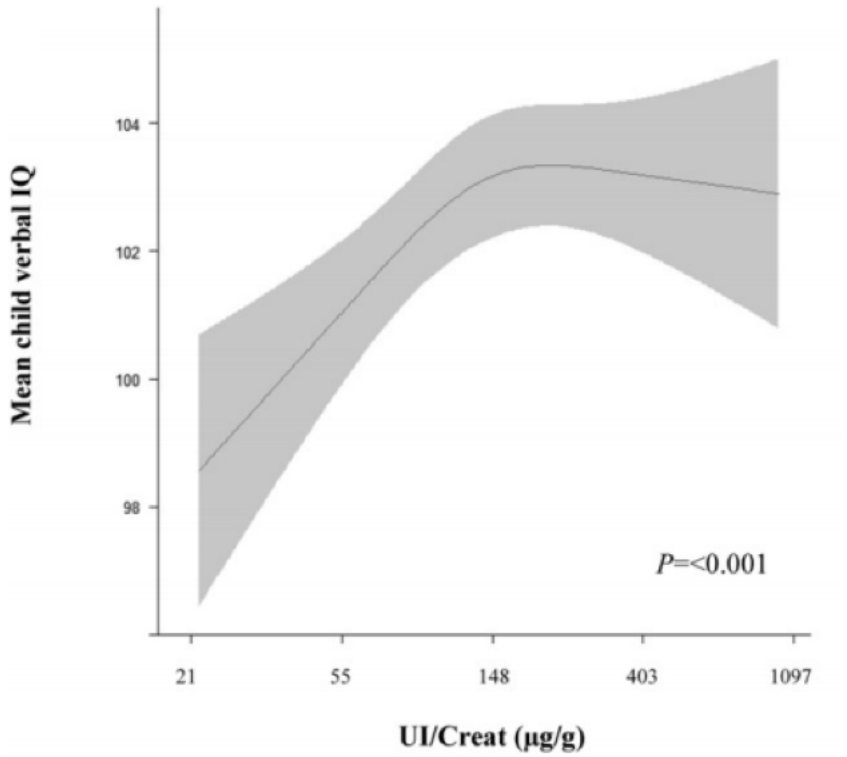

***Figure** from the paper illustrating the relationship between urinary iodine and verbal IQ scores, which linearly increased up to around 150ug/g before plateauing in effect.*

- ***Non-Verbal IQ*:** Using pooled data with all cohorts, there was a positive linear association between UI/C and mean non-verbal IQ score, which was not statistically significant. Compared to women with UI/C of 150-500ug/g, neither <150ug/g or >500ug/g were associated with non-verbal IQ scores, or suboptimal verbal IQ.

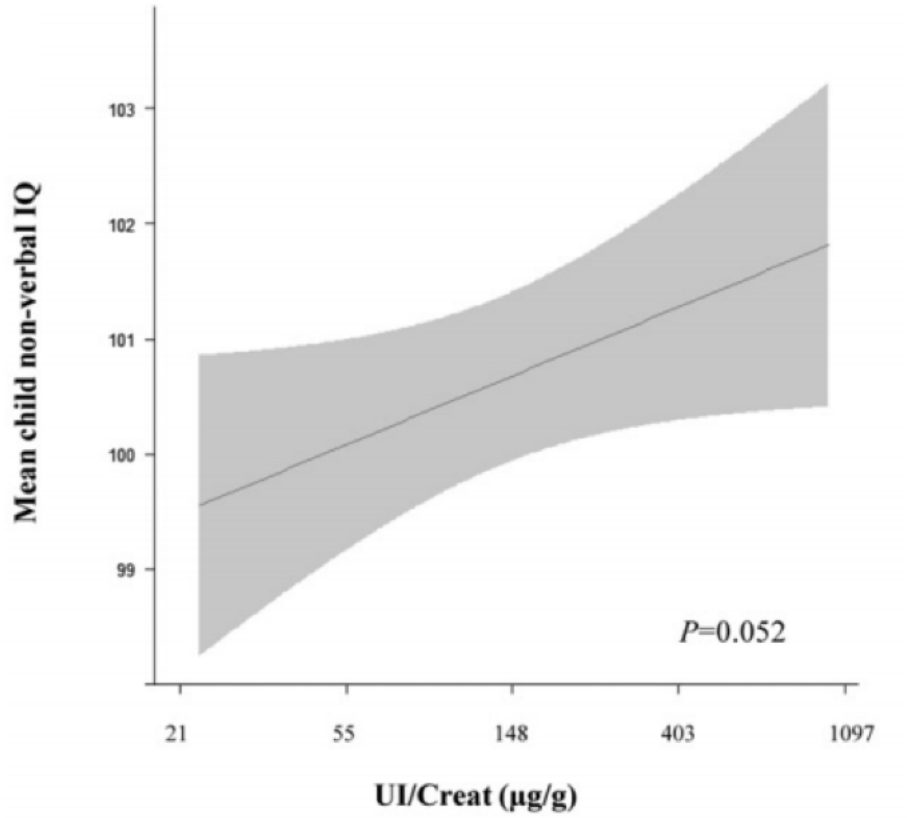

Figure *from the paper illustrating the relationship between urinary iodine and non-verbal IQ scores, which was linear across all measured levels of urinary iodine.*

- ***Associations by Gestational Age*:** There was no association with non-verbal IQ score and gestational age at time of iodine measurement. However, verbal IQ scores were modified by gestational age, with a significant association during the first 12-weeks gestation, and a further significant association with iodine status measured between 12-14 weeks gestation. There was no association beyond 14 weeks gestation [more under ***Interesting Finding***, below].

- ***Thyroid Function*:** There was no association between UIC and TSH, free T4, or effect modification between thyroid function status.

The Critical Breakdown

Pros: The use of UI/C as a biomarker of iodine is a highly reliable and accurate assessment of short-term iodine status in populations. The data encompassed three cohorts, with differing ranges of iodine status allowing for assessments of potential linear relationships. For a mother-child cohort, >6,000 participants is a strong sample size. The use of both one-step and two-step individual data approaches was a thorough way of conducting a meta-analysis with individual data [more under ***Key Characteristic***, below].

Cons: Although urinary iodine is highly accurate, single collections may introduce a wide range of variability and may underestimate or overestimate individual intake, thus distorting the overall averages in a final analysis. Different tools were used to assess IQ in the different cohorts, and IQ was measured at varying times in the children in each cohort. Finally, it is possible that the use of UI/C may have been insensitive to detect true effects at different levels of iodine status, as to average out variability in spot UI/C samples a minimum of 500 people are required to get accurate median levels of iodine [8]. This means the overall cohort averages are likely accurate, but stratifying by iodine status may be less accurate.

Key Characteristic

You may have noticed the clue to this in the title: a meta-analysis of *individual participant data*. So what is this, and how does it differ to a traditional meta-analysis? In a traditional meta-analysis, it is the aggregate data from the primary study that is included in the analysis. For example, in an intervention comparing the effects of butter on cholesterol, the mean difference between the intervention and control group would be used [or the change from baseline to end of intervention]. However, there could be substantial differences in individual level responses that are masked by only looking at the average treatment effect. In a meta-analysis with individual participant data, the data from each individual participant in the primary study is included. This may go beyond just the difference between treatments, and include data on the participant' s characteristics that may be relevant to the outcome.

So how does an individual participant data meta-analysis differ in the actual analysis? These types of meta-analysis use what is known as a 'one-step approach' and 'two-step approach' . In the one-step approach, all individual data is compiled together and analysed simultaneously [as if it was one big study]. In the two-step approach, the individual data is analysed within the primary study it was derived from [the first step], which creates new aggregate data, and then this data is analysed using the aggregate data [the second step]. The present study used both one-step and two-step approaches; the one-step approach produced the linear analyses [the graphs above in **Results**], while the two-step approach produced the comparison of adequate iodine levels.

Interesting Finding

The most interesting finding is the significant relationship observed between gestational age, iodine status, and verbal IQ. During the first 12-weeks of pregnancy, higher iodine status correlated with a ~5-point higher verbal IQ. When iodine was measured between weeks 12-14 of pregnancy, higher iodine status correlated with a ~3-point higher verbal IQ. This relationship was no longer evident after week 14 of pregnancy.

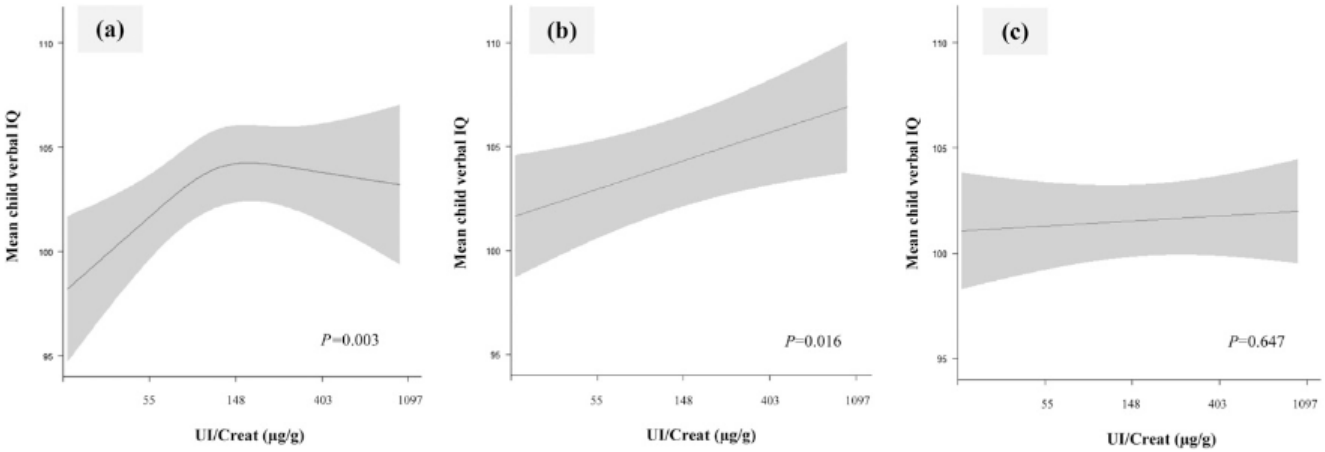

***Figure** from the paper illustrating the relationship between iodine status and verbal IQ at different stages of gestation: [**far left**] is up to 12-weeks gestation, in which there was a significant curvilinear association; [**middle**] between 12-14 weeks, in which there was a significant linear association; [**far right**] from beyond 14-weeks gestation, during which there was no association.*

Relevance

Research on the effects of hypothyroxinemia and iodine deficiency in offspring has produced mixed results. This may be due to whether the region studied has high prevalence of iodine deficiency, and difficulty in distinguishing the effects of in *utero* maternal iodine deficiency against the effects of current iodine status when tests are performed in children [3]. In this regard, the present study added a finding of particular importance by examining the effects of gestational age on the relationship between iodine status and child cognitive capacity.

The timing is instructive, suggesting that the primary benefit is derived primarily in the first trimester, and caps at 14-weeks of the pregnancy. Previously, low maternal T4 measured at 14-weeks was associated with cognitive deficits in children, while children of mothers with normal T4 at 14-weeks displayed no cognitive deficits [9]. Conversely, children born to mothers with normal T4 at 12-weeks, whose T4 levels had declined at 24-weeks or 32-weeks gestation, showed no signs of delayed cognitive development [10].

While much of the previous research has focused on T4 levels specifically, the present study indicates that lower maternal iodine status is associated with lower IQ in children. Early research on the effects of iodine deficiency in infant cognition suggested non-deficient children had a 13.5 point higher IQ than iodine deficient children [2]. The cohort in the current study did not have severely iodine deficient participants, and the mild-moderate deficiency level may explain the lower overall effect size difference.

Putting it all together, however, there is consistency in the association with delayed or impaired cognitive outcomes in children being observed primarily in the first trimester between studies measuring T4, and now the present analysis of iodine status, when measured within the first trimester. This may explain why some interventions targeting iodine supplementation for childhood cognition have had null findings; they may be supplementing too late in a pregnancy to observe a benefit [7].

Europe has the highest prevalence of iodine deficiency, and the lowest coverage of salt iodisation in the world, with up to 52% (~460 million people) in Europe estimated to have insufficient iodine intake. In countries with successful salt iodisation programs, pregnant women have adequate iodine status [2,3]. Recent data, however, has questioned whether salt iodisation is adequate to ensure sufficiency in pregnant women in iodine deficient regions, of which the UK is now in the top 10 countries [11,12].

We must also consider changes in diet in the population. Due to cow' s milk providing a substantial contribution to population iodine intakes, vegans are at a higher risk of iodine insufficiency. Cow' s milk may contain up to 430mcg/L iodine, while in the UK only 3 of 47 commercially available plant "milk" substitutes were fortified with iodine, and the average iodine concentration in plant "milk" substitutes was 1.7% of the value for cow' s milk [13]. Until such time as fortification is more widespread, for individuals' following a vegan diet, it may be prudent to look for iodine-fortified "milk" substitutes.

Application to Practice

Recommendations for pregnant women include a intake of 200mcg iodine, to cover the increased maternal requirements. Given the importance of iodine repletion during the first trimester, it may be prudent to ensure sufficient iodine pre-natally. The recommended intake can be made up through a combination of supplementation and foods. Supplementation of 150mcg in the form of potassium iodine (KI), in addition to dietary intake, would ensure a 200mcg/d intake. It is also recommended to continue with 200mcg/d through breastfeeding. This is important given that only around 20% of women in a UK survey sample were aware of the increased requirements for iodine [14].

References

1. Zimmermann M. Research on Iodine Deficiency and Goiter in the 19th and Early 20th Centuries. The Journal of Nutrition. 2008;138(11):2060-2063.
2. World Health Organisation. Assessment of iodine deficiency disorders and monitoring their elimination. Geneva: WHO; 2007 p. 1-108.
3. Zimmermann M. Iodine Deficiency. Endocrine Reviews. 2009;30(4):376-408.
4. de Escobar G, Obregón M, del Rey F. Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutrition. 2007;10(12A):1554-1570.
5. Delange F. Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. Public Health Nutrition. 2007;10(12A):1571-1580.
6. Glinoer D, Delange F, Laboureur I, de Nayer P, Lejeune B, Kinthaert J et al. Maternal and neonatal thyroid function at birth in an area of marginally low iodine intake. The Journal of Clinical Endocrinology & Metabolism. 1992;75(3):800-805.
7. Santiago P, Velasco I, Muela J, Sánchez B, Martínez J, Rodriguez A et al. Infant neurocognitive development is independent of the use of iodised salt or iodine supplements given during pregnancy. British Journal of Nutrition. 2013;110(5):831-839.
8. Berbel P, Mestre J, Santamaría A, Palazón I, Franco A, Graells M et al. Delayed Neurobehavioral Development in Children Born to Pregnant Women with Mild Hypothyroxinemia During the First Month of Gestation: The Importance of Early Iodine Supplementation. Thyroid. 2009;19(5):511-519.
9. Pop V, Kuijpens J, van Baar A, Verkerk G, van Son M, de Vijlder J et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clinical Endocrinology. 1999;50(2):149-155.
10. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Andersen S, Rasmussen L et al. Estimation of Iodine Intake from Various Urinary Iodine Measurements in Population Studies. Thyroid. 2009;19(11):1281-1286.
11. Zhang H, Lv S, Mu Z, Li W, Zhang X, Wang Y et al. Iodised salt contribution to iodine nutrition status of pregnant and lactating women – CORRIGENDUM. British Journal of Nutrition. 2016;115(5):935-935.
12. Vanderpump M. Commentary: Iodine deficiency as a new challenge for industrialized countries: A UK perspective. International Journal of Epidemiology. 2012;41(3):601-604.
13. Bath S, Hill S, Infante H, Elghul S, Nezianya C, Rayman M. Iodine concentration of milk-alternative drinks available in the UK in comparison with cows' milk. British Journal of Nutrition. 2017;118(7):525-532.
14. McMullan P, Hunter A, McCance D, Woodside J, Mullan K. Knowledge about iodine requirements during pregnancy and breastfeeding among pregnant women living in Northern Ireland. BMC Nutrition. 2019;5(1).