Women were recruited to the Norwegian Mother and Child Cohort Study (MoBa) in their first trimester and completed three questionnaires during their pregnancy. One was an extensive food frequency questionnaire asking about their habitual diet (1). The mothers also donated blood and urine samples in gestational week 18. Their children’s development has been continuously followed since birth through regular questionnaires and linkage to national registers (e.g., the Norwegian Patient Registry for clinical diagnoses and the Norwegian Prescription Database for dispensed drugs). The cohort includes 114,000 mother-child pairs. Up until now, there have been six publications from MoBa focusing on iodine (2–7), and two more are in preparation.

MoBa: studying the impact of mild iodine deficiency on development

The low iodine intake in Norwegian pregnant women came as a surprise to the researchers. Although Norway has had a long history of endemic goiter due to iodine deficiency, fortification of cow fodder in the 1950s boosted the iodine content in Norwegian milk and the goiter disappeared. However, changes in the diet, including a large decrease in milk consumption, can explain why iodine deficiency has now re-emerged. Although milk intake has decreased since the 1990s, milk is still the main source of maternal iodine intake together with supplement use (2,3). Neither salt nor drinking water are important sources of iodine in the Norwegian diet.

In MoBa, we calculated that the median iodine intake from food in the pregnant women was less than a half of the WHO recommended daily intake of ≥150 µg/L (Figure 1) (9). The urinary iodine concentration (UIC) was measured in a subsample of the MoBa women (n=3,000), and the result confirmed an insufficient intake (median UIC: 68 µg/L; mean UIC: 88 µg/L, SD: 80). About one-third of the MoBa women reported using iodine-containing supplements, and their median UIC was higher than in the women not using any supplements (98 µg/L vs. 59 µg/L).

Thousands of mother-child pairs participate in the Norwegian Mother and Child Cohort Study (MoBa).
The extensive data collection in MoBa makes it possible to examine associations between maternal iodine intake and a range of maternal and child outcomes. The published papers to date include:

- A validation study of iodine intake measured by the FFQ (2);
- Determinants of suboptimal iodine intake in MoBa (3);
- Maternal iodine intake and thyroid function in pregnancy (6);
- Associations between iodine intake and measures of child neurodevelopment:
  - Child language, motor skills, and behaviour at age 3 years (4);
  - Child risk of attention deficit/hyperactivity disorder (ADHD) (5);
  - Child language and learning at age 8 years (7).

In addition, two papers are in preparation, one on pregnancy- and birth outcomes and the other on child risk of autism.

**Iodine intake of <150 µg/day in pregnancy is associated with poorer child development**

Findings thus far indicate that maternal habitual iodine intake of less than about 150 µg/day is associated with changes in maternal thyroid hormone levels in pregnancy (free T4 and free T3) (6) and suboptimal child neurocognitive development at ages 3 and 8 years. Children of iodine deficient mothers had an increased risk of language delay (4,7), poorer fine motor skills (4), more behavior problems (4,7), poorer school performance in reading and writing (7), and an increased likelihood of receiving special educational services in school (7). We found no significant associations with child gross motor skills (4) or with an ADHD diagnosis in the patient registry (5). The latter might be explained by the low prevalence of ADHD diagnosis in MoBa children at the time of data collection (2%). Overall, effect sizes were small. This may indicate that mild-to-moderate iodine deficiency has only minor consequences for child neurodevelopment, but it is also likely that measurement errors of the exposure and outcomes weaken these associations.

**Iodine supplement use in pregnancy may not be beneficial**

Short-term use of iodine-containing supplements may have a different impact on maternal thyroid function and child neurodevelopment than habitual long-term iodine intake. Thus, we explored iodine supplement use as a separate exposure. Additionally, we examined whether the time of initiation of the supplement (i.e., before pregnancy, in the first trimester, or later in pregnancy) was of importance.

Interestingly, there was no indication of beneficial effects of iodine supplement use in pregnancy. In fact, we found that initiating use in the first trimester was associated with more child behaviour problems (4) and ADHD symptoms, and an increased risk of an ADHD diagnosis (5). We also found that pregnant women who had initiated supplement use within the past 5 weeks had lower thyroid function (significantly lower FT4 and non-significantly lower FT3), which might indicate that an abrupt increase in iodine intake in pregnant women with mild-to-moderate ID might transiently inhibit thyroid function (6). The foetus is most vulnerable to changes in maternal thyroid hormone levels in the first trimester, and thus this transient inhibition might explain the negative impact on the behaviour outcomes. Importantly, these results need to be confirmed in sufficiently powered randomized controlled trials. It is, however, fair to conclude that knowledge to date suggests that it is important to prevent ID before conception to secure optimal fetal brain development.
However, maternal iodine intake did not differ by maternal age, marital status, or income, and varied only to a very small extent (up to ±8 µg/day) by BMI, parity, education, and smoking (3).

When testing multiple associations, some associations may turn out to be significant simply due to chance. However, the associations between maternal habitual iodine intake and child neurodevelopmental outcomes were very consistent. When studying the associations between maternal iodine supplement use and the same outcome measures, the only significant associations were with behavioural outcomes. Thus, we cannot rule out that this may represent a chance finding.

The measures of habitual iodine intake of the mothers and of child neurocognitive development are inherently inaccurate. However, a validation study demonstrated that the MoBa FFQ provides a realistic estimate of iodine intake and is valid for ranking women from low to high intake (2,6).

Strengths and limitations
Strengths of the MoBa study include its large sample size, extensive data collection, and the population-based prospective design. In addition, the fact that data on iodine intake is available at the individual level, that ID is highly prevalent in the MoBa mothers, and that iodine intake varied a lot between the mothers make MoBa a unique opportunity to explore the impact of ID in pregnancy. There is limited data on iodine status of the MoBa children, but based on data from other Norwegian studies, their iodine intake is likely to be adequate (7). Thus, ID is most likely to occur primarily in pregnancy and during breastfeeding.

An important limitation is that MoBa is an observational study, and consequently, we cannot know if the associations we study represent causal relationships. Residual confounding by other factors associated with maternal iodine intake may still exist. However, maternal iodine intake did not differ by maternal age, marital status, or income, and varied only to a very small extent (up to ±8 µg/day) by BMI, parity, education, and smoking (3).

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Conclusions
Overall, studies from MoBa support the growing body of evidence from observational studies and animal studies that maternal mild-to-moderate ID adversely affects child neurocognitive development. The results from MoBa add to the growing body of evidence that timing prevention of maternal mild-to-moderate iodine deficiency is essential to ensure that children reach their full developmental potential.

Key implications
- Habitual iodine intake of below the recommended 150 µg/day in women of childbearing age should be prevented to ensure optimal foetal brain development.
- Initiating iodine supplement use in pregnancy to correct mild-to-moderate ID may be too late to have beneficial effects on child development. Whether supplement use can be harmful remains to be further explored in studies with a randomized controlled design.
- It is probably important to differentiate between maternal habitual iodine intake from food and short-term/recent iodine intake from supplements when studying associations with maternal and child outcomes.
- Results from observational studies indicate that the effects of mild-to-moderate ID and iodine supplement use on child development are small, thus randomized controlled trials need to be large and sufficiently powered to detect potential effects.
- When studying mild-to-moderate ID, it is important that the women are truly iodine deficient, and based on the result from MoBa, the median UIC should ideally be <100 µg/L.

References: