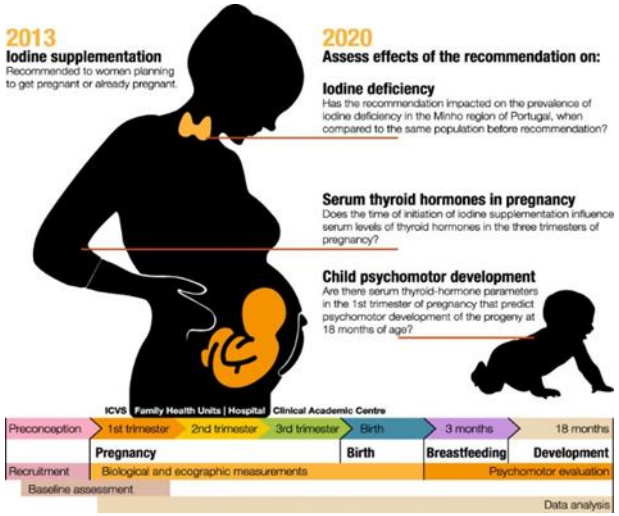
In the name of GOD,
The Compassionate & The merciful

Iodine deficiency in pregnancy &lactation



Fahimeh Ramezani Tehrani

Professor
Reproductive Endocrinology Research Center
Research Institute for Endocrine Sciences
Shahid Beheshti University of Medical Sciences
February 2024

Agenda

- Iodine metabolism in pregnancy
- Definition of iodine deficiency in pregnancy and lactation
- Iodine recommendations for pregnant and lactating women
- Iodine deficiency and adverse pregnancy outcomes
- Iodine deficiency and fetal neurocognitive development
- Iodine deficiency during lactation and infant health
- Take home messages

General concept on iodine

- Iodine is an essential mineral nutrient, mainly involved in thyroid metabolism.
- It is essential for kidney, liver and brain metabolism.
- A healthy adult individual contains 15–20 mg of iodine.
- 70–80% of iodine is located in the thyroid gland.
- Iodine deficiency (ID) is frequent worldwide, affecting approximately 40% of the world’s population.
- Thyroid and iodine metabolism are modified during pregnancy to ensure proper maternal and fetal thyroid function

Metabolites 2023

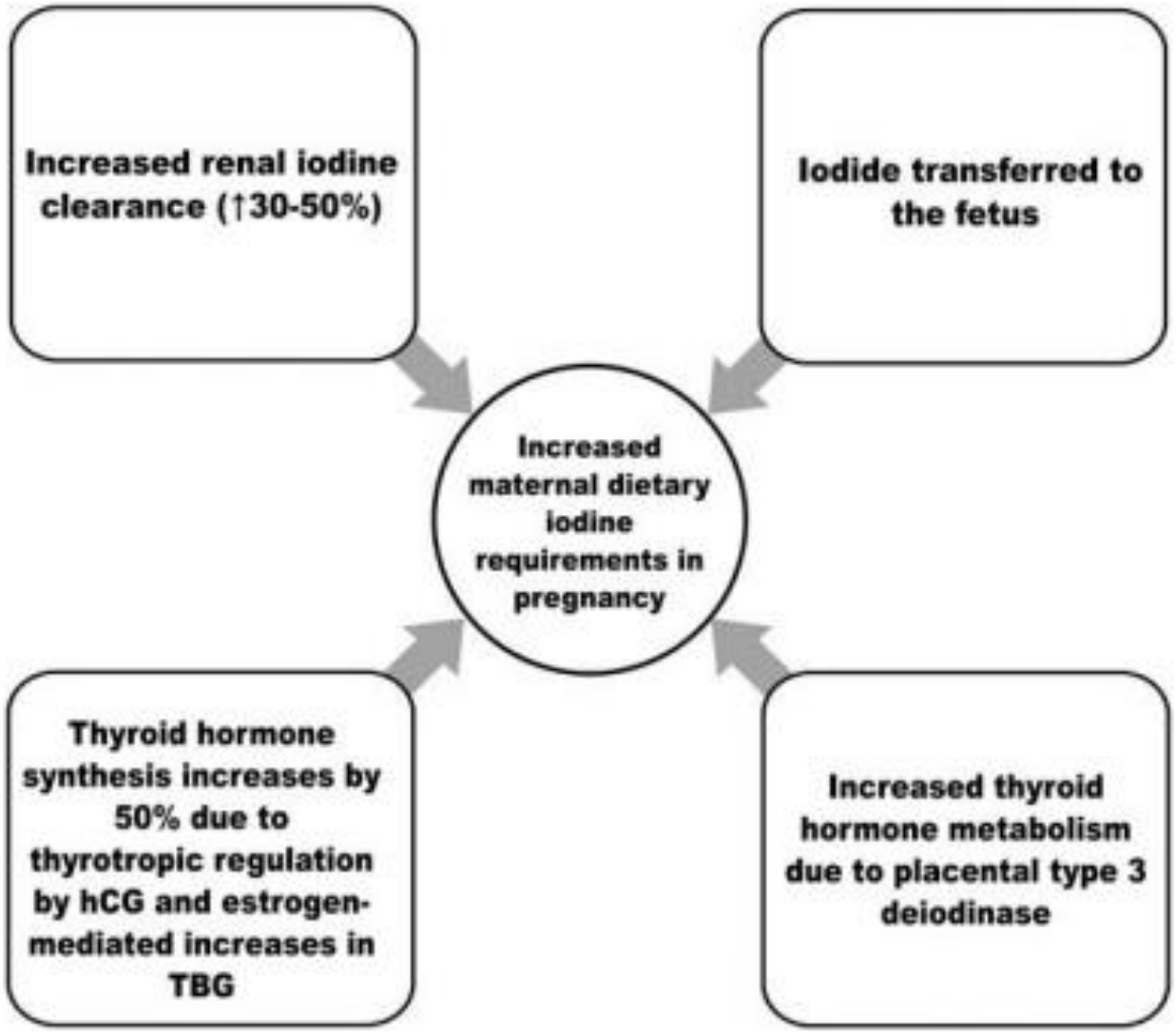
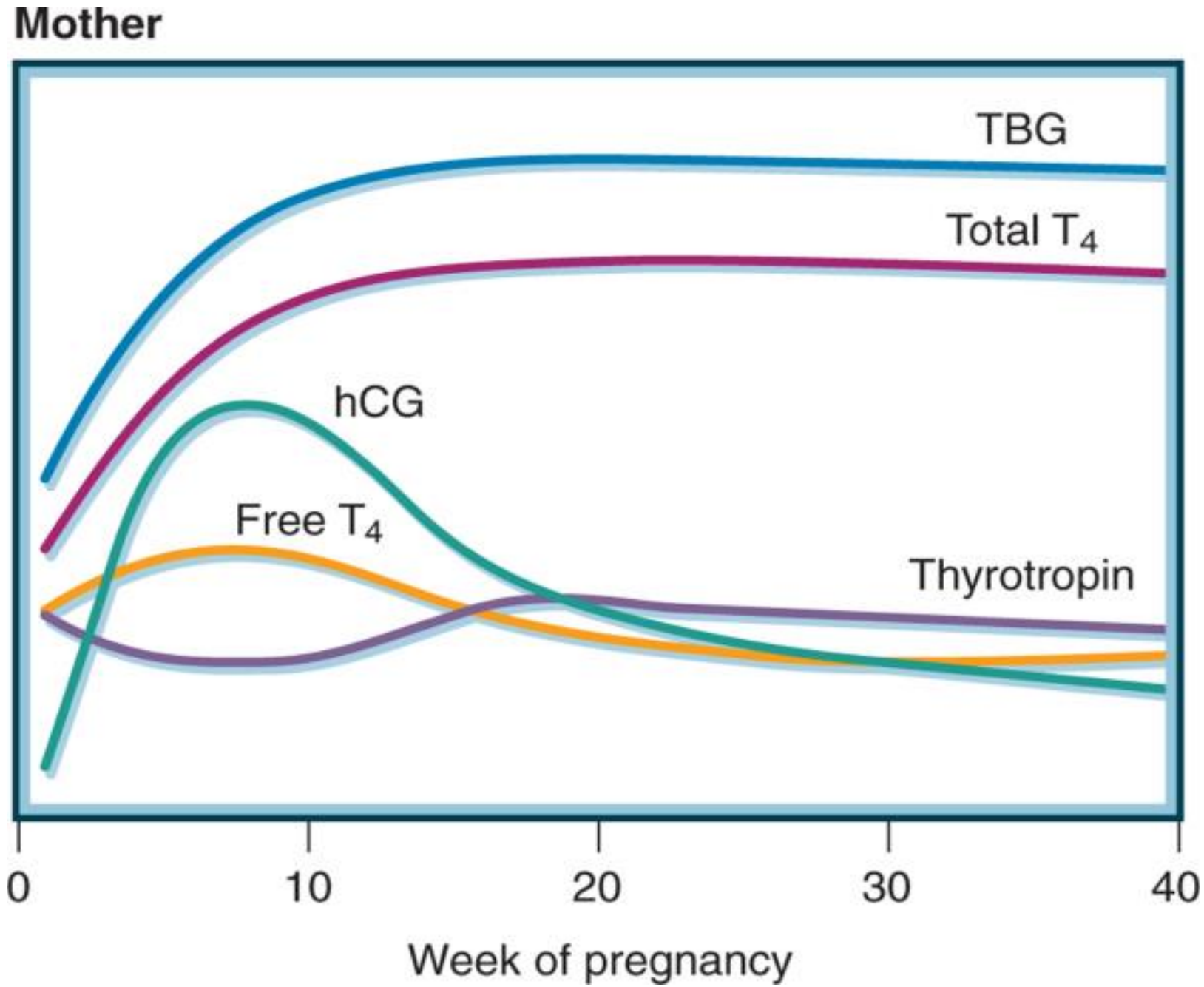


FIGURE 1. Mechanism of increased maternal dietary iodine requirments in pregnancy. hCG indicates human chorionic gonadotropin; TBG, thyroxine-binding globulin.

Clinical obstetrics and gynecology 2019


Mother
TBG
Total T_4
hCG
Free T_4
Thyrotropin
0
10
20
30
40
Week of pregnancy

Why dietary iodine requirements is increased in pregnancy?

- In early gestation the thyroid is stimulated not only by TSH but by hCG, which also binds to and stimulates the TSH receptor.
- High estrogen levels in pregnant women increase TBG concentrations by 1.5-fold, resulting an increasing total T3 and T4.
- Requiring an increase in thyroid hormone production in order to maintain free thyroid hormone levels.
- Type 3deiodinase (D3), which inactivates thyroid hormones, is present in high concentrations in the placenta.
- Starting at about 20 weeks gestation, the fetus requires iodine supply for its own thyroid hormone production.
- The increase in glomerular filtration rate in pregnancy, results in increased losses of ingested iodine.

Iodine Requirement (µg/day)

During pregnancy

Basal	150
40-50 % increased T4 requirements	50-100
Transfer of T4 and I from mother to fetus	50
Increased renal clearance of I	?

250-300

During lactation

Basal	150
0.5-1.1 L milk/day x 150-180 µgI/L	75-200

225-350

Delange: Int.J. Endocrinol. Metab. 2: 1, 2004

Recommended Iodine Intake (micrograms/day)

Subjects	IOM (2001)	WHO (2005)
Pregnant women	160 (EAR) 220 (RDA)	250
Lactating women	209 (EAR) 290 (RDA)	250
Infants 6-12 months	110 (AI)	90
Infants 7-24 months	130 (AI)	90

IOM: Institute of Medicine
WHO: World Health Organization
EAR: Estimated Average Requirement
RDA: Recommended Dietary Allowance
AI: Average Intake

Azizi F, et al. Clin Endocrinol 2009; 70: 803-809.

Method for identification of the iodine status of a population

- Median urinary iodine concentrations can be used to assess population iodine status
- Thresholds for median urinary iodine sufficiency have been identified for populations, but not for individuals
- There is a significant day-to-day variation of iodine intake.
- Population iodine sufficiency is defined by median urinary iodine concentrations 100–199 µg/l in non-pregnant adults.

The median urinary iodine concentration for classification of the iodine status of pregnant and lactating women and children

Subjects	UIC (µg/l)	Category
Pregnant women	<150 150–249 250–499 ≥ 500	Insufficient Adequate More than adequate Excessive
Lactating women	< 100 ≥ 100	Insufficient Adequate
Children < 2 years old	< 100 ≥ 100	Insufficient Adequate

WHO, United Nations Children's Fund, and ICCIDD. 3rd ed. Geneva, Switzerland: 2007.
Azizi F, et al. Clin Endocrinol 2009; 70: 803-809.

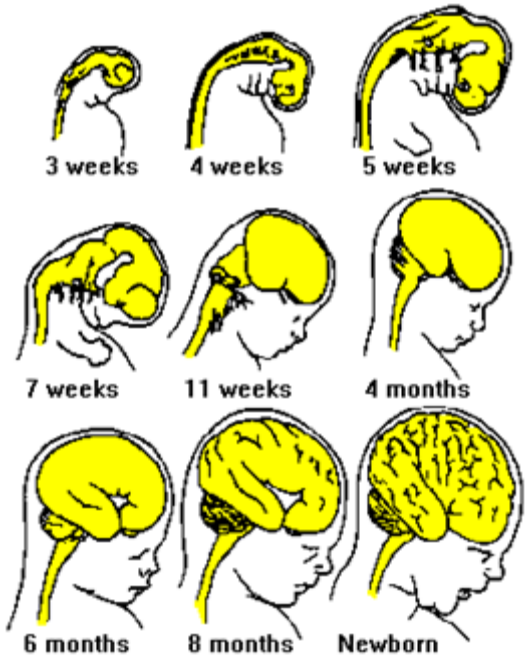
Criteria for Assessing Iodine Nutrition in Pregnant Women

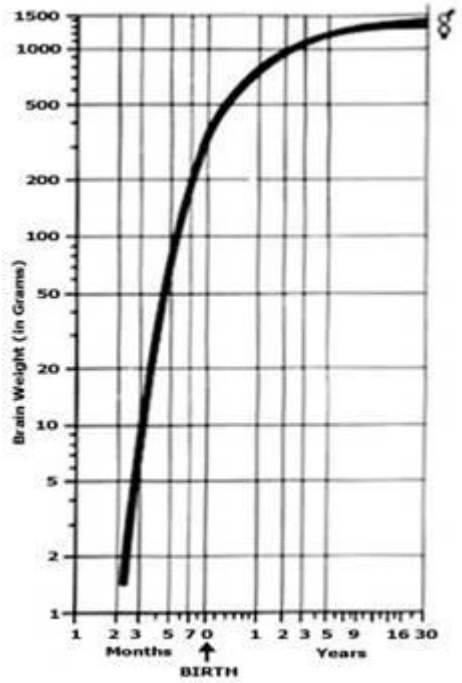
Median Urinary Iodine (MUI) (μg/L)	Iodine Intake
≥ 500	Excessive
250～499	More than adequate
150～249	Adequate
100-149	Mild insufficient
50-99	Moderate insufficient
<50	Sever insufficient

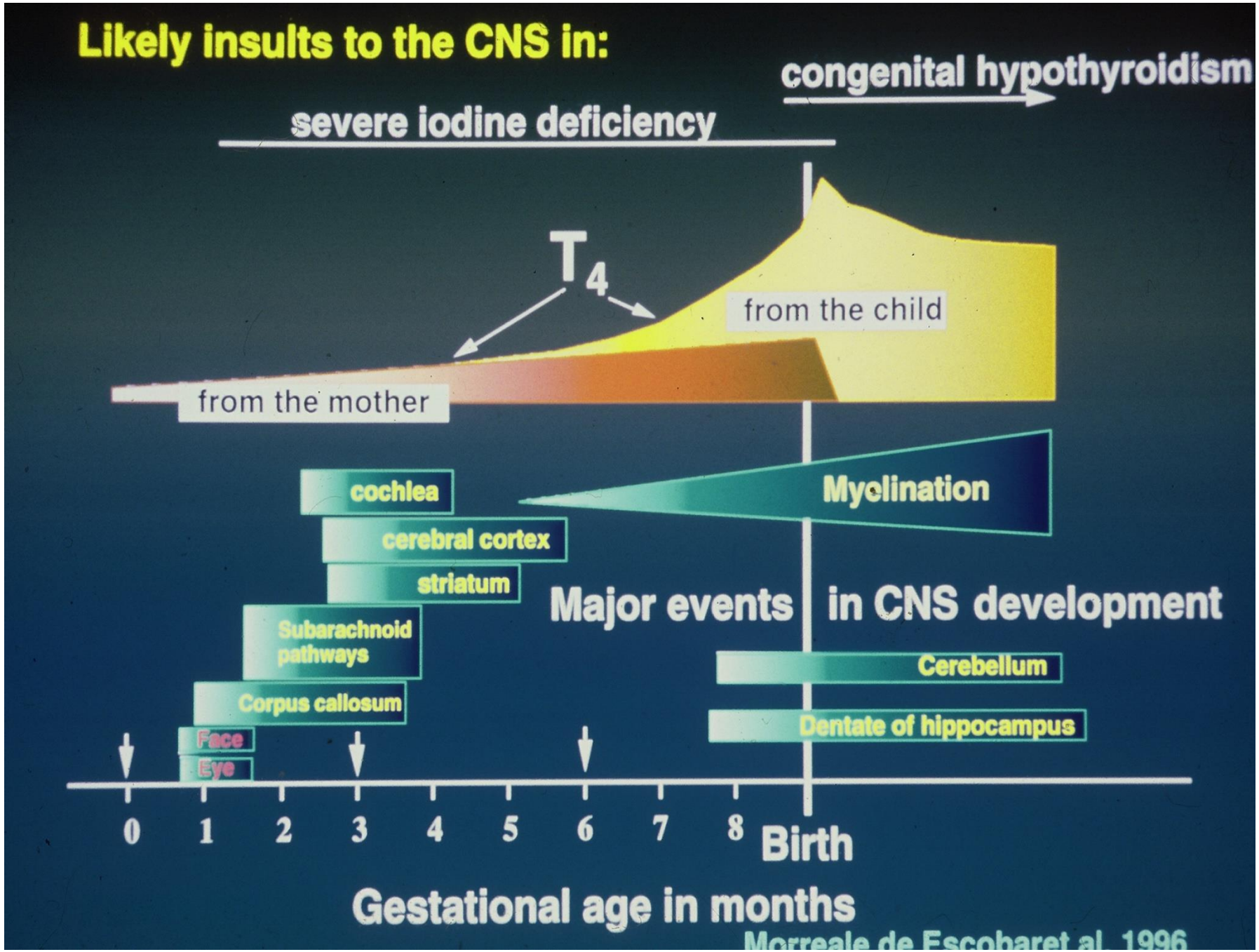
WHO, 2011

Importance of iodine in brain development

90 % of human brain development occurs between 3rd month of pregnancy & 3rd year of life (Critical period)






Likely insults to the CNS in:
congenital hypothyroidism
severe iodine deficiency
T4
from the child
from the mother
cochlea
Myelination
cerebral cortex
striatum
Major events
in CNS development
Subarachnoid pathways
Cerebellum
Corpus callosum
Dentate of hippocampus
Face
Eye
0
1
2
3
4
5
6
7
8
Birth
Gestational age in months
Morreale de Escobaret al. 1996

During fetal life

- First half: Fetus depend on maternal thyroid hormones
- Second half: Fetus thyroid function increase due to Axis development

Mild to moderate iodine deficiency during pregnancy

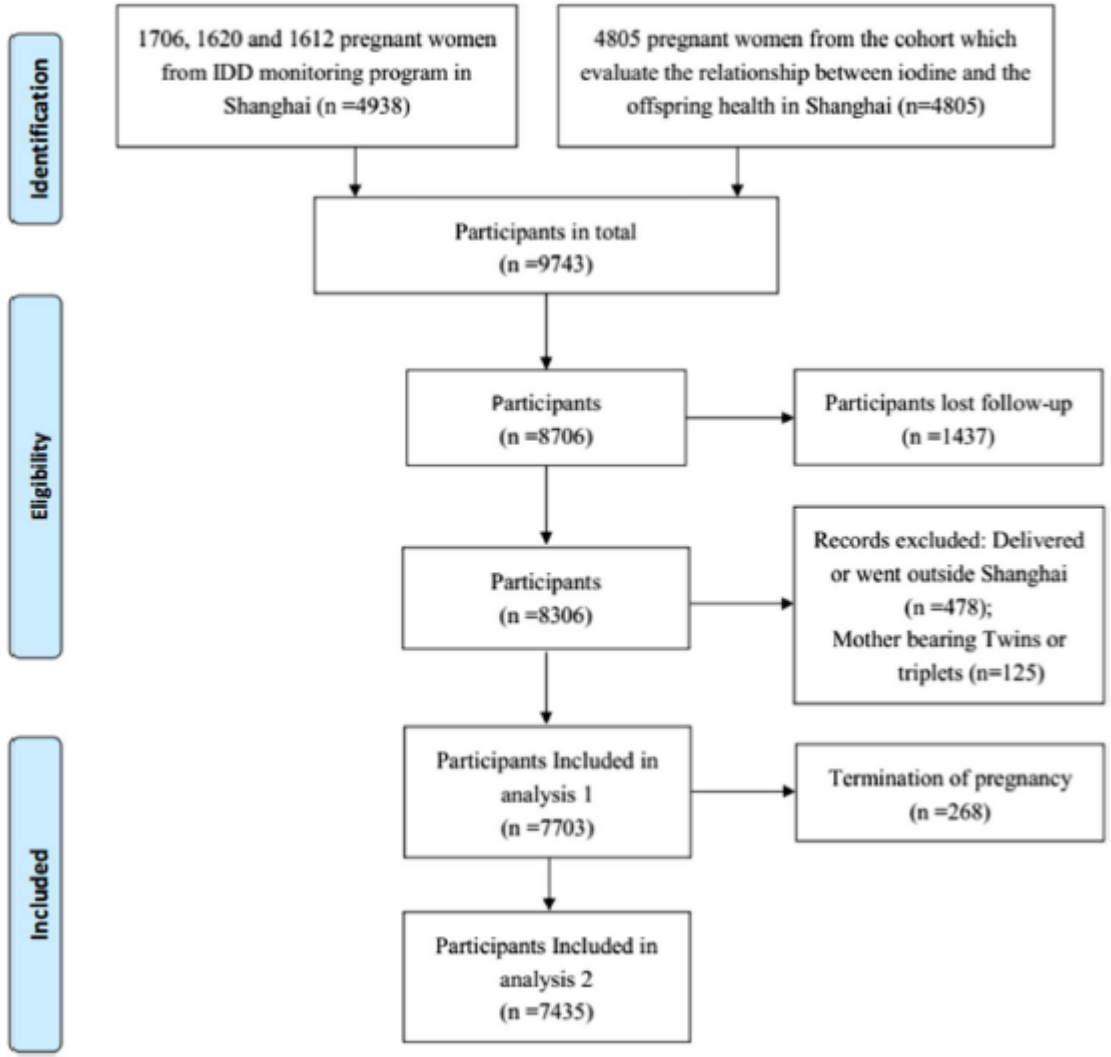
- The potential adverse effects are uncertain
- Inability to distinguish between the persistent effects of fetal iodine deficiency and the ongoing effects of iodine deficiency in childhood and adolescence.
- Inability to distinguish between the effects of iodine deficiency per se and its combination with hypothyroidism.
- Not reported the subgroup analysis according to the severity of iodine deficiency.
- Heterogenicity in observational and interventional studies studies

Biological Trace Element Research (2022) 200:4267–4277
https://doi.org/10.1007/s12011-021-03028-y

No Association Was Found Between Mild Iodine Deficiency During Pregnancy and Pregnancy Outcomes: a Follow-up Study Based on a Birth Registry

Xueying Cui[1] · Huiting Yu[1] · Zhengyuan Wang[1] · Hai Wang[2] · Zehuan Shi[1] · Wei Jin[1] · Qi Song[1] · Changyi G
Hongmei Tang[3] · Jiajie Zang[1]

- UIC of 50 to 100 μg/L moderate insufficient; UIC of 100 to150 mild insufficient.
- The incidence of pregnancy termination, preterm birth, congenital malformations, low birth weight, and cesarean section did not differ significantly



Abel *et al. BMC Medicine* (2020) 18:211
https://doi.org/10.1186/s12916-020-01676-w

BMC Medicine

RESEARCH ARTICLE Open Access

Insufficient maternal iodine intake is associated with subfecundity, reduced foetal growth, and adverse pregnancy outcomes in the Norwegian Mother, Father and Child Cohort Study

Marianne Hope Abel[1], Ida Henriette Caspersen[2], Verena Sengpiel[3], Bo Jacobsson[3,4,5], Helle Margrete Meltzer[6], Per Magnus[7], Jan Alexander[6] and Anne Lise Brantsæter[2*]

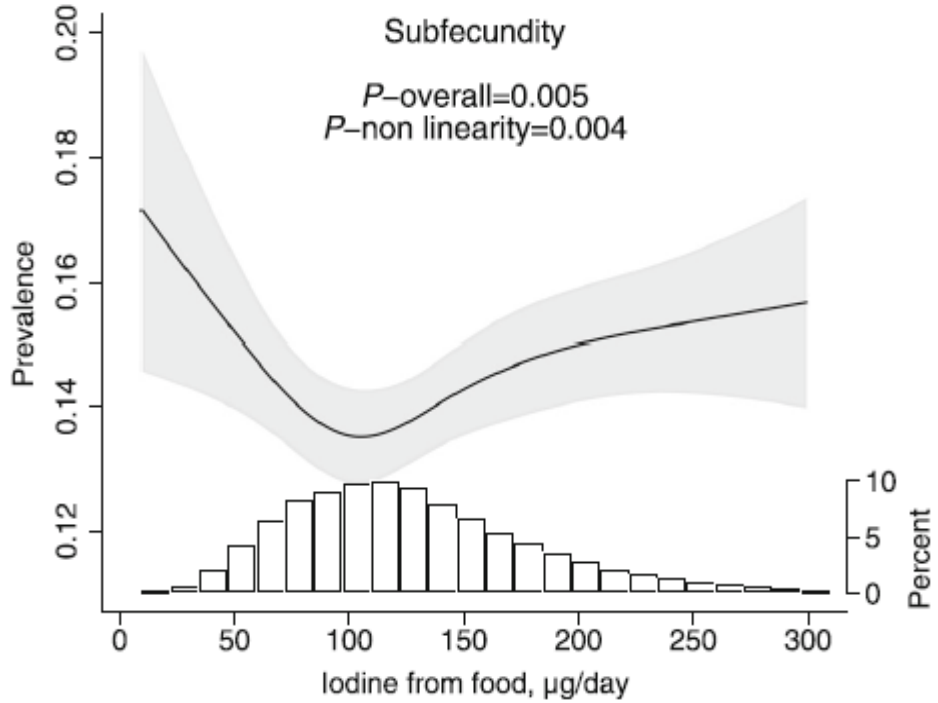


Fig. 2 Habitual iodine intake from food (GW 0–22) and estimated prevalence of subfecundity (> 12 months trying to get pregnant) in planned pregnancies ($n = 56{,}416$, 10.8% subfecundity). The association was modelled by logistic regression adjusting for maternal age, BMI, parity, education, smoking before pregnancy, energy intake, and fibre intake. The curve represents the estimated prevalence when all covariates are set to their means, and the shaded area illustrates the 95% robust confidence interval. The histogram shows the distribution of the exposure. For the crude association, see Additional file 1: Figure S2

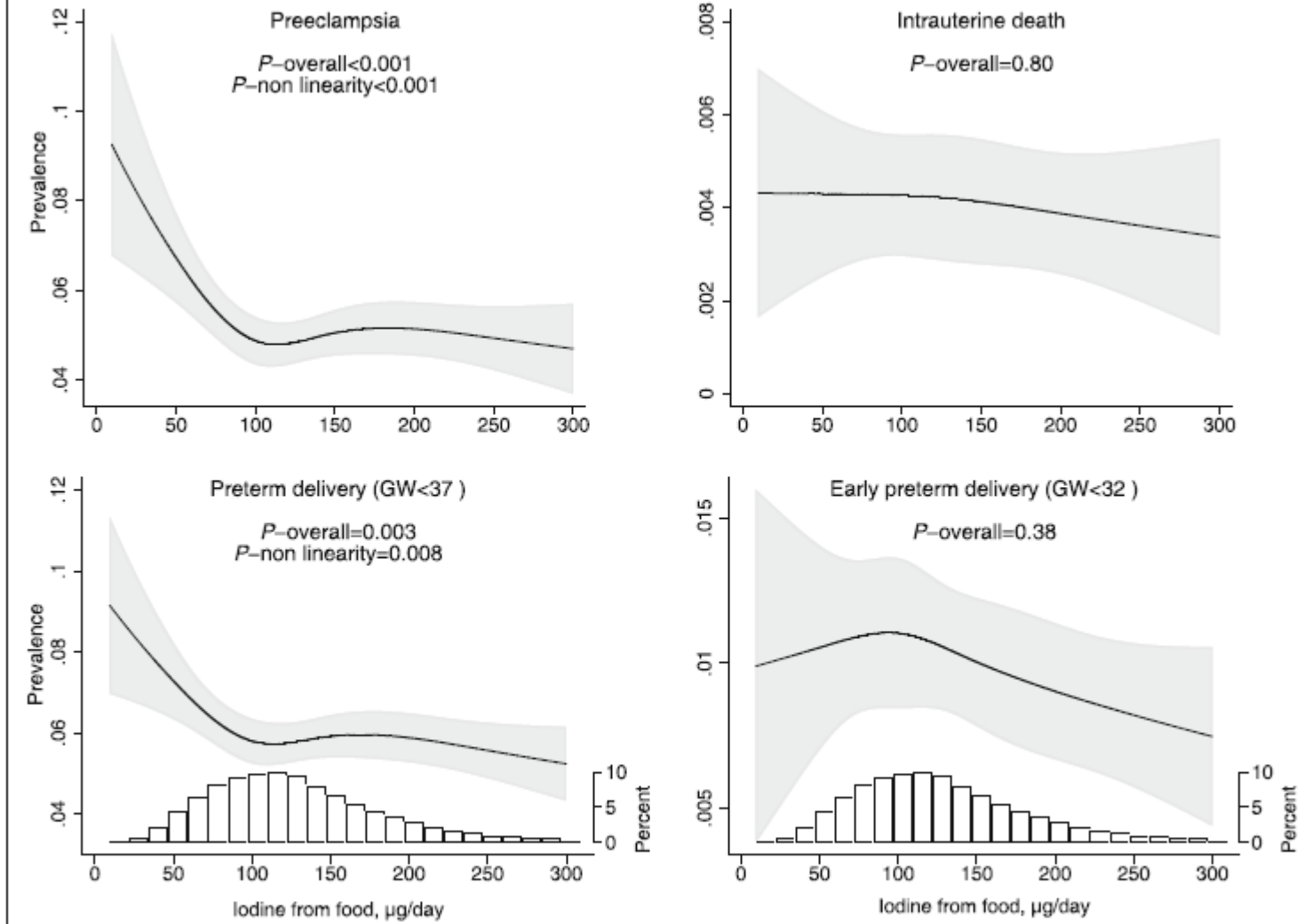


Fig. 3 Iodine from food and adverse pregnancy outcomes in non-users of iodine-containing supplements. Sample size: intrauterine death $n =$ 49,187 (0.35% intrauterine deaths), preeclampsia $n = 49{,}187$ (3.8% preeclampsia), and preterm delivery $n = 48{,}981$ (5.0% preterm and 0.84% early preterm). The associations were modelled by logistic regression adjusting for maternal age, BMI, parity, education, smoking in pregnancy, energy intake, and fibre intake. For the crude associations, see Additional file 1: Figure S3

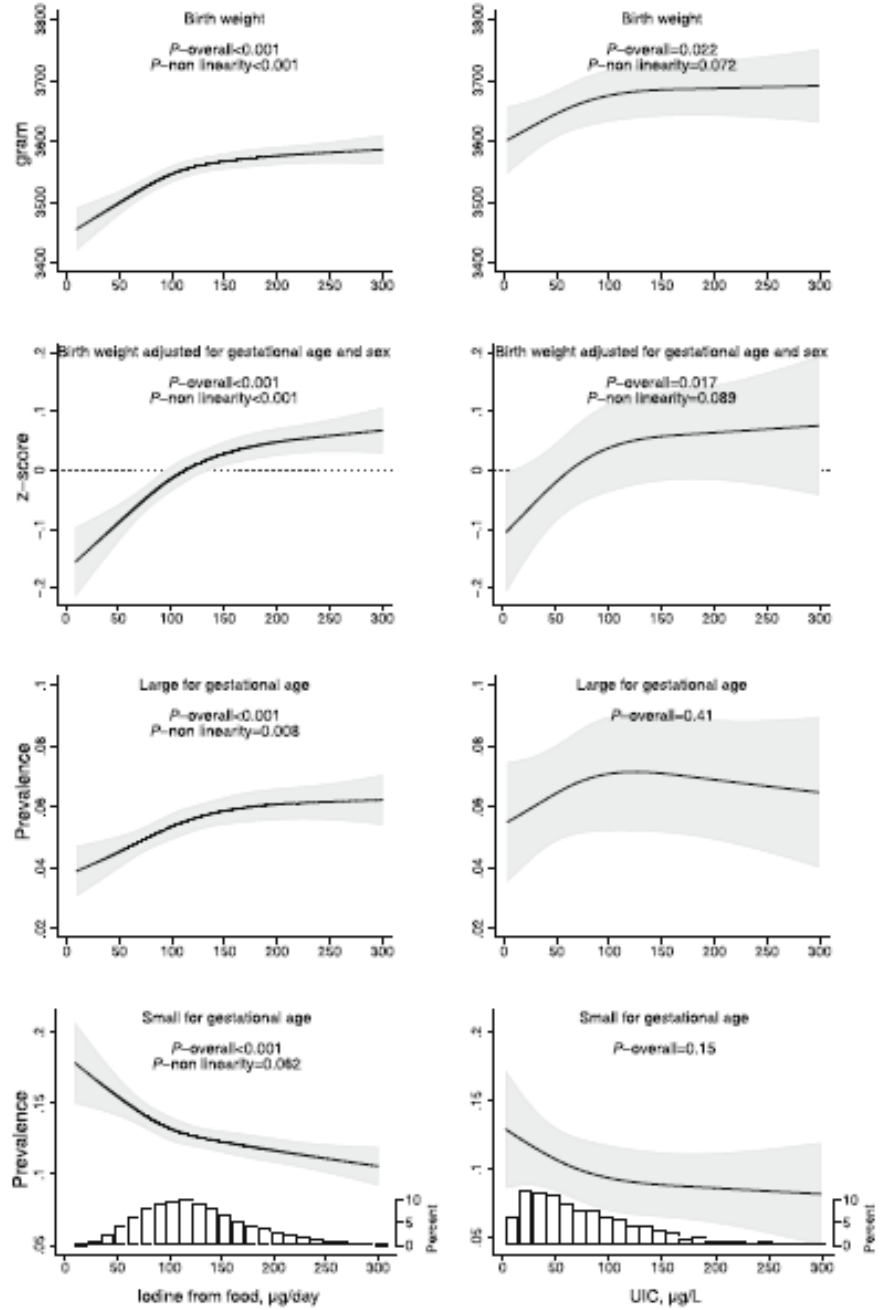


Fig. 4 Associations between measures of maternal iodine intake and child birth weight. In the left column, the exposure is iodine from food in non-users of iodine-containing supplement, and in the right column, the exposure is urinary iodine concentration (including supplement users) ($n = 2795$). Associations are adjusted for maternal age, BMI, parity, education, smoking in pregnancy, energy intake, and fibre intake. Sample size: birth weight $n = 49{,}119$, z-score $n = 48{,}951$ (incl. 9.8% SGA, 9.9% LGA). For the crude associations, Additional file 1: Figure S7

Do maternal urinary iodine concentration or thyroid hormones within the normal range during pregnancy affect growth parameters at birth? A systematic review and meta-analysis

Pantea Nazeri, Sakineh Shab-Bidar, Elizabeth N. Pearce, and Mamak Shariat

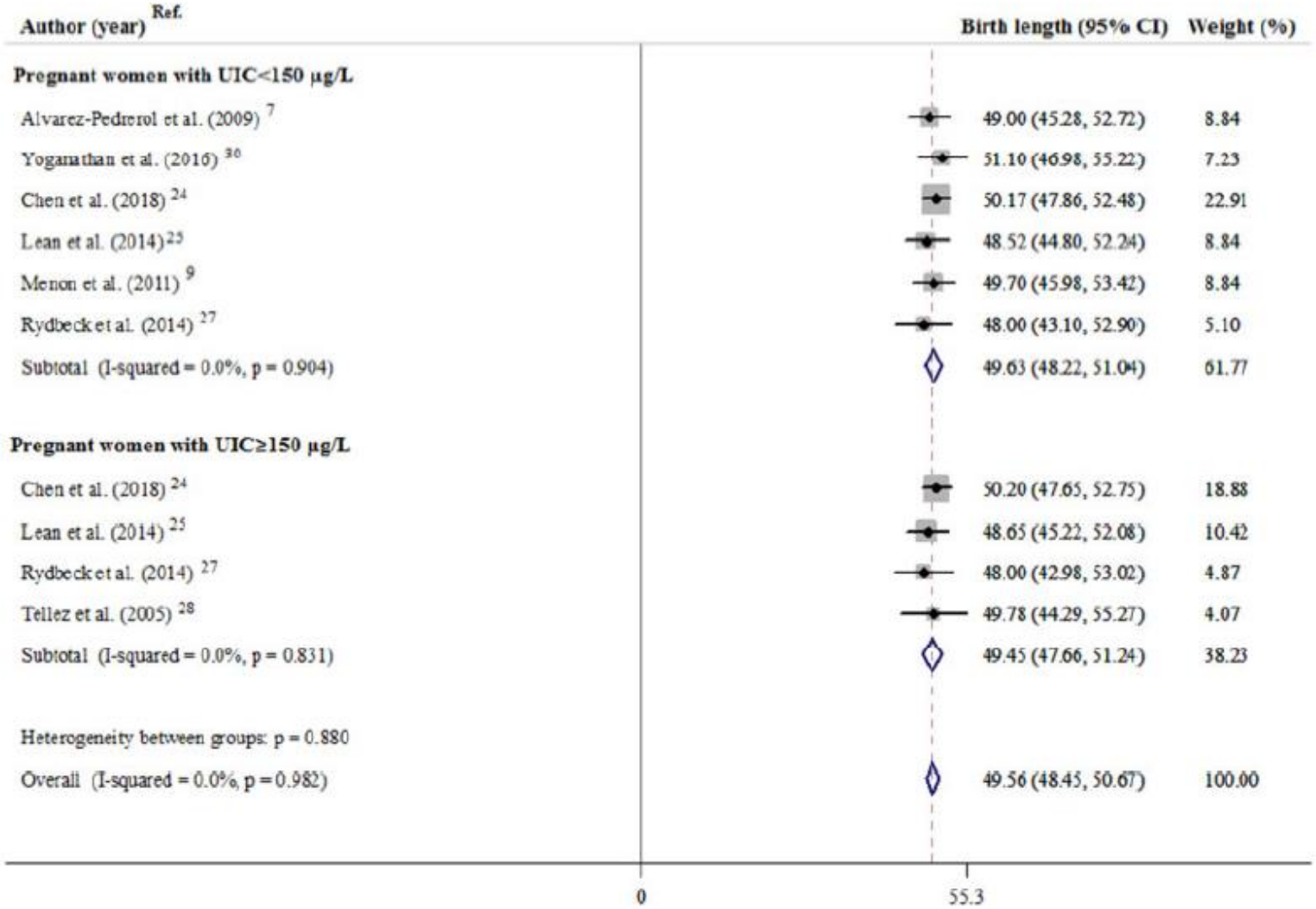


Figure 3 **Mean and 95%CI and the pooled estimates for mean of birth length of newborns whose mothers had UIC < 150 µg/L vs**

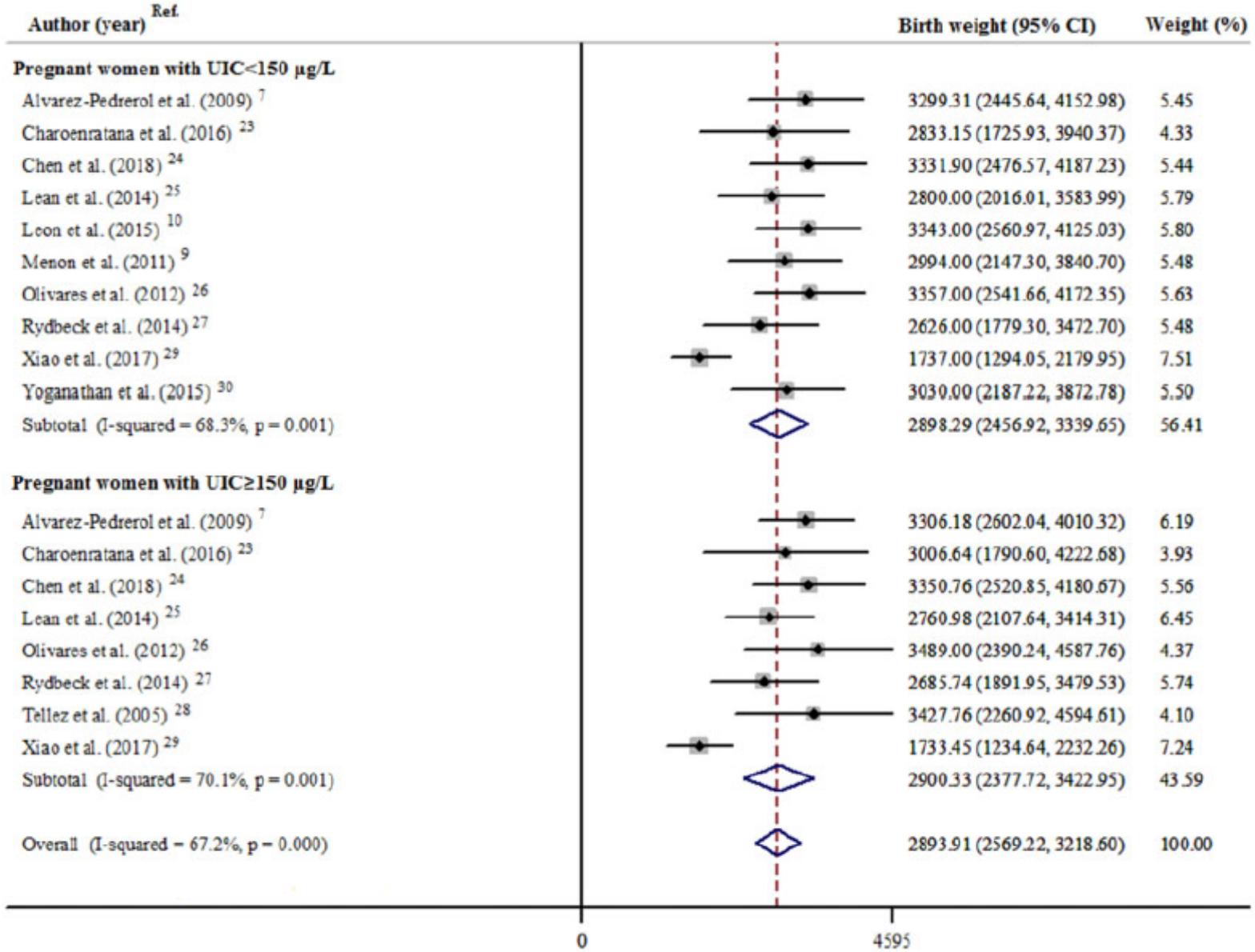


Figure 2 **Mean and 95%CI and the pooled estimates for mean of birth weight of newborns whose mothers had UIC < 150 µg/L vs**

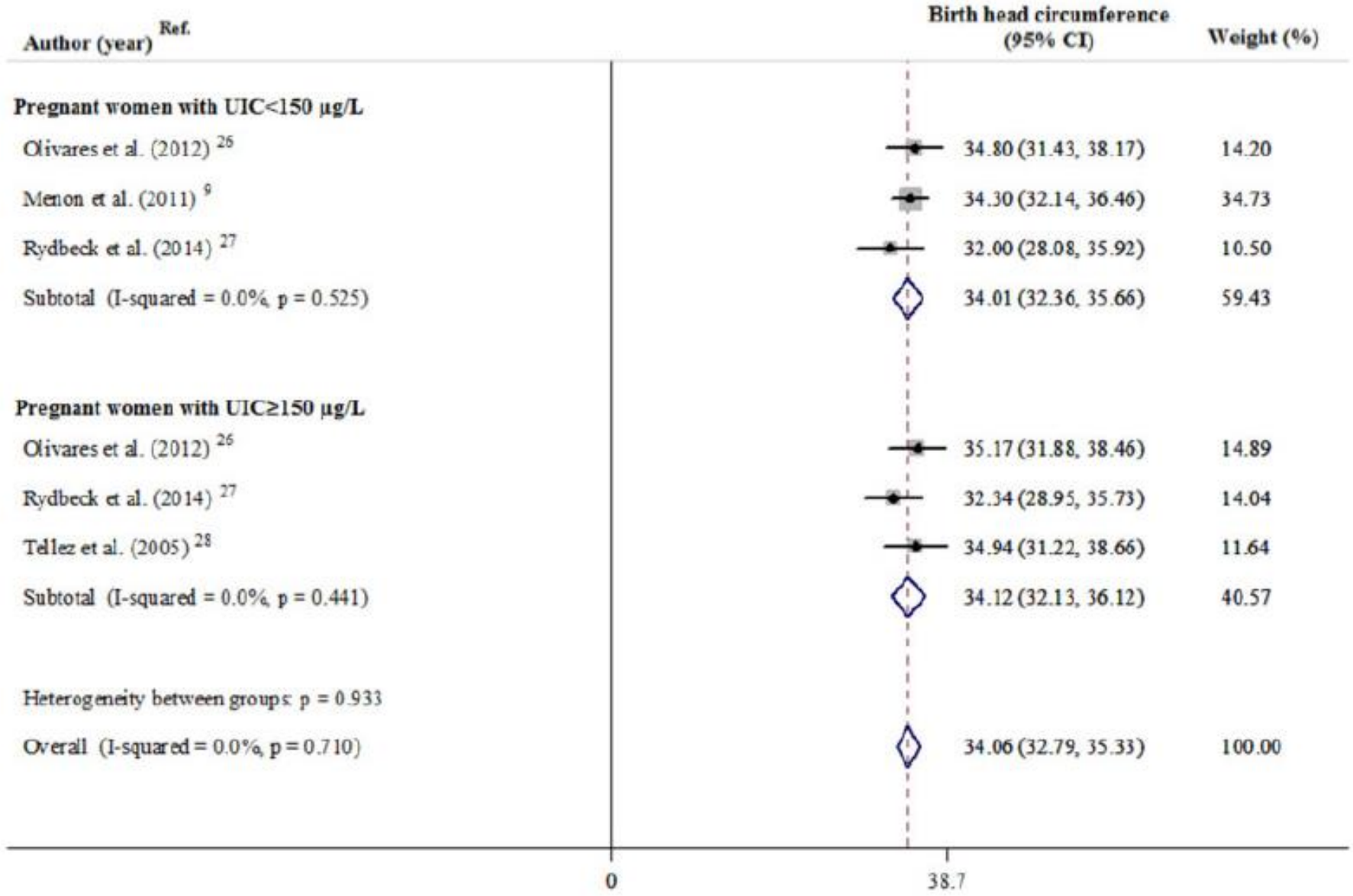


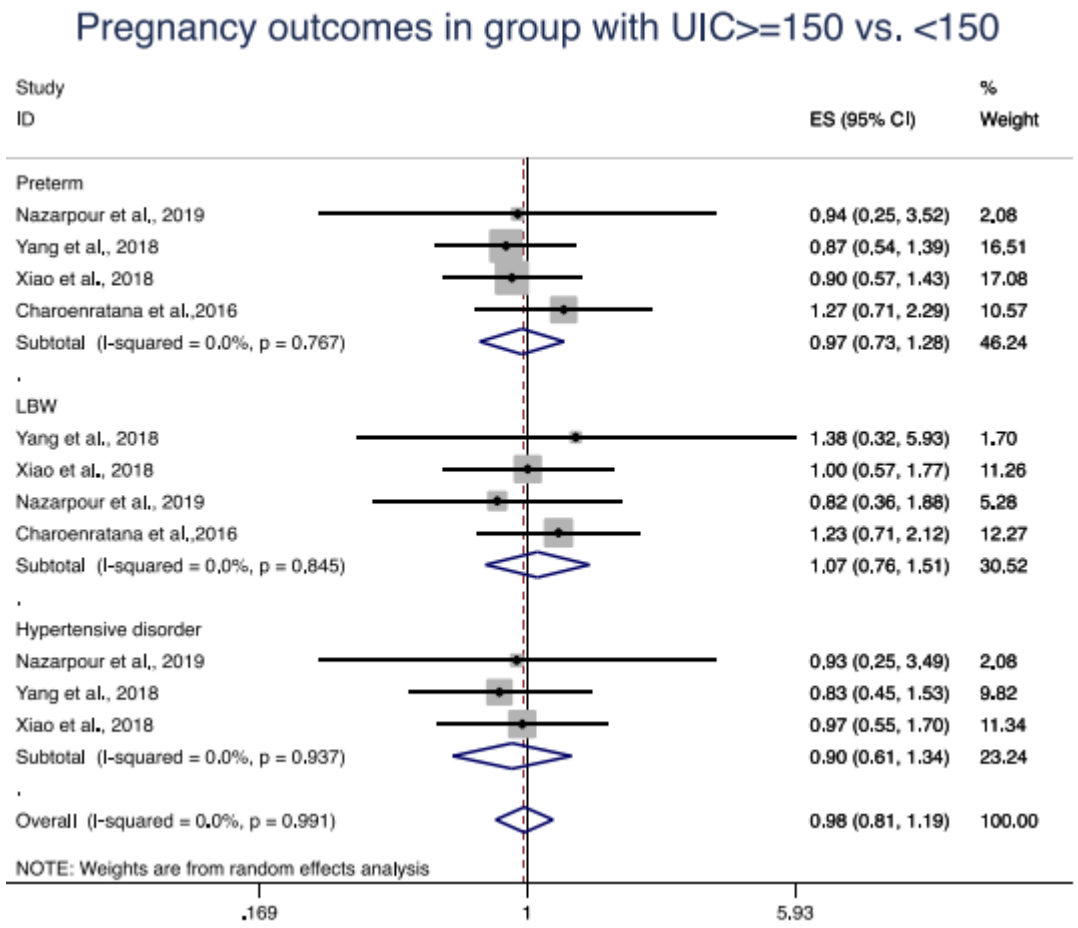
Figure 4 **Mean and 95%CI and the pooled estimates for mean of birth head circumference of newborns whose mothers had UIC < 150 µg/L vs UIC ≥ 150 µg/L.** Subgroup analysis was based on maternal UIC during pregnancy. Open diamonds represent the pooled

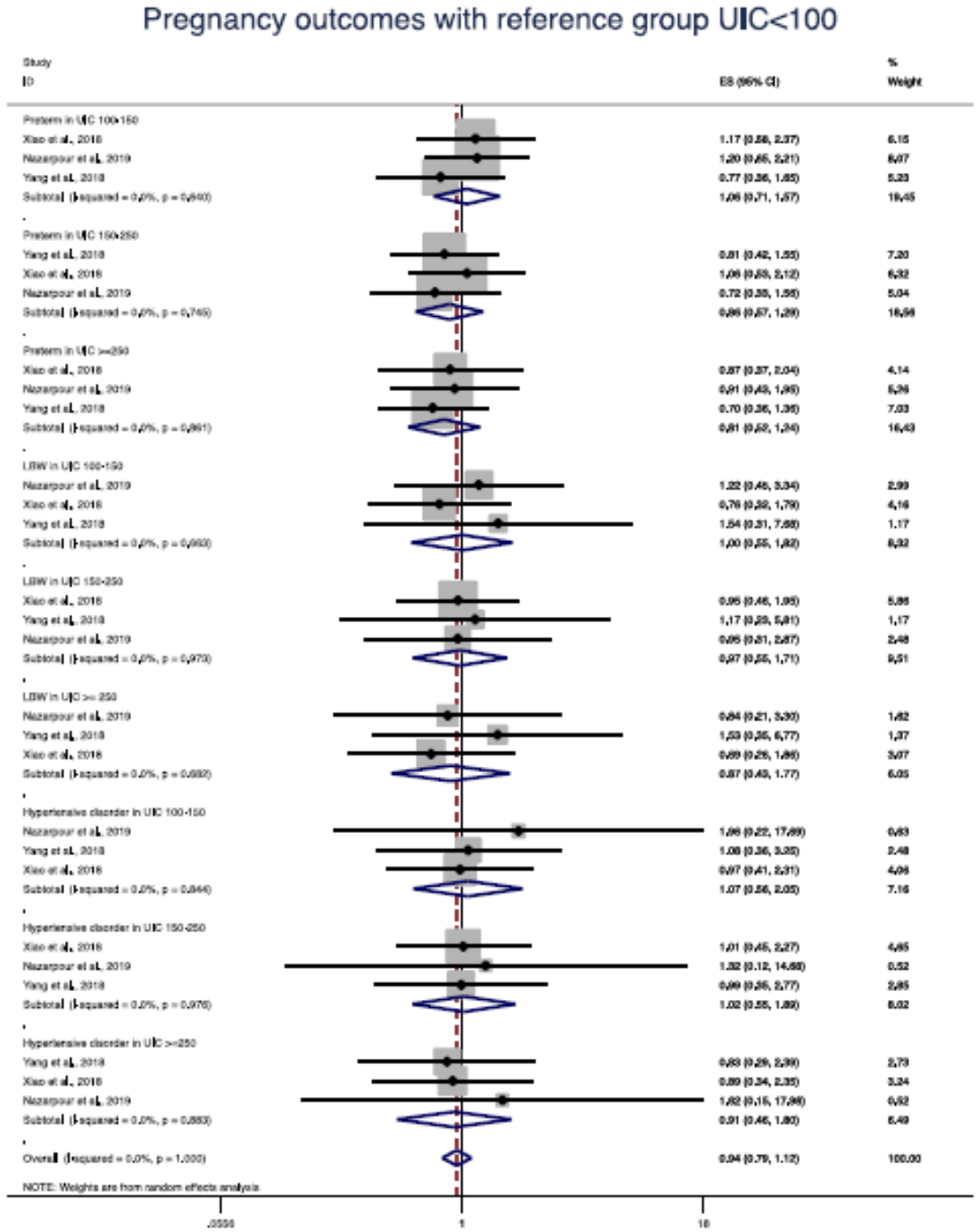
Biological Trace Element Research
https://doi.org/10.1007/s12011-019-02020-x

Maternal Urinary Iodine Concentration and Pregnancy Outcomes in Euthyroid Pregnant Women: a Systematic Review and Meta-analysis

Sima Nazarpour[1,2] · Fahimeh Ramezani Tehrani[2] · Samira Behboudi-Gandevani[2] · Razieh Bidhendi Yarandi[2,3] · Fereidoun Azizi[4]

Received: 29 September 2019 / Accepted: 16 December 2019





Iodine Deficiency and Intelligence Quotient (IQ)

- The brain and pituitary T3 level appears to be very sensitive to iodine deficiency as its level falls below the normal level even in mild or moderate iodine deficiency.

- Several meta-analyses have concluded iodine deficient populations have **13.5**, **8-10**, **8.7-12.5** and **6.9-10.2** IQ points lower than iodine replete populations.

Bleichrodt N, Born PM. The Damaged Brain of Iodine Deficiency: New York, NY, USA, 1994; pp. 195–200.
Verhoef H, et al. Micronutrient Deficiencies in the First Months of Life: Basel, Switzerland, 2003; pp. 327–357.
Qian M, et al. Asia Pac. J. Clin. Nutr. 2005; 14, 32–42.
Bougma K, et al. Nutrients 2013; 5, 1384-1416.

Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

Sarah C Bath, Colin D Steer, Jean Golding, Pauline Emmett, Margaret P Rayman

- Mother–child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC)(n=1040)
- Measuring urinary iodine concentration in stored samples.
- Measure of intelligence quotient (IQ) in the off spring at age 8 years.
- Iodine deficiency was defined as 150 μg/g
- Adjusted for 21 socioeconomic, parental, and child factors variables.
- Children of those ID were more likely to have
  - Scores in the lowest quartile for verbal IQ (odds ratio 1·58, 95% CI 1·09–2·30)
  - Reading accuracy (1·69, 1·15–2·49)
  - Reading comprehension (1·54, 1·06–2·23; p=0·02)

	Unadjusted			Adjusted model one			Adjusted model two			Adjusted model three		
	OR (95% CI)	p value	n	OR (95% CI)	p value	n	OR (95% CI)	p value	n	OR (95% CI)	p value	n
IQ at age 8 years												
Verbal	1·66 (1·20–2·31)	0·002	958	1·46 (1·04–2·05)	0·03	945	1·68 (1·16–2·42)	0·006	901	1·58 (1·09–2·30)	0·02	880
Performance	1·38 (1·00–1·89)	0·05	958	1·26 (0·91–1·75)	0·16	945	1·26 (0·89–1·76)	0·19	901	1·22 (0·86–1·72)	0·27	880
Total	1·43 (1·04–1·98)	0·03	958	1·27 (0·91–1·78)	0·16	945	1·40 (0·98–2·02)	0·07	901	1·35 (0·93–1·94)	0·11	880
Reading at age 9 years												
Words read per minute	1·44 (1·03–2·00)	0·03	904	1·26 (0·89–1·78)	0·18	893	1·26 (0·87–1·80)	0·22	855	1·20 (0·83–1·74)	0·33	838
Accuracy	1·78 (1·26–2·50)	0·001	905	1·57 (1·10–2·24)	0·01	894	1·71 (1·17–2·50)	0·005	856	1·69 (1·15–2·49)	0·007	839
Comprehension	1·58 (1·13–2·19)	0·007	905	1·39 (0·99–1·97)	0·06	894	1·54 (1·07–2·21)	0·02	856	1·54 (1·06–2·23)	0·02	839
Reading score	1·60 (1·13–2·26)	0·008	911	1·41 (0·98–2·02)	0·06	900	1·47 (1·00–2·15)	0·05	862	1·47 (1·00–2·16)	0·05	844

Suboptimum outcome defined as scores in the bottom quartile. We used maternal iodine status 150 µg/g or more as the reference group. OR=odds ratio. IQ=intelligence quotient.

Table 3: **Risk of suboptimum outcomes in children according to urinary iodine-to-creatinine ratio (<150 µg/g *vs* ≥150 µg/g), unadjusted and adjusted for potential confounders**

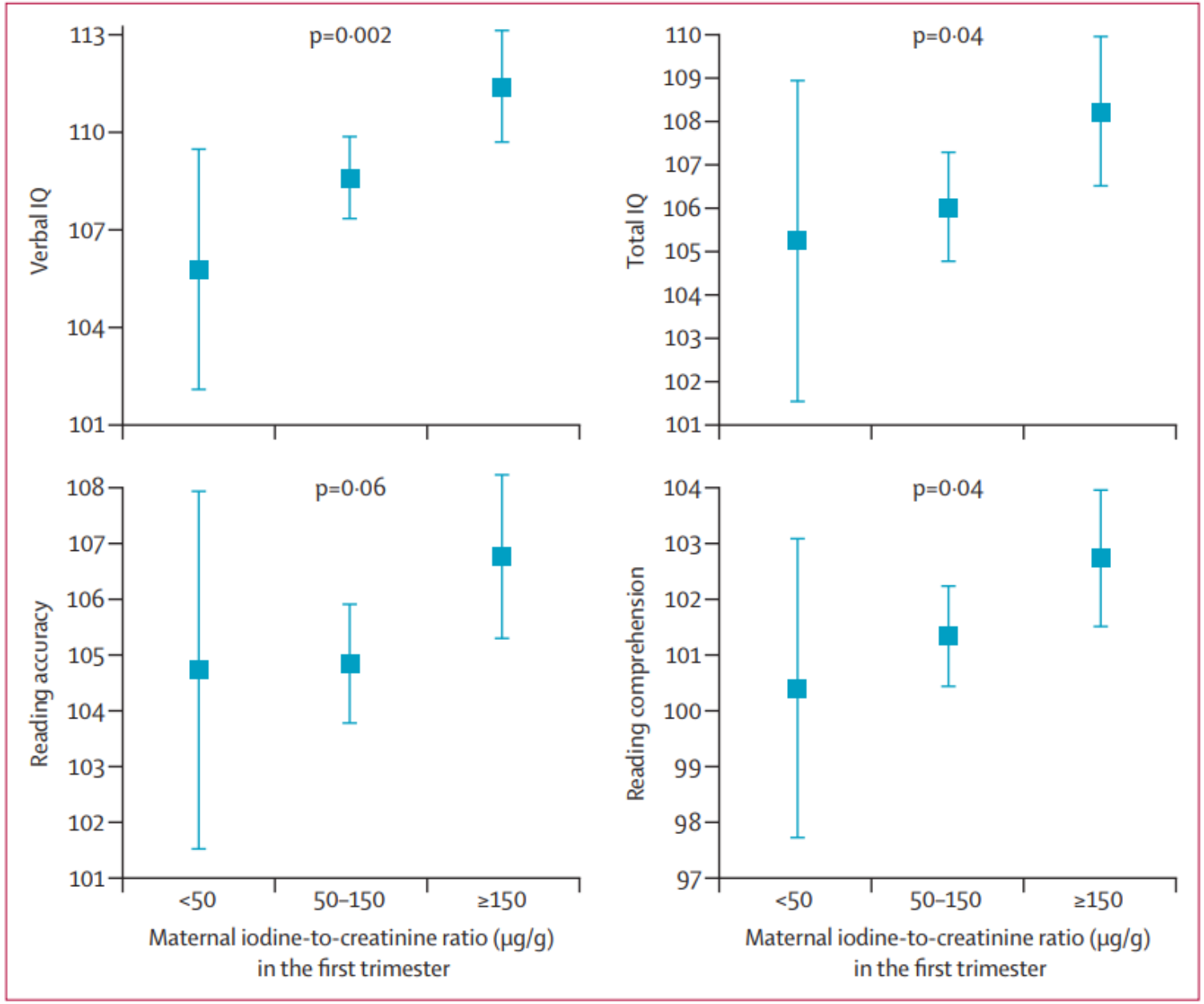


Figure: **Means (95% CIs) for child cognitive outcomes according to maternal iodine status in the first trimester**
Values are adjusted for the effect of confounders (model three). Child verbal and total IQ were assessed at age 8 years and reading accuracy and comprehension at age 9 years. IQ=intelligence quotient.

Conclusion

- While iodine deficiency in developing countries is a serious nutritional problem, it was thought that this was not an issue for the rest of the world.
- **This study was performed in the United Kingdom, which was thought to be a country with no iodine issues at all.**

Women with only a mild-to-moderate iodine deficiency were more like to have children
in the lowest 25% of IQ and reading ability.

Nutrients **2013**, *5*, 1384-1416; doi:10.3390/nu5041384

OPEN ACCESS

nutrients

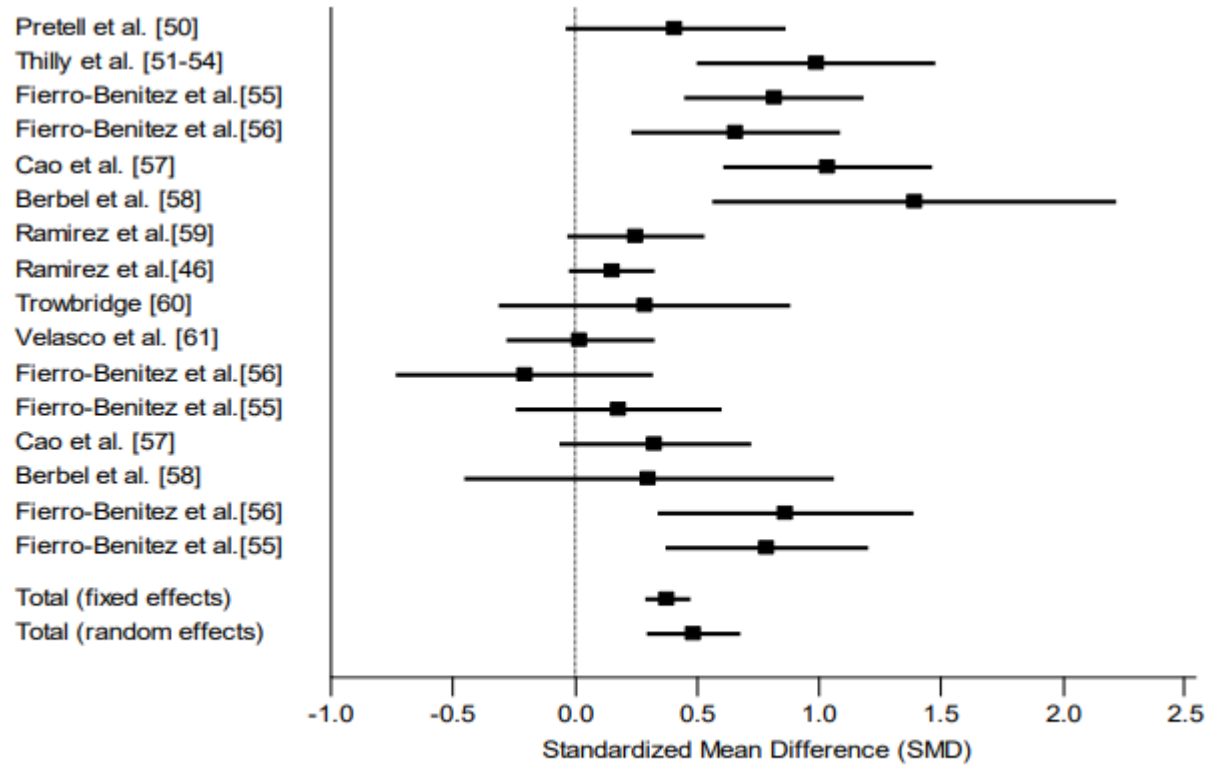
ISSN 2072–6643

www.mdpi.com/journal/nutrients

Review

Iodine and Mental Development of Children 5 Years Old and Under: A Systematic Review and Meta-Analysis

Karim Bougma [1], Frances E. Aboud [2], Kimberly B. Harding [3] and Grace S. Marquis [1,*]



3. Observational Cohort Prospective Studies Stratified by Maternal Iodine Status

ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Clin Endocrinol Metab. 2019 Dec; 104(12): 5957–5967. PMCID: PMC6804415
Published online 2019 Mar 28. doi: 10.1210/jc.2018-02559: 10.1210/jc.2018-02559 PMID: 30920622

Association of Maternal Iodine Status With Child IQ: A Meta-Analysis of Individual Participant Data

- Population based cohort study: Generation, INMA, ALSPAC
- 6180 mother -child pair
- Child non verbal-verbal IQ at 1.5-8 years
- Mild-moderate iodine deficiency is associated with lower verbal IQ
- Stratification is only significant for those with mild-moderate iodine deficiency at GA<14 weeks

Iodine deficiency &hearing loss

- In animal studies association were observed.
- In humans, auditory impairment is reported frequently in relation to hypothyroidism.
- Congenital hypothyroidism has been related more explicitly to auditory impairment than acquired hypothyroidism.
- The effect of iodine deficiency on hearing function is likely to be largest during pregnancy.
- An association between iodine deficiency and impaired hearing function has been found in most of the human observational studies.
- Several non randomized clinical trials reported that iodine supplementation resulted in an improvement in hearing.

Azizi F et al1995; Van den Briel et al 2001; Azizi F et al 2005; Melse-Boonstra et al 2013

Subclinical neurologic defects

- Minor neuropsychological defects
- may be detected by appropriate neuropsychological tests

Breastfeeding and maternal and infant iodine

- Loss of iodide in breast milk occurs during lactation, causing an increase in dietary iodine requirement in the lactating mother.
- The infant needs a supply of iodine for normal thyroid activity, vital for brain development in the first 2 years of life.
- The neonatal full-term thyroid gland contains about 100 μg of iodine under conditions of iodine sufficiency.
- The supply of iodine to the neonate and infant comes exclusively from

breast in the first 6 months of life in those with exclusive breast feeding.

- Concentration of iodine in human milk is 20–50 times higher than that of plasma.

Azizi et al 2009

Active Iodide transport to breast milk

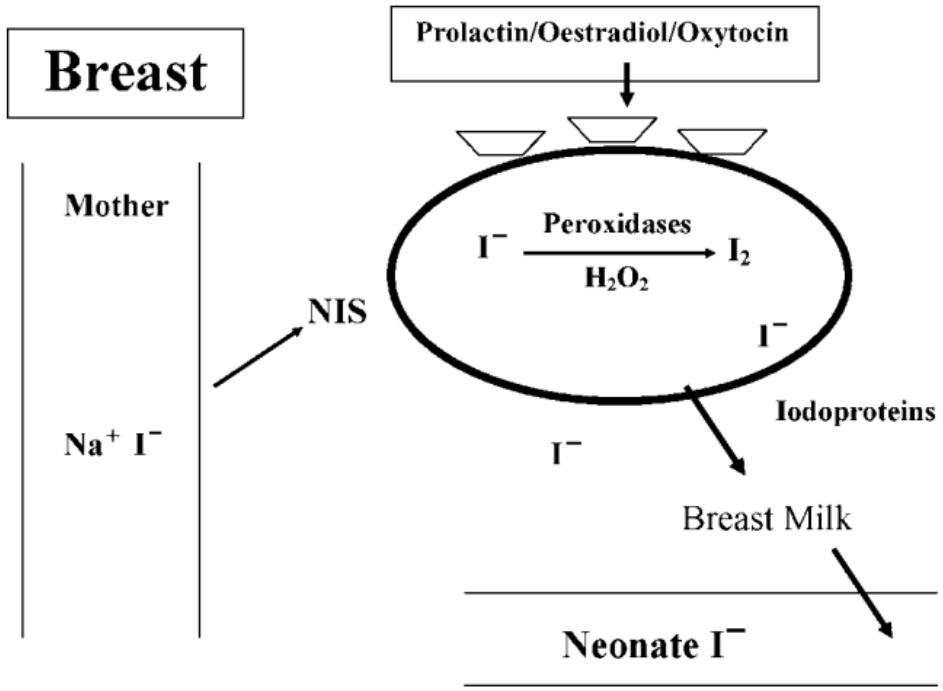


Fig. 1 Iodine secretion in human milk and the role of sodium iodide symporter (NIS). Mammary gland is controlled by NIS and its expression increases during lactation.

Azizi et al 2009

Iodine Requirement during Lactation

- Milk production: 0.5-1.1 l/day
- In conditions of iodine sufficiency, iodine content of breast milk is 150–180 μg/l.
- Loss of iodine into breast milk: 75-200 μg/day
- Basal iodine requirement: 150 μg/day
- Iodine requirement during breastfeeding: 225-350 μg/day
- Iodine concentration in human milk is approximately 200–400 μg/l in colostrum, but decreases during the next few weeks

Azizi F, et al. Clin Endocrinol 2009; 70: 803-809.
Delange F. Int J Endocrinol Metab 2004; 2: 1-12.

Clinical Endocrinology (2009) 70, 803–809 doi: 10.1111/

ORIGINAL ARTICLE

Breastfeeding and maternal and infant iodine nutrition

Fereidoun Azizi* and Peter Smytht

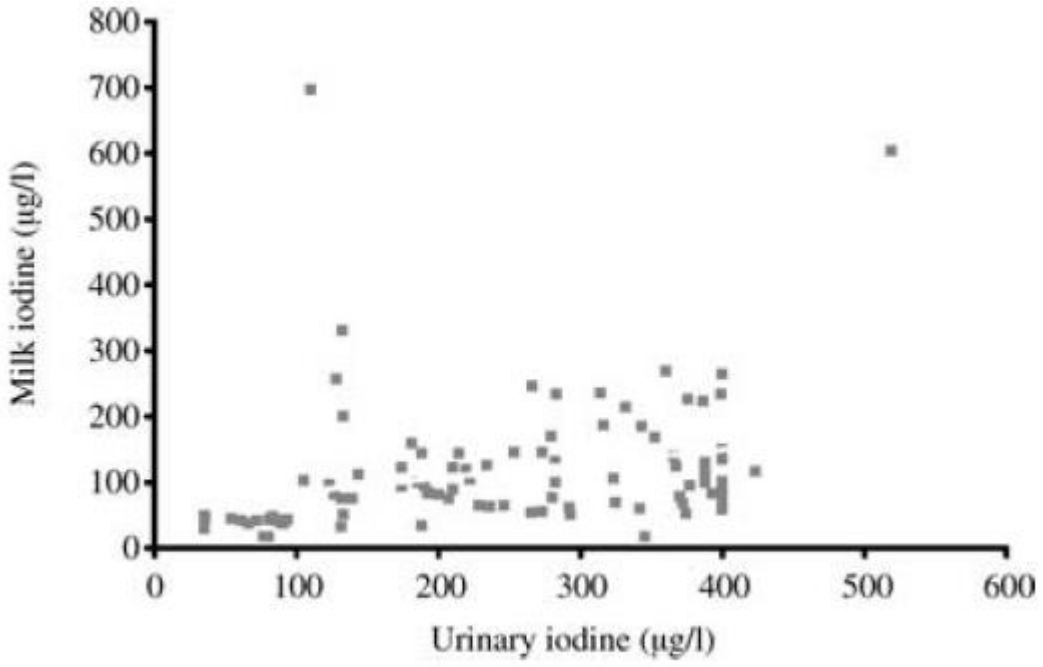


Fig. 2 Scatter plot showing moderate correlation between urinary iodine and milk iodine values in 142 lactating mothers from Iran ($r = 0{\cdot}40$, $P < 0{\cdot}01$),

- Adequate concentration of iodine in breast milk is essential to provide for optimal neonatal thyroid hormone stores and to prevent impaired neurological development in breast-fed neonates.
- Daily iodine intake of 250µg is recommended for lactating mothers to ensure that iodine deficiency dose not occur in the postpartum period.

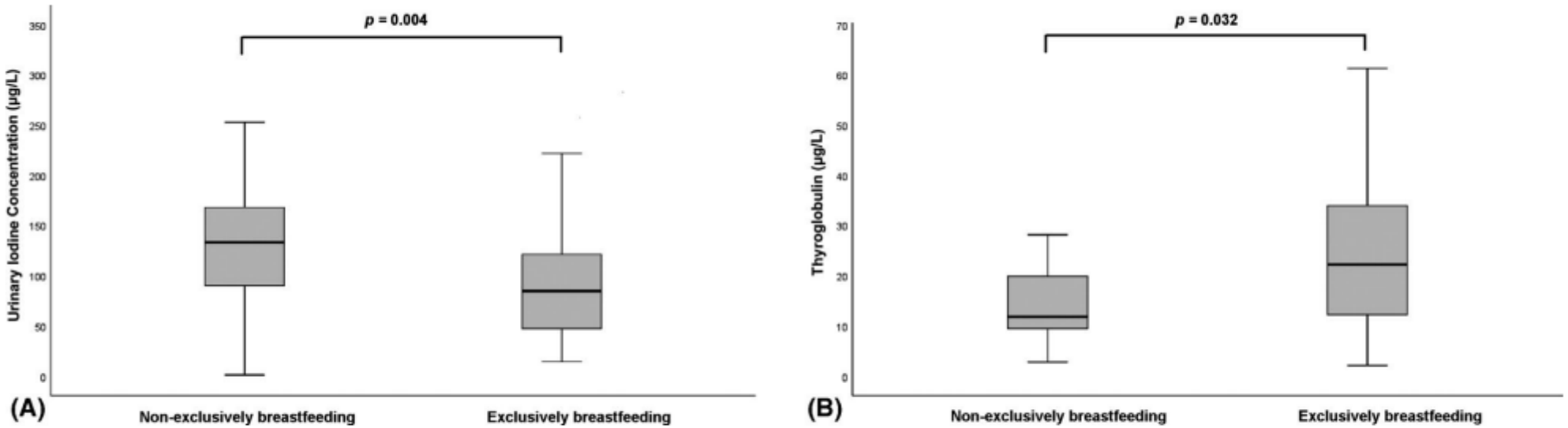


FIGURE 4 Boxplot illustrating (A) urinary iodine concentration of non-exclusively breastfeeding women vs exclusively breastfeeding women, and (B) thyroglobulin of non-exclusively breastfeeding women vs exclusively breastfeeding women at 4 months postpartum

Bhutta ZA, Hurrell RF, Rosenberg IH (eds): Meeting Micronutrient Requirements for Health and Development. Nestlé Nutr Inst Workshop Ser, vol 70, pp 137–146,
Nestec Ltd., Vevey/S. Karger AG., Basel, © 2012

Are Weaning Infants at Risk of Iodine Deficiency Even in Countries with Established Iodized Salt Programs?

Michael B. Zimmermann

Iodine Deficiency Disorders in Infants and Children

- Infants are at high risk for iodine deficiency because their requirements per kilogram body weight for iodine and thyroid hormone are much higher than at any other time in the life cycle.

- Infants may be at particularly high risk for iodine deficiency during the weaning period.

Andersson M, et al. J Clin Endocrinol Metab 2010; 95: 5217-5224.

Iodine Deficiency Disorders in Infants and Children

- Goiter and hypothyroidism
- Impaired cognitive function
- Impaired psychomotor development
- Attention deficit and hyperactivity disorders
- Autism
- Increased mortality

Cao XY, et al. N Engl J Med 1994; 331:1739–1744.
Stagnaro-Green A, et al. Thyroid 2011; 21(10): 1081-1125

Nutrients **2013**, *5*, 1384-1416; doi:10.3390/nu5041384

OPEN ACCESS

nutrients

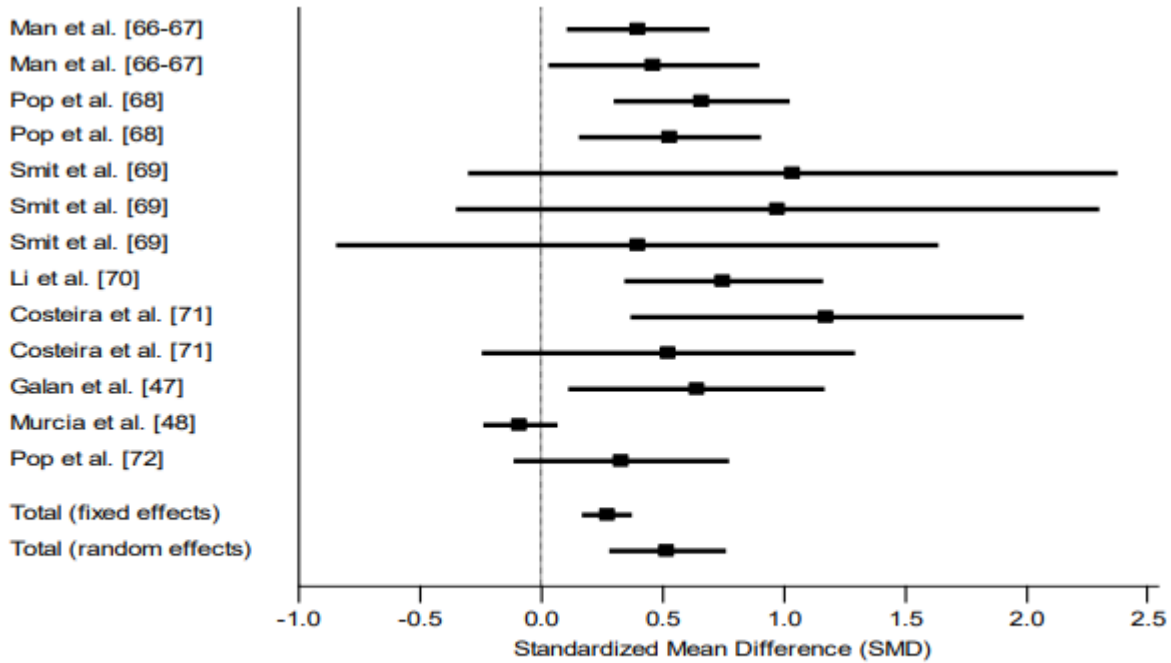
ISSN 2072–6643

www.mdpi.com/journal/nutrients

Review

Iodine and Mental Development of Children 5 Years Old and Under: A Systematic Review and Meta-Analysis

Karim Bougma [1], Frances E. Aboud [2], Kimberly B. Harding [3] and Grace S. Marquis [1,*]



4.4. Observational Cohort Prospective Studies Stratified by Newborn Iodine Status

Take home messages

- Thyroid and iodine metabolism are modified during pregnancy to ensure proper maternal and fetal thyroid function.
- Dietary iodine requirements is increased in pregnancy and lactation period.
- Mild/moderate iodine deficiency may not be associated with adverse pregnancy outcomes.
- Even mild/moderate iodine deficiency affect the neurodevelopment status of infants.
- Exclusive breast feeding infants are at risk of iodine deficiency during the weaning period.
- Iodine deficiency in breast feeding period is associated with adverse effect on the neurodevelopment status of infants.