





NEON lunch seminar, April 26th, 2023

Is iodine nutrition in Nordic countries a cause of concern? Result from a Norwegian pregnancy cohort

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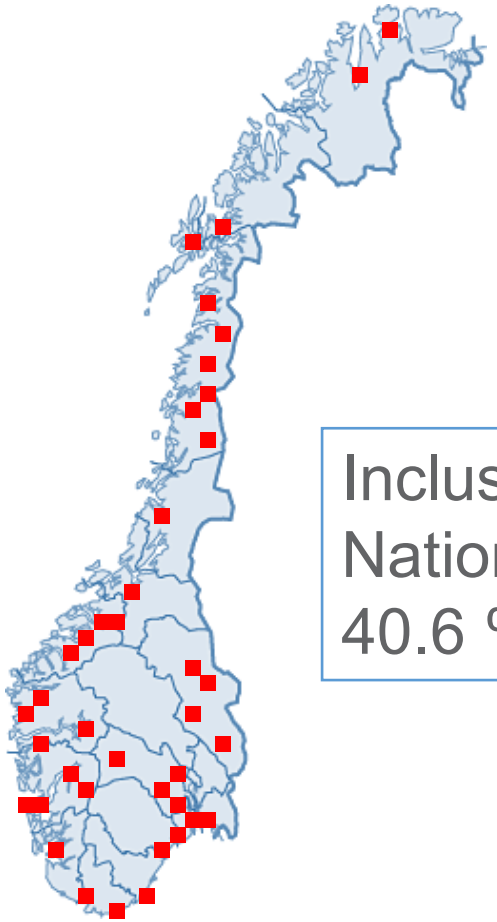
FHI | Den norske **mor, far og barn**-undersøkelsen

Outline

- Introduction to MoBa
- Iodine – why study iodine?
- Maternal iodine intake
  - Associations with child developmental outcomes
  - Associations with pregnancy outcomes and maternal health
- Potential explanation
- Discussion and implications

The Norwegian **Mother, Father and Child** Cohort Study



Overall aim:

To prevent childhood and adult diseases by understanding early environmental and genetic factors

Inclusion 1999-2008
Nationwide from 2005
40.6 % participation rate

n=95 200 n=75 200

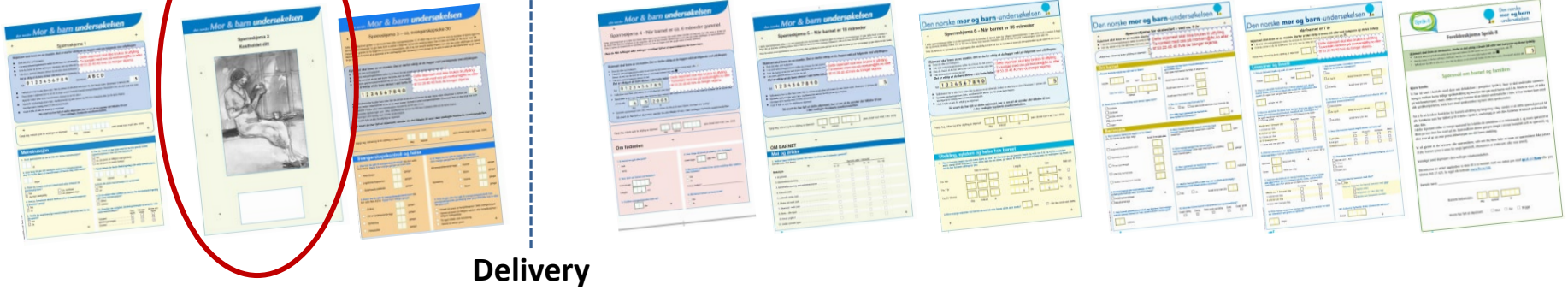
n=114 500

Data collection: questionnaires, biological material, sub-studies
Follow up: questionnaires, linkage to Health Registries




Prenatal period | Postnatal period | Childhood | Adolescence | Adulthood


gw 15-17 | gw 22 | gw 30 | Delivery | 6 mo | 18 mo | 3 y | 5 y | 7 y | 8 y | 13y | 14 y (web-questionnaires)



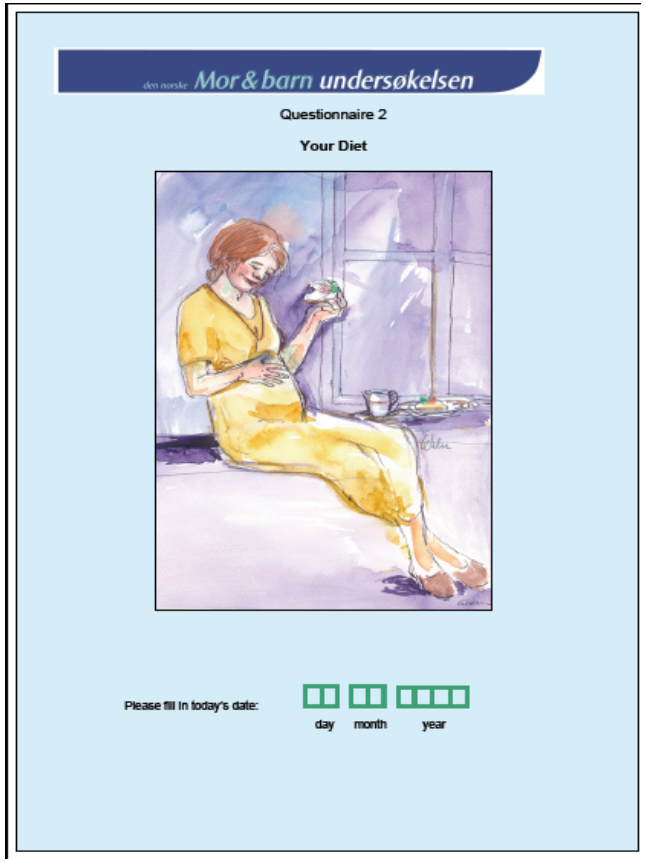
Linkage to health Registries:
- Birth Registry
- Patient Registry
- Prescription Registry
- Cancer Registry

3 quest. for mother and 1 for father

Assessment of maternal diet during pregnancy

Comprehensive semi-quantitative FFQ

- Asked about average intake over the first half of pregnancy
- Included 255 foods and dishes
- Use of dietary supplements
- Meal patterns
- Dietary preferences

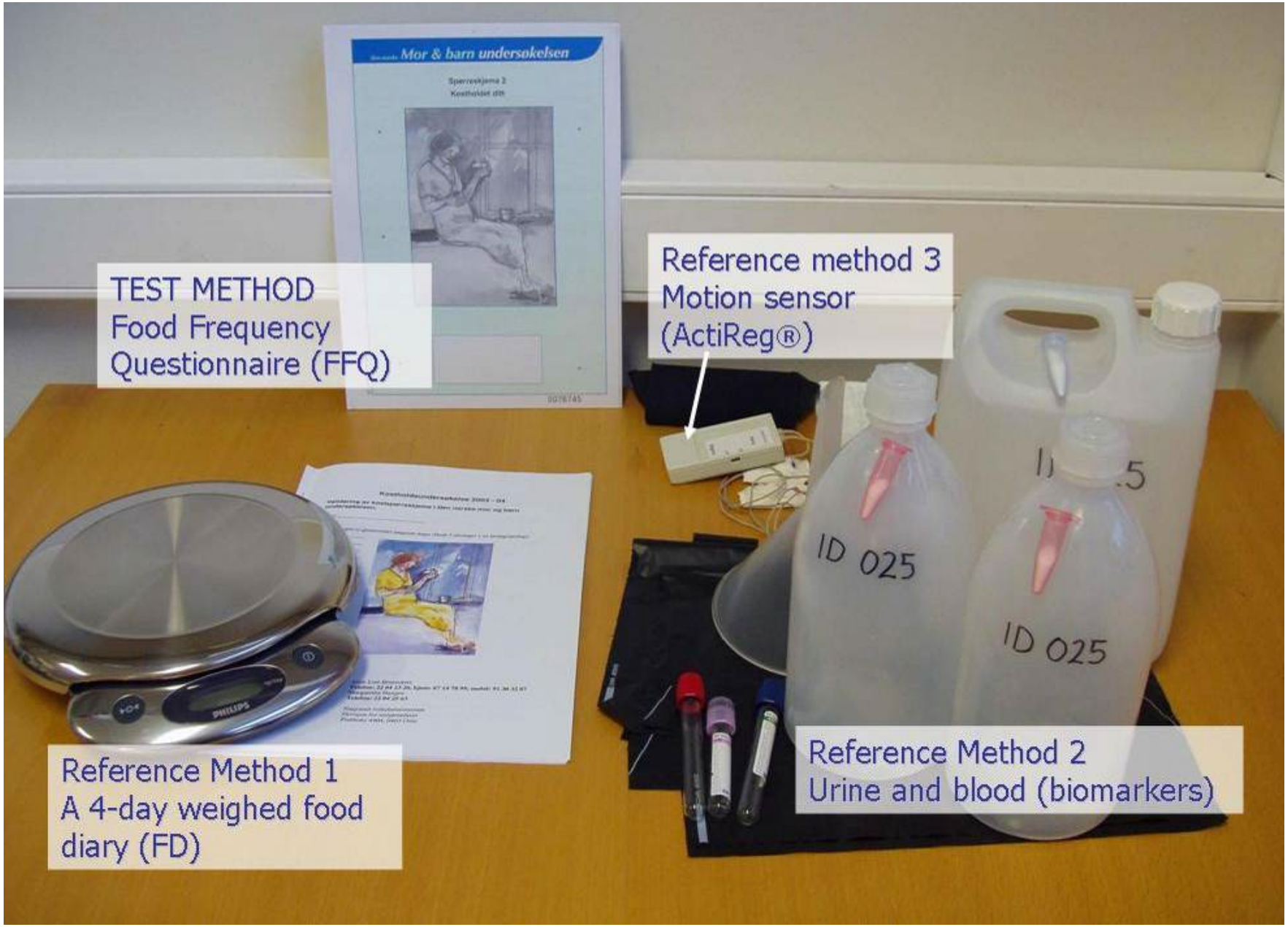


Meltzer et al. MCN; 2008: 4:14-27

Validation of the FFQ

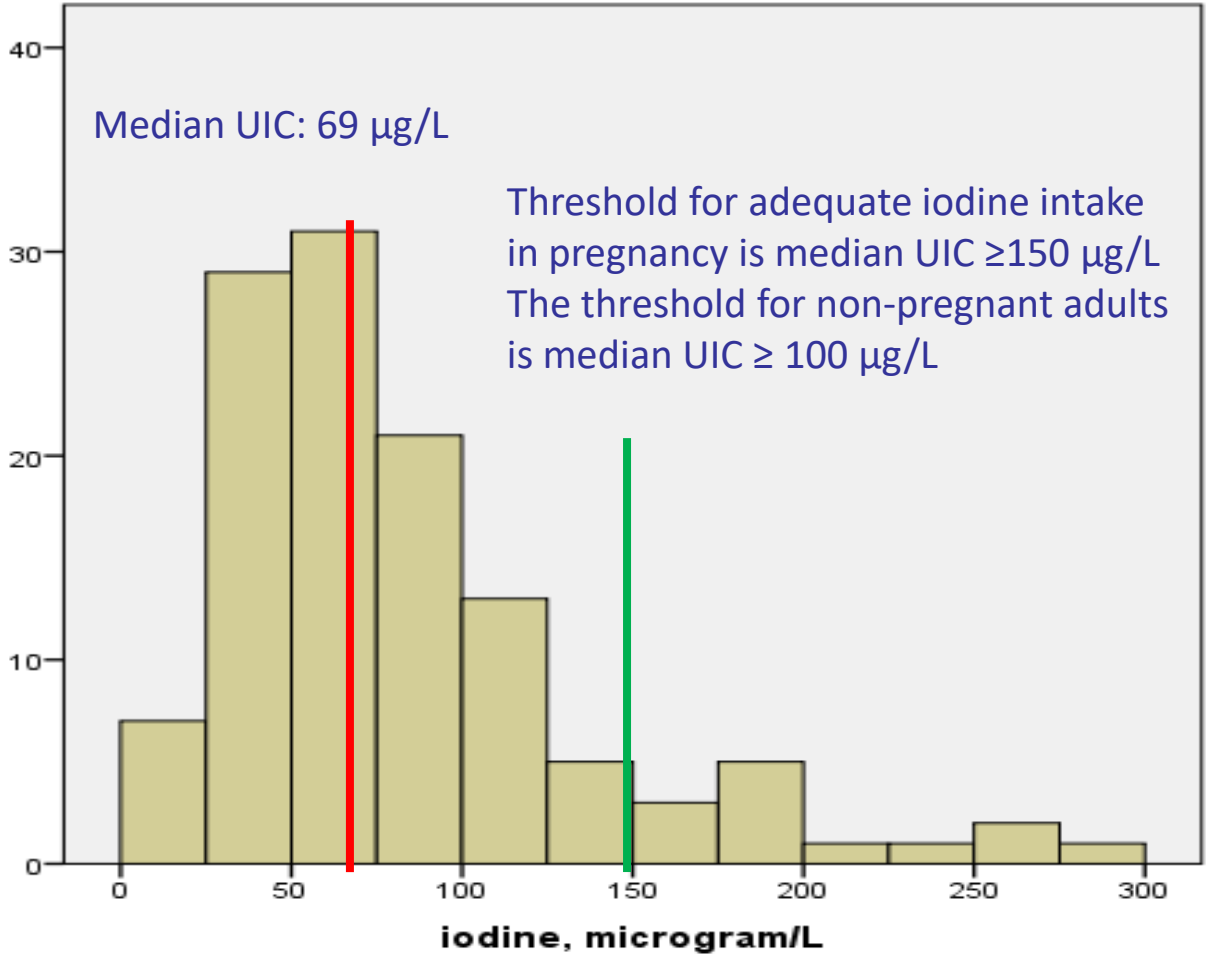
- Reference methods included biomarkers in blood and urine

- 24-hour urine collection



Brantsæter et al. 2007, 2008a, 2008b, 2010

Urinary iodine was measured for validation of milk intake – revealed low iodine intake



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Nutrients. 2013 Feb 6;5(2):424-40. doi: 10.3390/nu5020424.

Risk of suboptimal iodine intake in pregnant Norwegian women

Anne Lise Brantsæter [1], Marianne Hope Abel, Margaretha Haugen, Helle Margrete Meltzer

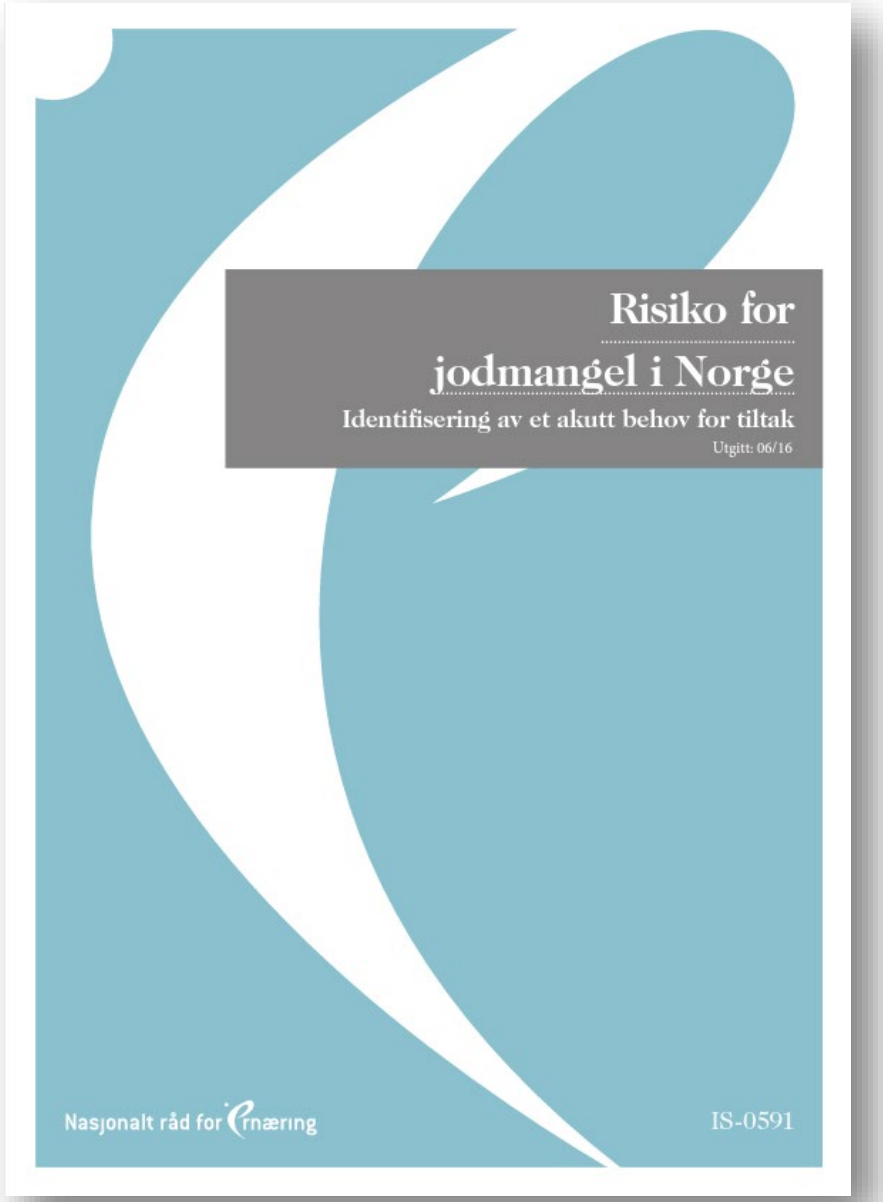
Affiliations + expand

PMID: 23389302 PMCID: PMC3635203 DOI: 10.3390/nu5020424

Free PMC article

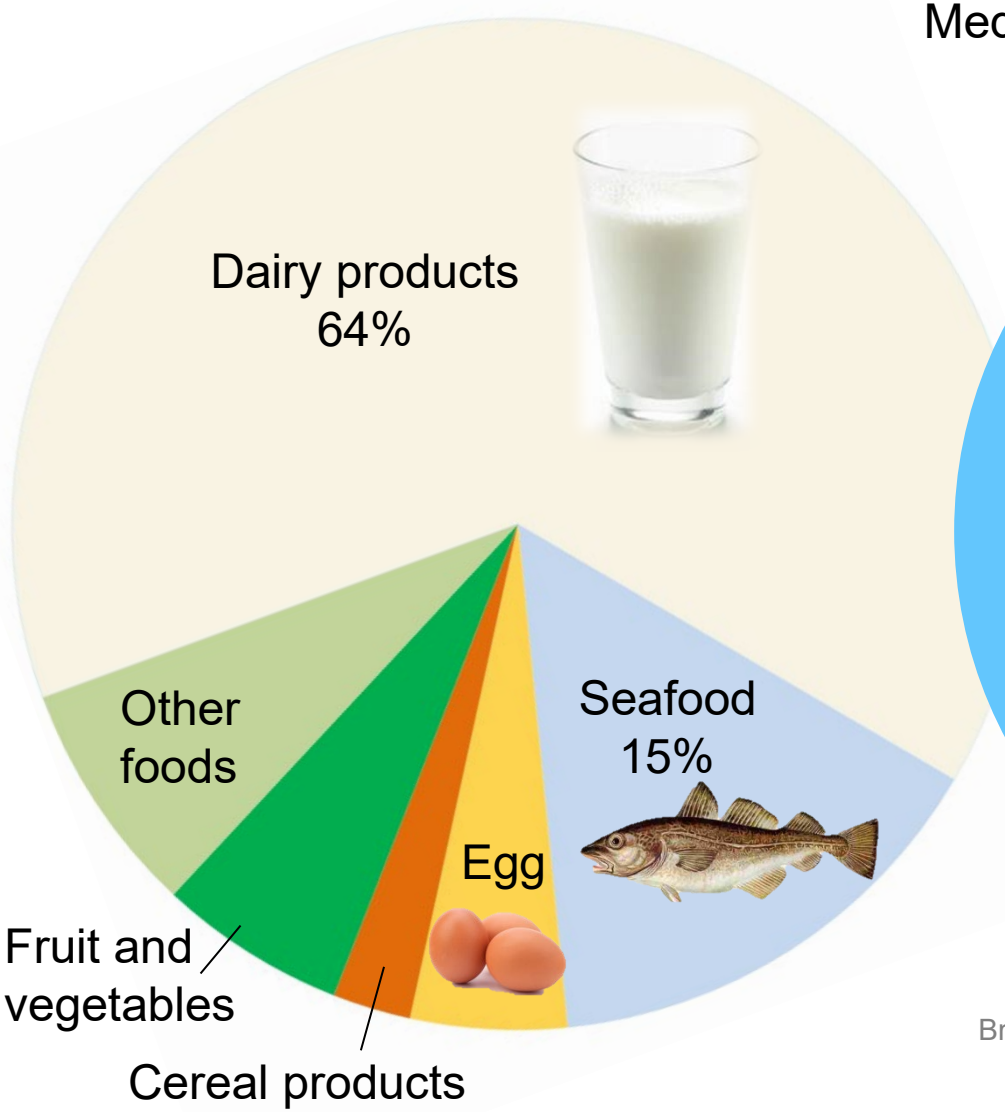
Abstract

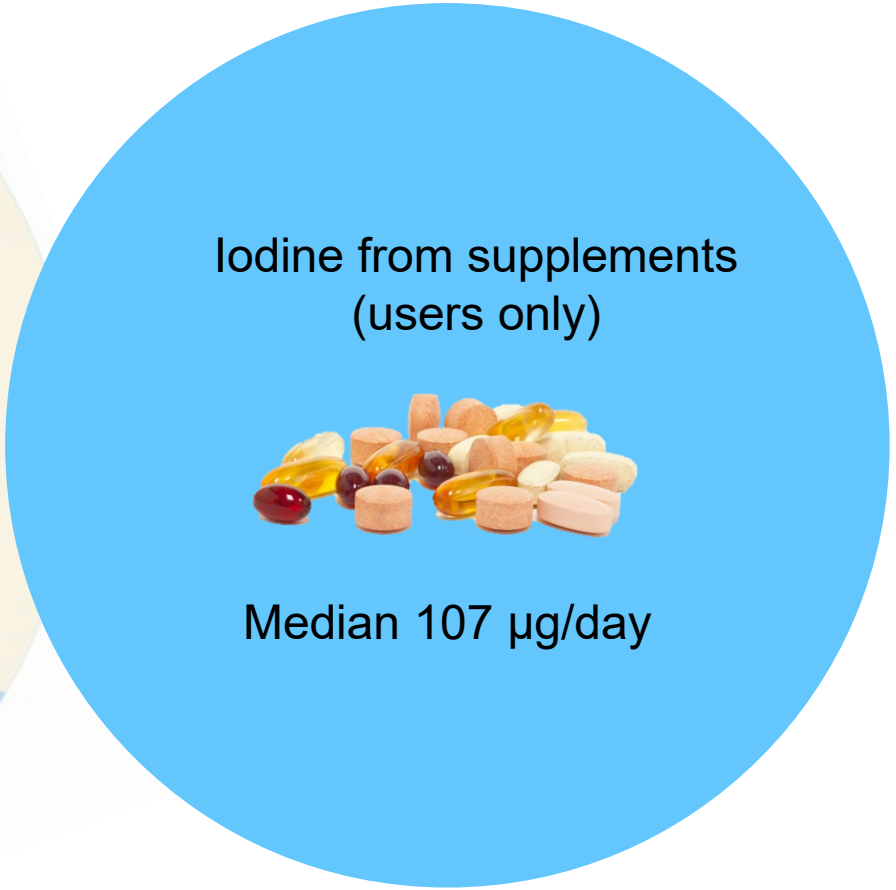
Pregnant women and infants are exceptionally vulnerable to iodine deficiency. The aims of the present study were to estimate iodine intake, to investigate sources of iodine, to identify predictors of low or suboptimal iodine intake (defined as intakes below 100 µg/day and 150 µg/day) in a large population of pregnant Norwegian women and to evaluate iodine status in a sub-population. Iodine intake was calculated based on a validated Food Frequency Questionnaire in the Norwegian Mother and Child Cohort. The median iodine intake was 141 µg/day from food and 166 µg/day from food and supplements. Use of iodine-containing supplements was reported by 31.6%. The main source of iodine from food was dairy products, contributing 67% and 43% in non-supplement and iodine-supplement users, respectively. Of 61,904 women, 16.1% had iodine intake below 100 µg/day, 42.0% had iodine intake below 150 µg/day and only 21.7% reached the WHO/UNICEF/ICCIDD recommendation of 250 µg/day. Dietary behaviors associated with increased risk of low and suboptimal iodine intake were: no use of iodine-containing supplements and low intake of milk/yogurt, seafood and eggs. The median urinary iodine concentration measured in 119 participants (69 µg/L) confirmed insufficient iodine intake. Public health strategies are needed to improve and secure the iodine status of pregnant women in Norway.



Iodine from food and supplements in MoBa pregnant women

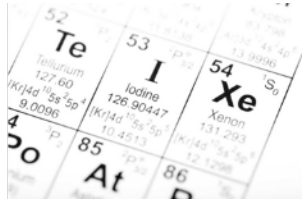
Median (total) 141 µg/day

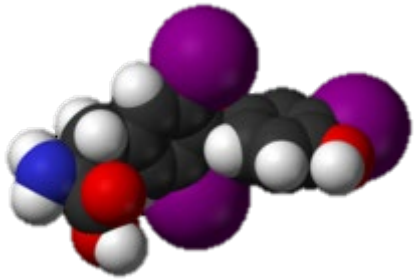




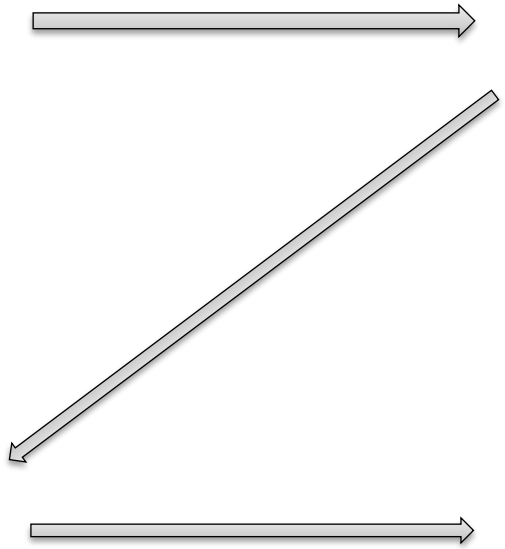
Brantsæter A.L. *et al.* Nutrients 2013;5(2):424-40

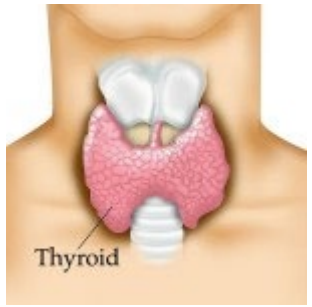
Iodine – an essential micronutrient



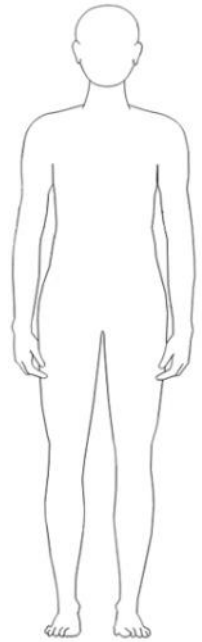


Thyroid hormones:
thyroxin (T4) and T3



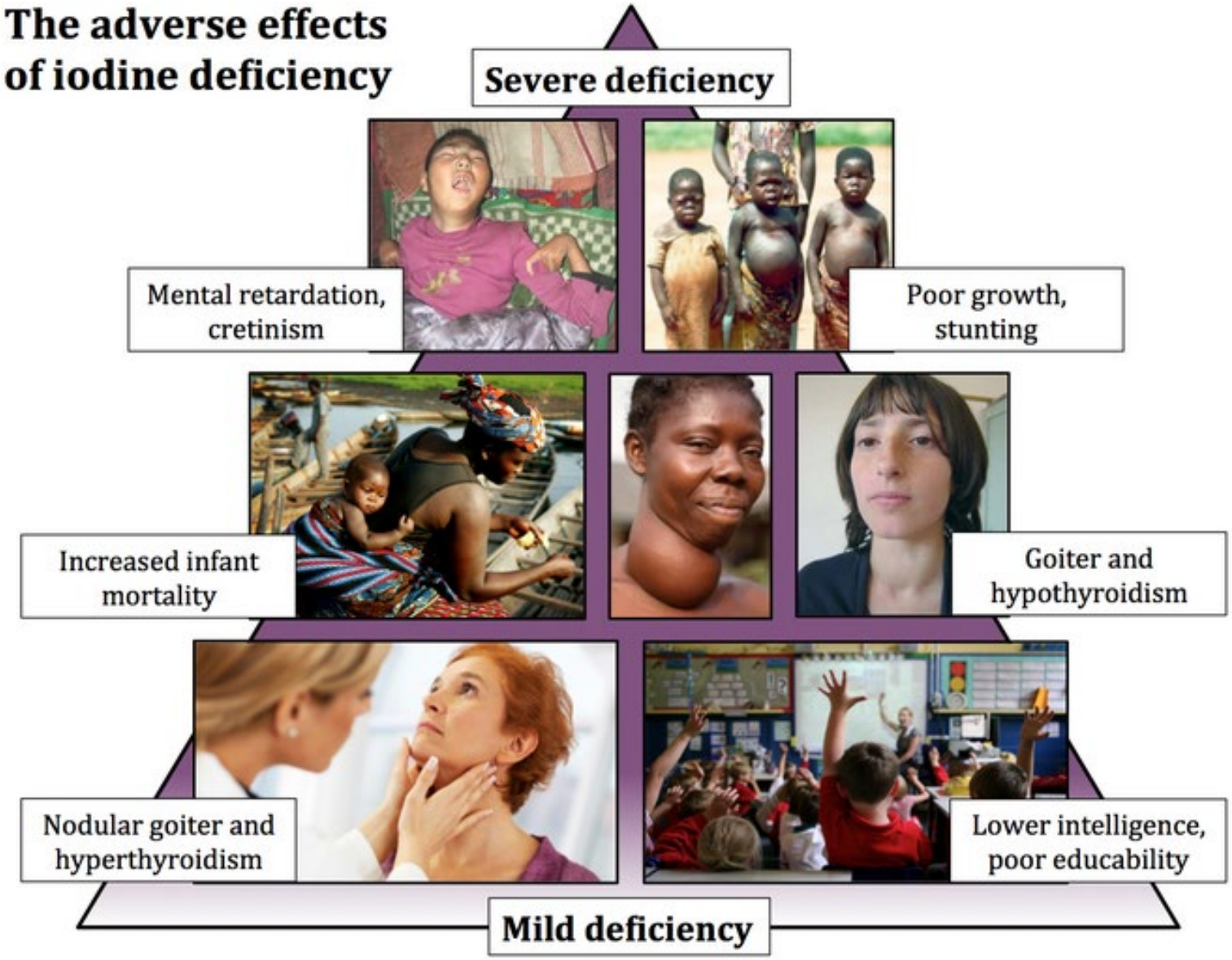


Thyroid:
0-20 mg iodine



Regulates

- Metabolism
- Brain growth and development
- Growth and development of other tissues

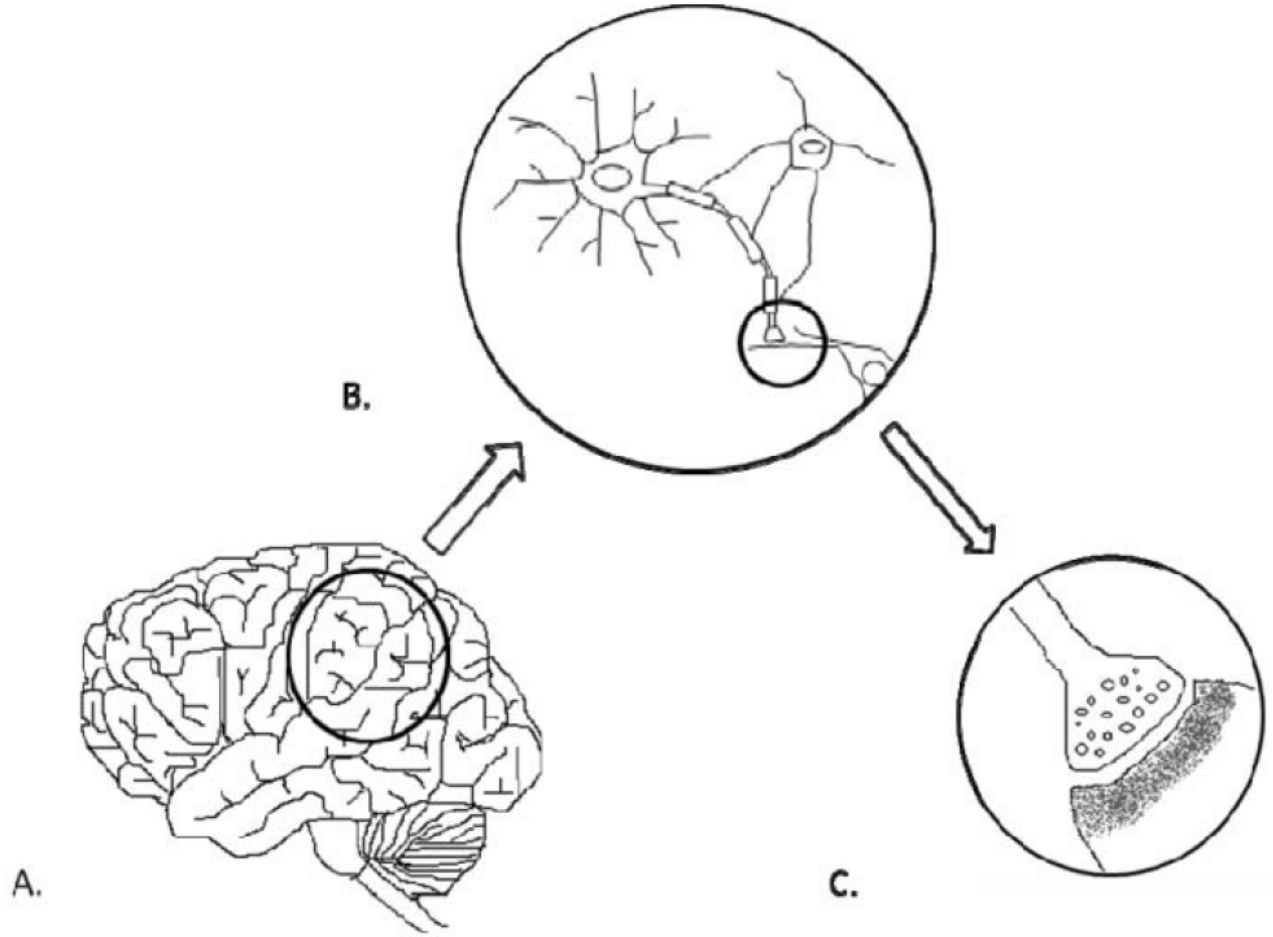


Source: Iodine Global Network idn.org

A. Macrostructure involves whole regions and structures of the brain such as the cerebral cortex, hippocampus, and cerebellum.

B. Microstructure makes up the larger components of macrostructure, and includes the cellular level, with structures such as myelin for neuronal axons.

C. The axons of nerves end in a synaptic terminal, from which neurotransmitters are released. Neurotransmitters allow the transfer of signals from cell to cell.



Redman *et al*. (2015). Iodine Deficiency and the Brain: Effects and Mechanisms. Critical Reviews in Food Science and Nutrition

Aims: To Investigate associations between maternal iodine intake and

Neurocognitive development in children

- Language, motor-development and behavioral problems at age 3 y
- ADHD diagnosis and ADHD symptoms at 8 y
- School performance and prevalence of special educational needs at 8 years
- Maternal thyroid function

Pregnancy outcomes and maternal mental health

- subfecundity, preeclampsia, birth weight and preterm birth
- symptoms of anxiety and depression in pregnancy and postpartum

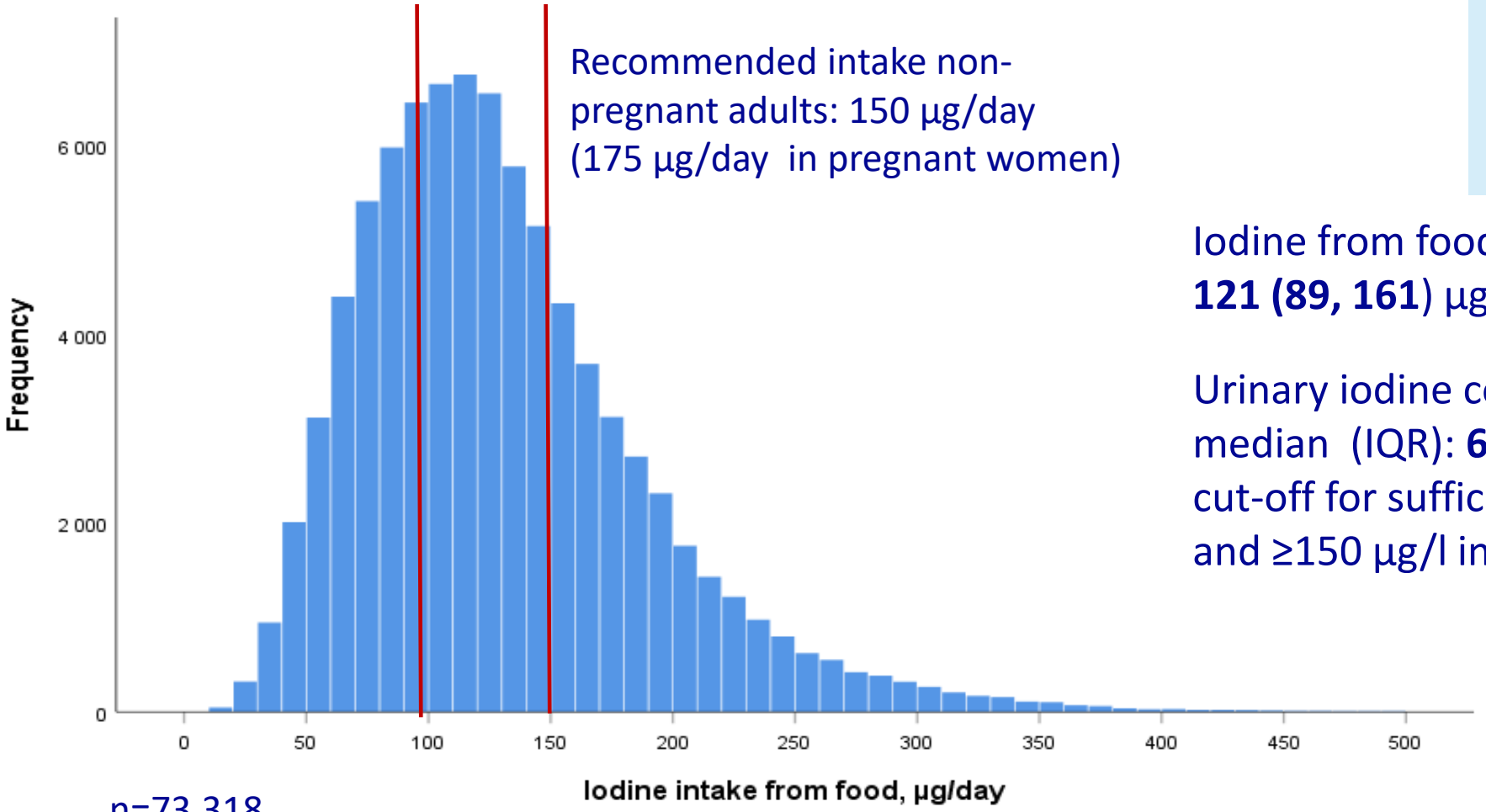




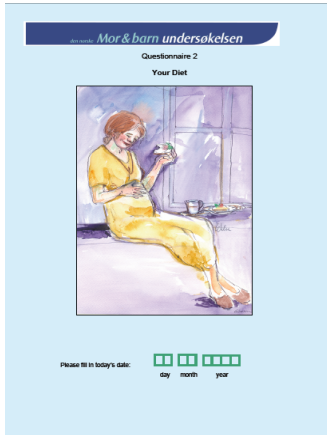
Maternal iodine intake from food

Estimated average requirement (IOM): 95 µg/day

Recommended intake non-pregnant adults: 150 µg/day
(175 µg/day in pregnant women)



n=73,318



Iodine from food, median (IQR):
121 (89, 161) µg/day

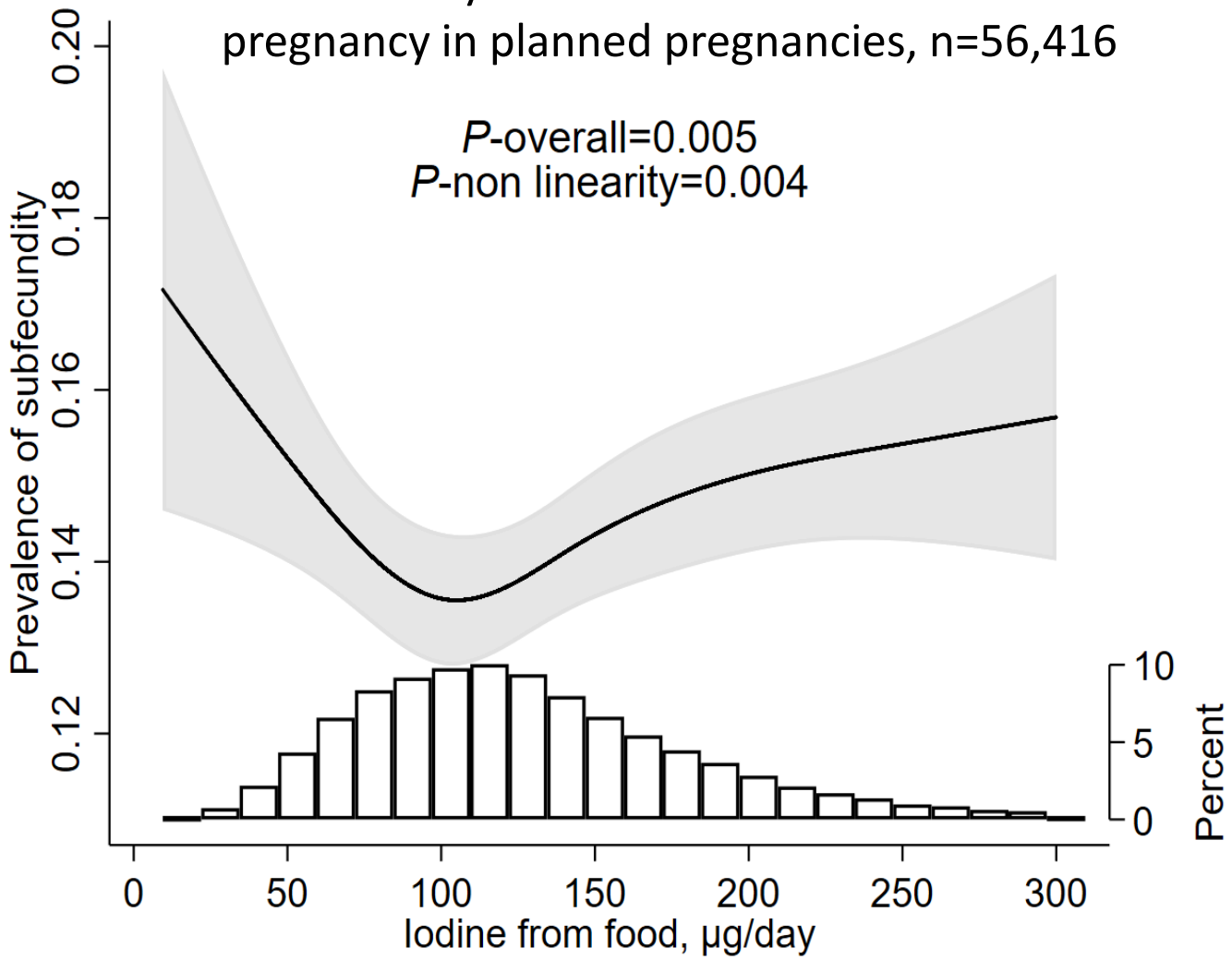
Urinary iodine concentration (UIC), median (IQR): **69 (35, 116) µg/L** (n=2910)
cut-off for sufficiency is ≥100 µg/L in adults and ≥150 µg/l in pregnancy

Low iodine intake associated with:

Pregnancy outcomes: *Reference: Abel et al. 2020*

- **Time to pregnancy (sub-fecundity)**
- Preeclampsia
- Preterm delivery
- Reduced foetal growth

Subfecundity defined as >12 months to achieve pregnancy in planned pregnancies, n=56,416



Low iodine intake associated with:

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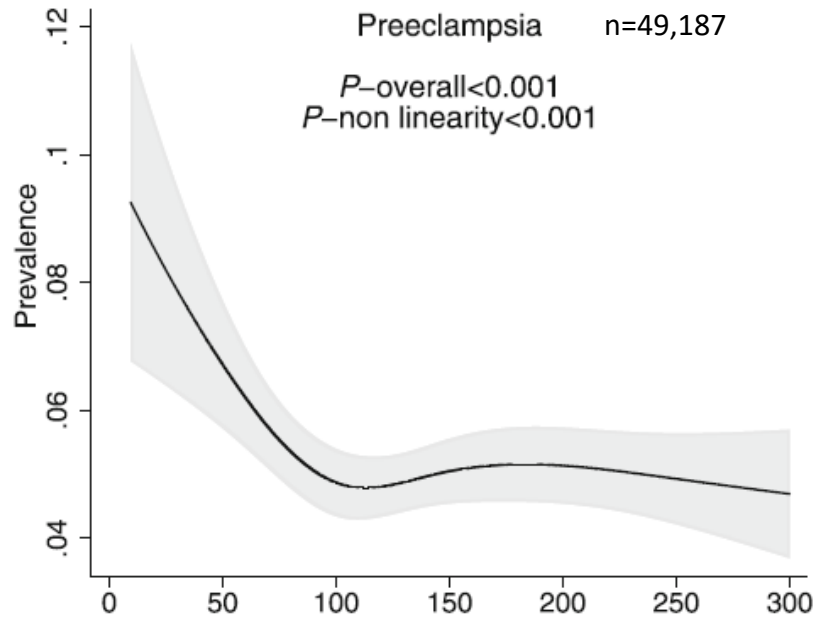

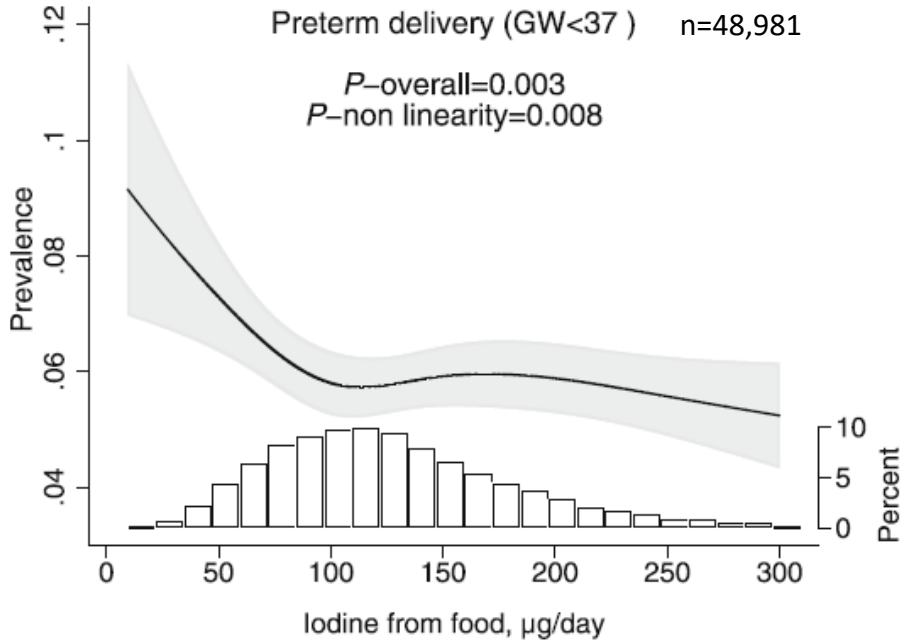

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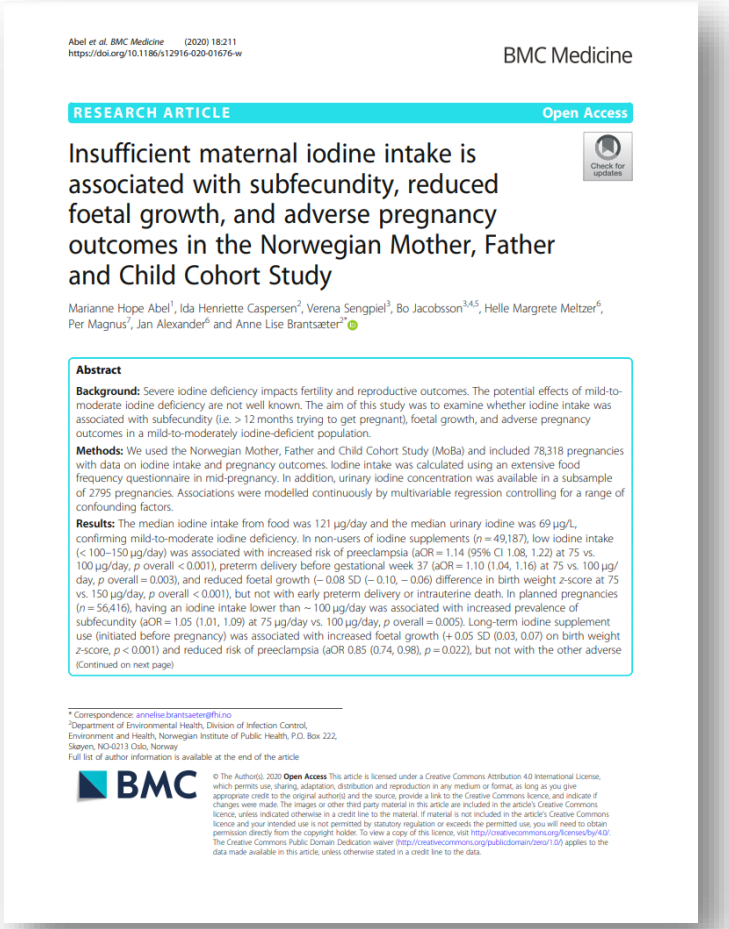

Abel et al. BMC Medicine (2020) 18:211
https://doi.org/10.1186/s12916-020-01676-w

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*]

Abstract

Background: Severe iodine deficiency impacts fertility and reproductive outcomes. The potential effects of mild-to-moderate iodine deficiency are not well known. The aim of this study was to examine whether iodine intake was associated with subfecundity (i.e. > 12 months trying to get pregnant), foetal growth, and adverse pregnancy outcomes in a mild-to-moderately iodine-deficient population.

Methods: We used the Norwegian Mother, Father and Child Cohort Study (MoBa) and included 78,318 pregnancies with data on iodine intake and pregnancy outcomes. Iodine intake was calculated using an extensive food frequency questionnaire in mid-pregnancy. In addition, urinary iodine concentration was available in a subsample of 2795 pregnancies. Associations were modelled continuously by multivariable regression controlling for a range of confounding factors.

Results: The median iodine intake from food was 121 μg/day and the median urinary iodine was 69 μg/L, confirming mild-to-moderate iodine deficiency. In non-users of iodine supplements ($n = 49,187$), low iodine intake (< 100–150 μg/day) was associated with increased risk of preeclampsia (aOR = 1.14 (95% CI 1.08, 1.22) at 75 vs. 100 μg/day, p overall < 0.001), preterm delivery before gestational week 37 (aOR = 1.10 (1.04, 1.16) at 75 vs. 100 μg/day, p overall = 0.003), and reduced foetal growth (− 0.08 SD (− 0.10, − 0.06) difference in birth weight z-score at 75 vs. 150 μg/day, p overall < 0.001), but not with early preterm delivery or intrauterine death. In planned pregnancies ($n = 56,416$), having an iodine intake lower than ~ 100 μg/day was associated with increased prevalence of subfecundity (aOR = 1.05 (1.01, 1.09) at 75 μg/day vs. 100 μg/day, p overall = 0.005). Long-term iodine supplement use (initiated before pregnancy) was associated with increased foetal growth (+ 0.05 SD (0.03, 0.07) on birth weight z-score, $p < 0.001$) and reduced risk of preeclampsia (aOR 0.85 (0.74, 0.98), $p = 0.022$), but not with the other adverse

(Continued on next page)

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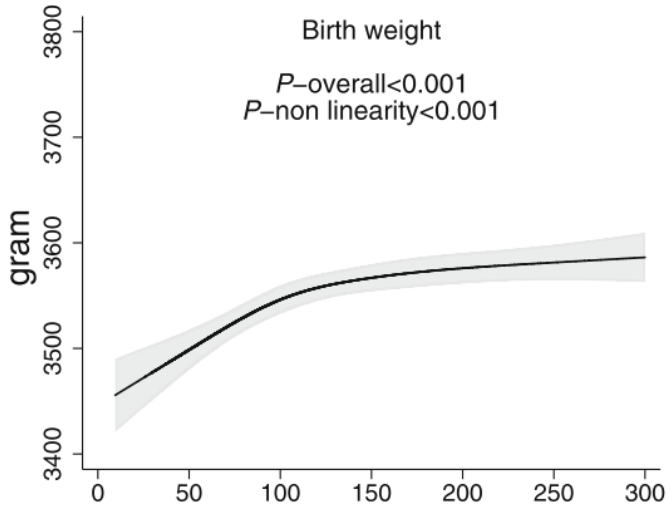
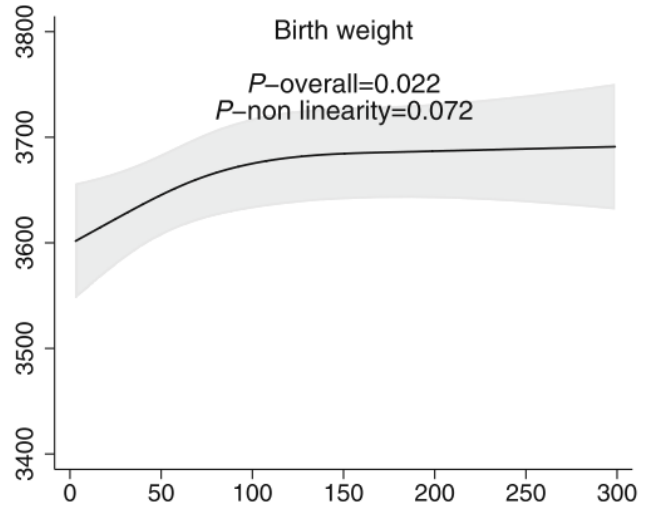
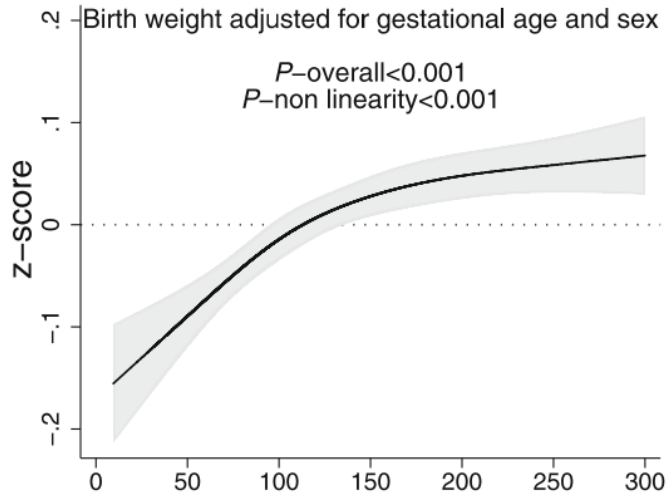
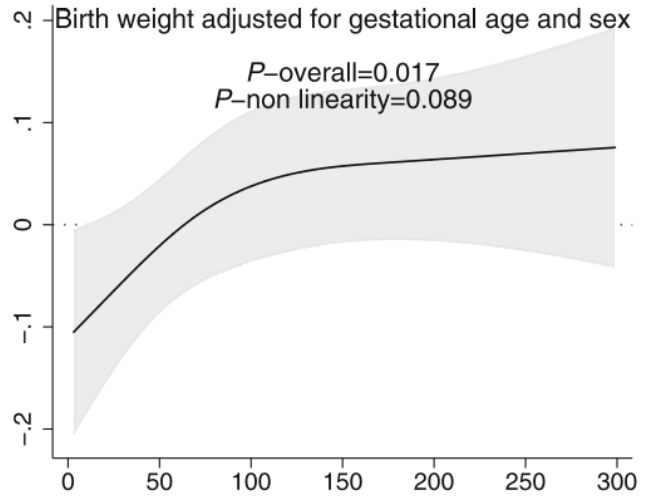






Iodine from food (µg/dag)



Urinary iodine (µg/L)

Low iodine intake associated with:

Pregnancy outcomes: *Reference: Abel et al. 2020*

- Time to pregnancy (sub-fecundity)
- Preeclampsia
- Preterm delivery
- Reduced foetal growth

Thyroid function in pregnancy: *Reference: Abel et al. 2018*

- fT4 og fT3

THYROID
Volume 28, Number 10, 2018
Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2018.0305

Iodine Intake is Associated with Thyroid Function in Mild to Moderately Iodine Deficient Pregnant Women

Marianne Hope Abel,[1,2,3] Tim I.M. Korevaar,[4,5] Iris Erlund,[6] Gro Dehli Villanger,[7] Ida Henriette Caspersen,[1] Petra Arohonka,[6] Jan Alexander,[1] Helle Margrete Meltzer,[1] and Anne Lise Brantsæter[1]

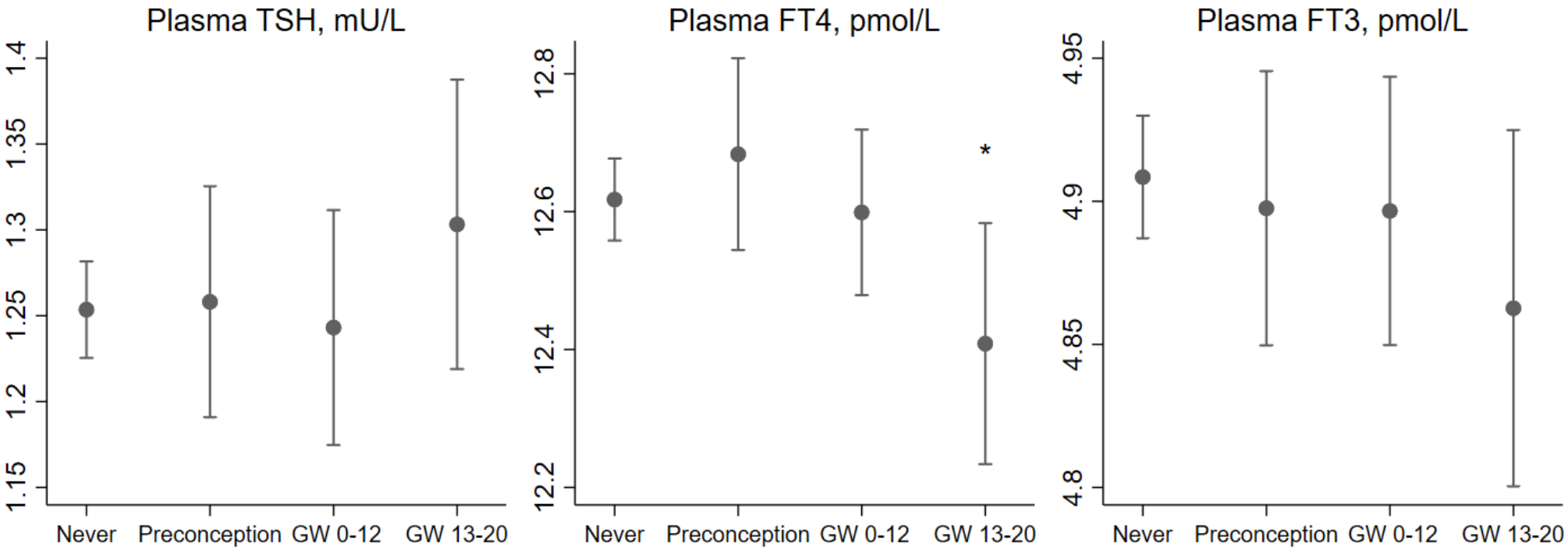
Background: Studies indicate that mild to moderate iodine deficiency in pregnancy may have a long-term negative impact on child neurodevelopment. These effects are likely mediated via changes in maternal thyroid function, since iodine is essential for the production of thyroid hormones. However, the impact of iodine availability on thyroid function during pregnancy and on thyroid function reference ranges are understudied. The aim of this study was to investigate the association between iodine intake and thyroid function during pregnancy.
Design: In a population-based pregnancy cohort including 2910 pregnant women participating in The Norwegian Mother and Child Cohort Study, we explored cross sectional associations of maternal iodine intake measured (1) by a food frequency questionnaire and (2) as iodine concentration in a spot urine sample, with plasma thyroid hormones and antibodies.
Results: Biological samples were collected in mean gestational week 18.5 (standard deviation 1.3) and diet was assessed in gestational week 22. Median iodine intake from food was 121 μg/day (interquartile range 90, 160), and 40% reported use of iodine-containing supplements in pregnancy. Median urinary iodine concentration (UIC) was 59 μg/L among those who did not use supplements and 98 μg/L in the women reporting current use at the time of sampling, indicating mild to moderate iodine deficiency in both groups. Iodine intake as measured by the food frequency questionnaire was not associated with the outcome measures, while UIC was inversely associated with FT3 ($p=0.002$) and FT4 ($p<0.001$). Introduction of an iodine-containing supplement after gestational week 12 was associated with indications of lower thyroid hormone production (lower FT4, $p=0.027$, and nonsignificantly lower FT3, $p=0.17$). The 2.5th and 97.5th percentiles of TSH, FT4, and FT3 were not significantly different by groups defined by calculated iodine intake or by UIC.
Conclusion: The results indicate that mild to moderate iodine deficiency affect thyroid function in pregnancy. However, the differences were small, suggesting that normal reference ranges can be determined based on data also from mildly iodine deficient populations, but this needs to be further studied. Introducing an iodine-containing supplement might temporarily inhibit thyroid hormone production and/or release.

Keywords: iodine, pregnancy, thyroid function, dietary supplements, The Norwegian Mother and Child Cohort Study, MoBa

Introduction

RESULTS FROM OBSERVATIONAL STUDIES, including the (ID) in pregnancy might negatively affect child neurodevelopment (1–4). Iodine is an essential micronutrient, as it is an integral part of the thyroid hormones thyroxine (T4) and

Iodine from supplement and thyroid function



TSH, FT4 and FT3 measured in n= 2900 MoBa participants.

Timing of introduction is crucial, recent initiation resulted in significantly lower FT4.

We hypothesise that supplementation result in temporary thyroid “stunning” as reported by Moleti et al. Clin Endocrinol 2011;74(6):762-8.

Abel et al. Thyroid 2018;28(10).

Assessment of child neurocognitive development and behaviour in MoBa children

MOTOR

- Milestones at 18 months, fine and gross motor skills at 3 years (ASQ)

LANGUAGE AND LEARNING SKILLS

- Ages and Stages Questionnaire at 18 months, 3 years and 5 years
- In-depth assessment with multiple instruments at 8 years

BEHAVIOUR

- Abbreviated Child Behavioural Check List (CBCL) in follow up questionnaires at 18 months, 3 years, 5 years, 8 years: externalising and internalising behaviour
- Linkage to patient registry (ICD-10 codes): ADHD, AUTISM
- Sub-studies (ADHD and ASD – clinical examination)

Low iodine intake associated with:

Pregnancy outcomes: *Reference: Abel et al. 2020*

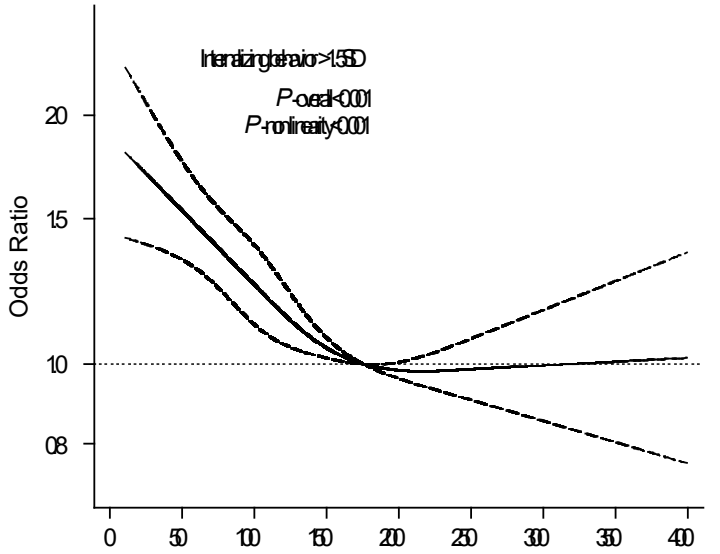
- Time to pregnancy (sub-fecundity)
- Preeclampsia
- Preterm delivery
- Reduced foetal growth

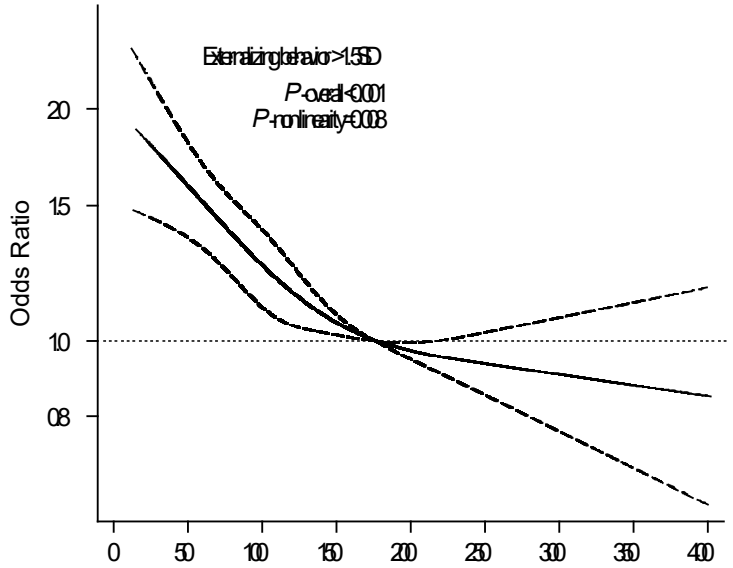
Thyroid function in pregnancy: *Reference: Abel et al. 2019*

- fT4 og fT3

Child neurodevelopment: *References: Abel et al. 2017, 2018, 2019*

- **Language development 3 y**
- **Fine motor development 3 y**
- **Externalizing and internalizing behaviour**, 3 and 8 y
- School achievement (reading and writing) 8 y
- Special education 8 y





Low iodine intake associated with:

Pregnancy outcomes: *Reference: Abel et al. 2020*

- Time to pregnancy (sub-fecundity)
- Preeclampsia
- Preterm delivery
- Reduced foetal growth

Thyroid function in pregnancy: *Reference: Abel et al. 2019*

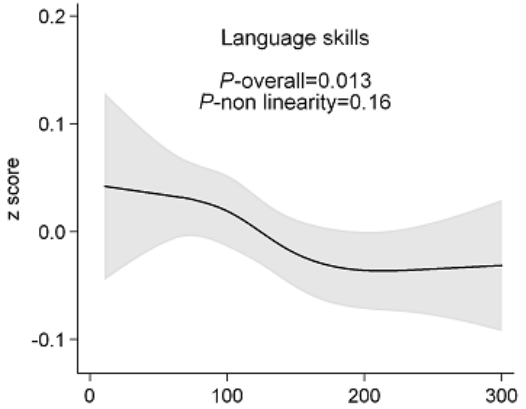
- fT4 og fT3

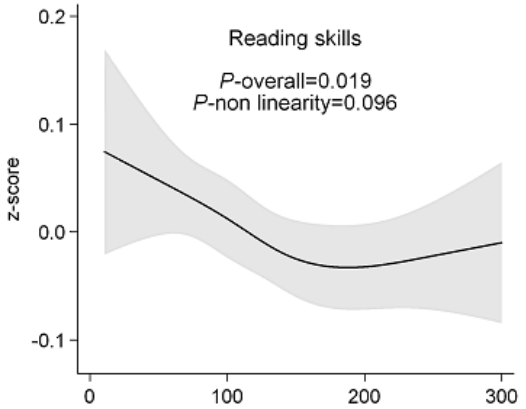
Child neurodevelopment: *References: Abel et al. 2017, 2018,2019*

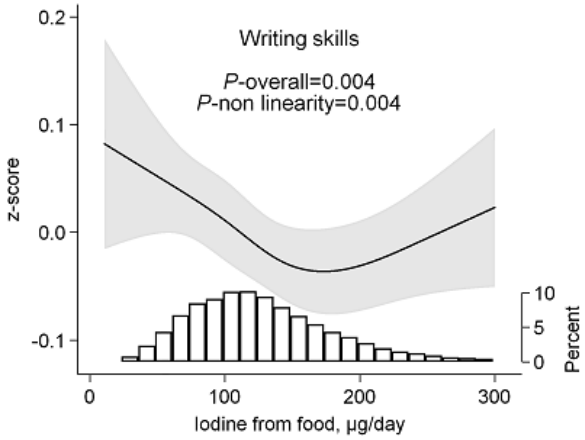
- Language development 3 y
- Fine motor development 3 y
- Externalizing and internalizing behaviour, 3 and 8 y
- **School achievement (reading and writing) 8 y**
- **Special education 8 y**

But **not** associated with:

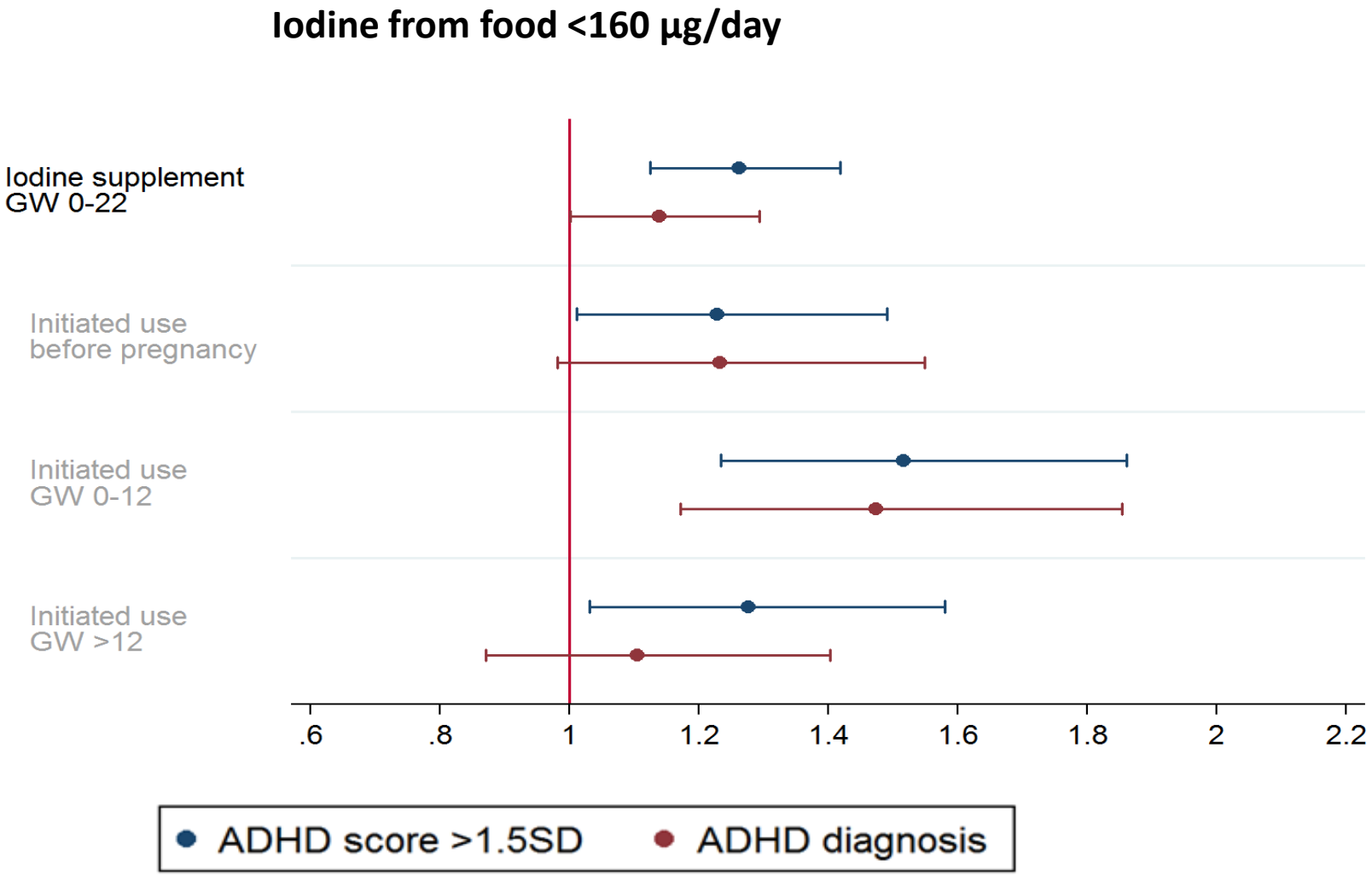
- Perinatal death
- Gross-motor development at age 18 mo
- ADHD diagnosis in the Norwegian patient registry up to 8 years







Maternal iodine supplement use and child ADHD at age 8 years



Reference groups (OR/HR=1) were non-users of iodine containing supplements.

Is iodine intake associated with maternal mental health?

Outcome variables

- Hopkins Symptom Checklist (HSCL-5) assessed in GW17 (Q1) and 6 months after delivery (Q4)
- Edinburgh Postnatal Depression Scale (EDPS) assessed 6 months after delivery

Both instruments are short versions of established scales and validated for use in observational studies.

Is iodine intake associated with maternal mental health?

Study sample

- N=77,927 had valid data on iodine from food and all covariates
- N=76,829 had answered HSCL-5 in GW17
  - 28,617 (37%) reported use of iodine-containing supplements
  - 48,212 reported no use of iodine-containing supplements
- N=43,154 had answered HSCL-5 and n=43,148 had answered EDPS six months after birth

Is iodine intake associated with maternal mental health?

Statistical model

- Iodine from food was modelled a continuous variable, iodine from supplements was modelled as a yes/no variable and the outcome was modelled dichotomously, 1=high symptom score (cut-off) vs 0
- All models were adjusted for pre-pregnant BMI, parity, education, age, smoking, total energy-intake, and dietary fibre (proxy for dietary quality)

Sensitivity analyses

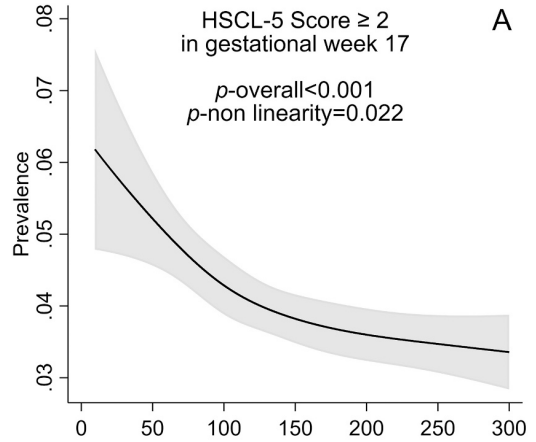
- Additional adjustment for maternal depression prior to pregnancy
- Adjusting the models for HSCL-5 after for HSCL-5 in GW17
- Restrict the sample to women with energy intake within the IQR
- Restrict the sample to women with iodine intake >50 µg/d (exclude those with the lowest intake)
- Restrict to supplement users and compare iodine-supplement users and non-iodine supplement user

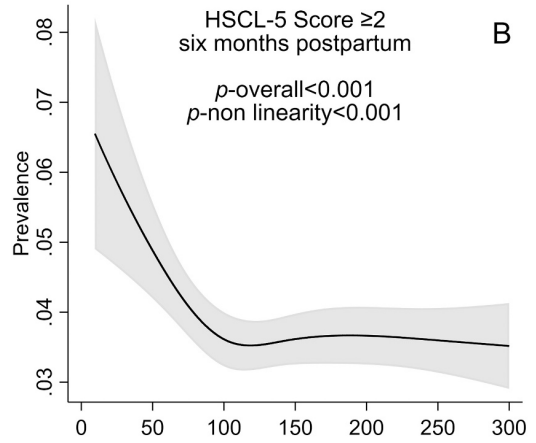
Results, iodine from food

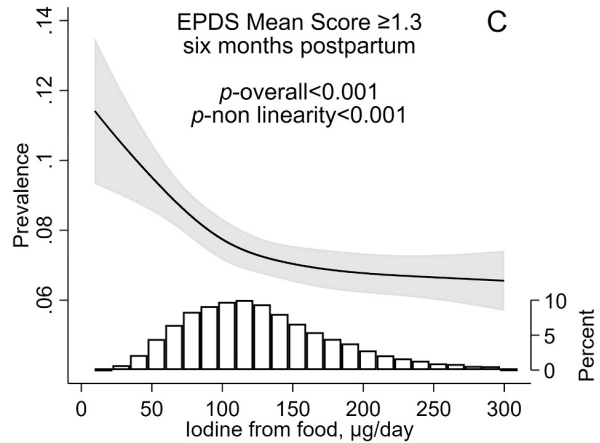
- Increasing prevalence of high symptoms of anxiety and depression (HSCL-5 ≥ 2) in GW 17 for decreasing iodine intake (Figure A)
- The same pattern seen for (HSCL-5) six months after delivery (Figure B)
- Increasing prevalence of high symptoms of postpartum depression (EDPS ≥ 1.3) for decreasing iodine intake (Figure C)

Figure A: cross-sectional association

Figures B and C: longitudinal associations







Results, iodine from supplements

Iodine supplement use and risk of scoring high on emotional distress and depression in gestational week 17

	n	Adjusted models [a]		Matched controls [a, b]	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
N (pregnancies)		76,829 (100%)		30,087 (100%)	
n with high score on HSCL-5 (score ≥2)		5,060 (6.6%)		1,980 (6.6%)	
Any iodine supplement use in GW 0–20	28,617	**1.19 (1.12, 1.27)**	<0.001	**1.17 (1.07, 1.28)**	0.001
Timing of iodine supplement initiation					
No supplement use (non-users[b])	48,212 (13,187)	1 (ref.)		1 (ref.)	
Before pregnancy [c]	7,380	**1.17 (1.05, 1.30)**	0.003	**1.14 (1.01, 1.28)**	0.040
GW 0–12	7,023	**1.20 (1.08, 1.32)**	<0.001	**1.17 (1.04, 1.31)**	0.010
GW >12	5,171	**1.17 (1.05, 1.31)**	0.006	**1.14 (1.00, 1.30)**	0.046

[a] Models were adjusted for maternal age, BMI, parity, education, smoking in pregnancy, fibre intake, chronic illness, and in vitro fertilization

[b] Restricting the reference group (non-users) to participants who reported use of one or more multivitamin/multimineral supplements in the food frequency questionnaire other than those routinely recommended in pregnancy care, but not any containing iodine

[c] One to 26 weeks before conception

Discussion

- It is confusing that iodine from food and iodine from supplements are oppositely associated with the outcome, but as for the child outcomes, this may have a biological explanation:
  - Iodine from food reflect long-term intake (including prepregnant intake), while iodine from supplements may block the thyroidal release of thyroid hormones adversely impact the outcome

- The main sources of iodine in the diet is milk/yoghurt
- Iodine is not associated with health awareness or diet quality
- This is the first study to examine iodine intake and perinatal anxiety and depression
- The study cannot establish causal inference

150 µg iodine

75 µg iodine

175 µg iodine

130,000 µg iodine

How to secure adequate iodine intake in women of fertile age?

Daily intake of 2 portions milk or yoghurt
Weekly intake of white saltwater fish
Iodized salt

Use of iodine containing supplements?

- Depend on dose, food intake and time of initiation,
- **Too late to initiate supplement use in pregnancy**

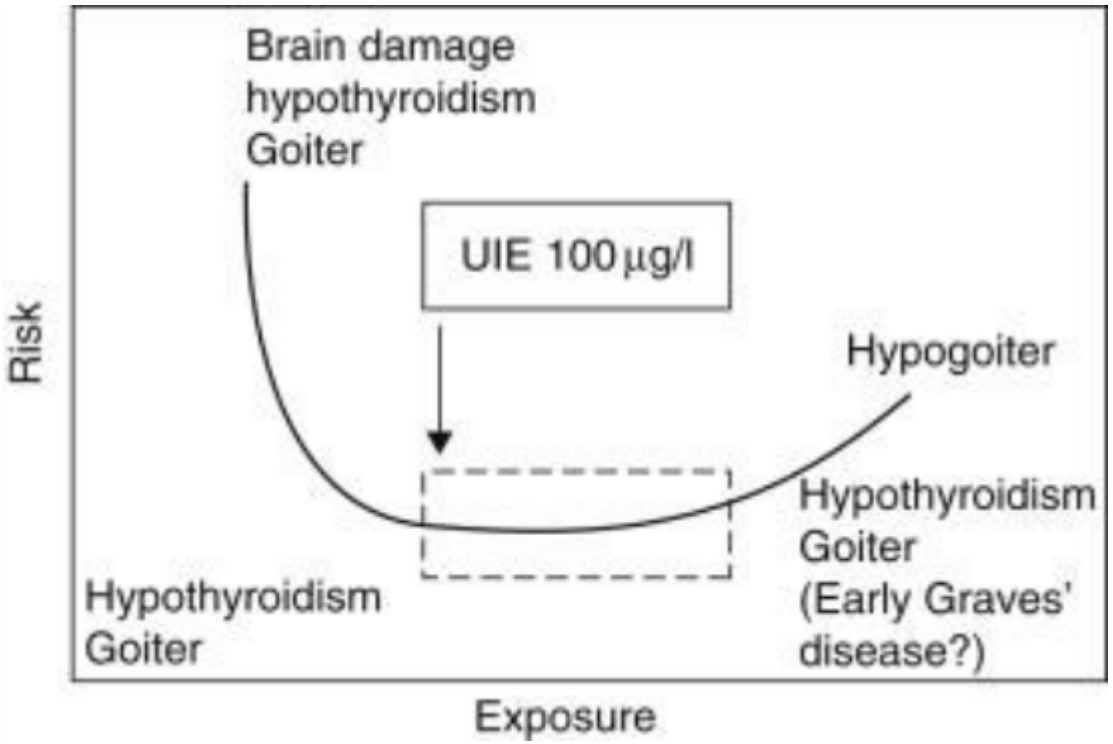
Need to secure adequate iodine intake before pregnancy, i.e., women of childbearing age

Low iodine intake is a particular concern in in vegetarians, vegans, and all with low intake of milk.

Iodine status in women of reproductive age in Sweden?

- Non-pregnant women of reproductive age:
  - mUIC **65 µg/L** in 89 women recruited 2013-2016 *(Manusou et al. Eur J Nutr. 2021)*
- Pregnant women
  - mUIC **112 µg/L** in 531 women a birth cohort in Northern Sweden recruited 2015-2018 *(Gustin et al. J.Nutr 2022)*
  - mUIC **110 µg/L** at baseline in 200 women participating in an RCT in Southwestern Sweden *(Manusou et al. Eur J Nutr. 2021)*
- Lactating women
  - 58% of mother had BMIC<100 µg/L, mUIC at 4 mo: 85 µg/L *(Manousou et al. AOGS 2021)*

What about too much iodine?



Source: Laurberg et al. 2009

TANGSANKER: Hvalforsker Tiu Similä fra Helsinki har de siste par årene blitt helt hekta på tang, nå holder hun matkurs og sankekurs. – Det er bare å gå ut å plukke, det er helt gratis og tang er god og sunn mat, sier hun. (Foto: Marianne Lovise Strand)

Hekta på tang

/ 2018-10-02 08:00:44

Hun har passion for makroalger og ønsker at flest mulig skal få øynene opp for alt det gode man kan bruke dem til. Tiu Similä arrangerer tangsafari, matkurs og har etablert en liten restaurant i Bø i Vesterålen.

What about too much iodine?

07/08/2018

FOOD AND NUTRITION

Seaweed consumption: remain vigilant to the risk of excess iodine intake

Over the last few years, seaweed has become increasingly common on our plates. Fresh, dried or as a food supplement, its iodine content varies and can sometimes be high. ANSES assessed the risk of excess iodine intake from the consumption of seaweed-based products. In view of the non-negligible risk of exceeding the upper limit of safe intake for iodine, the Agency advises against the consumption of seaweed and seaweed-







Thank you!

For more information about the

The Norwegian **Mother, Father and Child** Cohort Study

https://www.fhi.no/en/studies/moba/

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Norwegian Institute of Public Health

moba