Maternal and infant iodine nutrition and thyroid function

A cohort study of pregnant and postpartum women and their infants in Norway

Synnøve Næss

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Scientific environment

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Abstract

Background: Iodine is a micronutrient essential for the production of the thyroid hormones. The thyroid hormones are particularly important for neurodevelopment of the foetus during pregnancy and for the developing child in the first years of life. Whereas the adverse effects of severe iodine deficiency are well documented, the consequences of mild-to-moderate iodine deficiency during pregnancy and infancy are still uncertain and data are limited.

Objectives: The main objective of this thesis was to describe iodine nutrition and thyroid function and to explore associations between them in a cohort study of pregnant and postpartum women and their infants. The specific objectives were to:

I) Assess the validity and reproducibility of an iodine-specific food frequency questionnaire (I-FFQ) developed for pregnant women.

II) Explore whether iodine nutrition and timing of iodine supplement initiation were associated with altered thyroid function in mildly-to-moderately iodine-deficient pregnant and postpartum women.

III) Describe infant iodine status and thyroid function and further explore associations between them in the first year of life. In addition, assess the impact of maternal iodine nutrition and breastfeeding status on infant iodine status.

Methods: A total of 137 pregnant women were enrolled and followed-up at gestational weeks (GW) 18 and 36, and further with their infants at 3, 6 and 11 months postpartum. Dietary iodine intake from an I-FFQ and a six-day food diary, urinary iodine and creatinine concentrations (UIC and UIC:Cr), breast milk iodine concentration (BMIC) and thyroid function tests (thyroid-stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4)) were measured.

Results: Maternal iodine intake estimated from the I-FFQ showed acceptable correlation and agreement with iodine intake estimated from the six-day food diary and UIC, indicating that the I-FFQ can be used as a tool to estimate and rank iodine intake in this population.

The median maternal UIC was below 100 µg/L during pregnancy (GW18: 94 µg/L; GW 36: 85 µg/L) and in the postpartum period (3 months: 74 µg/L; 6 months: 84 µg/L), indicating mild-to-moderate iodine deficiency of the mothers. The median infant UIC was 82 µg/L at age 3 months, thus, below the recommended WHO cut-off (100 µg/L), also indicating insufficient iodine status. Median infant UIC increased during the first year of life and was 110 µg/L at ages 6 and 11 months, indicating adequate iodine status at these ages.

Infant UIC was associated with maternal iodine intake, UIC:Cr and BMIC. At ages 3 and 6 months, breastfed infants had a lower median UIC (76 and 105 µg/L, respectively) compared with formula-fed infants (190 and 315 µg/L, respectively). At age 11 months, no differences between breastfeeding categories were found.

The prevalence of maternal and infant thyroid dysfunction in this study population was low. Lower maternal iodine availability (measured by iodine intake and UIC:Cr) was associated with higher fT3 and fT4 concentrations, and lower TSH concentrations (intake only). Compared with no use of supplements, those initiating an iodine-containing supplement before conception and continuing through pregnancy had lower TSH, and higher fT3 and fT4 concentrations. No associations were found between infant UIC nor BMIC with infant thyroid function (TSH, fT3, fT4).

Conclusion: Pregnant and postpartum women and breastfed infants in their first months of life are at risk of iodine deficiency in Norway. No associations were found between infant iodine status and thyroid function. Maternal iodine nutrition was, however, associated with altered thyroid function tests, and initiation of iodine supplementation before conception and continuing through pregnancy was associated with possible improved thyroid function. Overall, to ensure normal thyroid function in the developing foetus and growing infant, maternal iodine nutrition should be optimised before conception and continued throughout pregnancy and the postpartum period. Awareness of promoting adequate iodine nutrition for these vulnerable population groups should be prioritised to secure sufficient iodine intake for mothers and, subsequently, their infants.

List of Publications

Paper I

Næss S, Aakre I, Kjellevold M, Dahl L, Nerhus I, Midtbø LK, Markhus MW. *Validation and reproducibility of a new iodine specific food frequency questionnaire for assessing iodine intake in Norwegian pregnant women.* Nutrition Journal. 2019;18(1):62.

Paper II

Næss S, Markhus MW, Strand TA, Kjellevold M, Dahl L, Stokland AEM, Nedrebø BG, Aakre I. *Iodine Nutrition and Iodine Supplement Initiation in Association with Thyroid Function in Mildly-to-Moderately Iodine-Deficient Pregnant and Postpartum Women.* The Journal of Nutrition. 2021;151(10):3187-96.

Paper III

Næss S, Aakre I, Strand TA, Dahl L, Kjellevold M, Stokland AEM, Nedrebø BG, Markhus MW. *Infant iodine status and thyroid function during the first year of life.* (In review, February 2022).*

* Paper III was published in the British Journal of Nutrition in May 2022 after this PhD thesis was submitted for evaluation. The published manuscript can be found at https://doi.org/10.1017/S0007114522001465

List of abbreviations

AI	Adequate Intake
BMI	Body mass index
BMIC	Breast milk iodine concentration
CV	Coefficient of variation
DIT	Diiodotyrosine
EFSA	European Food Safety Authority
FFQ	Food frequency questionnaire
fT3	Free triiodothyronine
fT4	Free thyroxine
GEE	Generalised Estimating Equations
ICP-MS	Inductively coupled plasma mass spectrometry
I-FFQ	Iodine-specific food frequency questionnaire
IGN	Iodine Global Network
IMR	Institute of Marine Research
IOM	Institute of Medicine
MIT	Monoiodotyrosine
MoBa	The Norwegian Mother, Father and Child Cohort
NIS	Sodium iodine symporter
NNR	Nordic Nutrition Recommendations
RCT	Randomised controlled trial
RDA	Recommended Dietary Allowance
RI	Recommended Intake
RNI	Recommended Nutrient Intake
Tg	Thyroglobulin
TgAb	Thyroglobulin antibody
TRH	Thyrotropin-realising hormone
TSH	Thyroid-stimulating hormone
TPO	Thyroid peroxidase
TPOAb	Thyroid peroxidase antibody
UIC	Urinary iodine concentration
UIC:Cr	Urinary iodine:creatinine ratio
WHO	World Health Organization

1. Introduction

1.1 Iodine — history and background

Iodine (I) is a micronutrient and an essential trace element for humans throughout life because it is needed for the production of thyroid hormones, which are particularly important for optimal development and growth in the first years of life (1).

Iodine was first discovered in 1811 by Bernard Courtois, a French chemist who observed an intense violet vapor arising from seaweed ash while producing gunpowder for Napoleon's army (2). The violet vapor crystallised on cold surfaces and was identified as a new element by the French chemist Gay-Lussac. He named the new element iodine, due to its intense violet colour, after Greek for 'violet' (3). In 1851, the French chemist Chatin was the first to hypothesise that iodine deficiency was the cause of endemic goitre (enlargement of the thyroid gland) (4). Some decades later, in 1895, iodine was recognised in the thyroid gland by the German chemist Baumann, and he proposed iodine to be crucial for thyroid function (5).

Insufficient iodine intake may lead to inadequate production of the thyroid hormones, which may have adverse effects on human health (6). Although goitre is the most visible effect of iodine deficiency, the most serious adverse effects are damage to foetal development and cognitive impairment (7). The World Health Organization (WHO) has defined iodine deficiency as '*the single most important preventable cause of brain damage*' (8). During the last decades, great effort has been made to prevent iodine deficiency throughout the world. This has mainly been performed through salt iodisation programs, and severe iodine deficiency has been almost completely eradicated (9). However, mild-to-moderate iodine deficiency is still present in several regions of the world and, particularly, in pregnant women and infants; the most vulnerable groups for iodine deficiency (10, 11).

1.2 Dietary iodine sources

Iodine is unevenly distributed in the earth's environment. While the iodine concentration in seawater is relatively stable (~50 µg/L), the iodine content in soil is highly variable and geographically dependent (12). This further affects the iodine content of different foods and water, and dietary iodine sources can vary both between and within countries (13). In many regions, however, the natural iodine content in the soil and drinking water is low, and few dietary iodine sources are available (14, 15).

The best natural dietary iodine sources are marine fish and other seafoods, owing to their ability to concentrate iodine from seawater (16). Also, marine foods such as algae, seaweeds and kelps are particularly high in iodine (17). However, the iodine content varies considerably between and within the type of marine species (18). While lean fish, such as cod, pollack and saithe have a high iodine content (190–550 µg/100 g) (18), fatty fish such as Atlantic salmon, mackerel and herring are relatively low in iodine (4–19 µg/100 g) (19). Compared to marine foods, plant-based foods and meats are, in most areas, low in iodine, due to a low iodine content of the soil (13). However, in areas where iodised fertilisers have been used, plant-based foods may have a higher iodine content (20). While fish has the highest natural iodine content, milk and dairy products are the main iodine sources in many countries because of a higher intake (21-24). The natural iodine content of cow's milk is low. However, as a result of iodine fortification of cow fodder and use of iodised disinfecting agents, milk and dairy products are now considered great iodine sources in many countries (13). This also applies for eggs, which may be a good source of iodine if it is present in the feed (25).

Globally, iodised salt is the most important source of iodine (26). However, the contribution to total iodine intake varies between countries, as the permitted level of iodine in salt differs and not all countries have mandatory use of iodised salt (26). In countries where iodised salt is mandatory in industrial and table salt, dietary sources such as processed foods and homemade foods with added salt may be good sources of iodine (27). In addition to dietary sources, use of iodine dietary supplements may contribute to iodine intake in several population groups (28, 29).

1.2.1 Dietary iodine sources in Norway

In Norway, the natural iodine content of the soil and drinking water is low (14). In addition, iodised salt is considered a negligible source of iodine in the Norwegian diet, as the use of iodised salt in the industry is not mandatory and the permitted level of iodine in table salt is low (5 µg/g) (21). There are, accordingly, few dietary iodine sources available in the Norwegian diet. At present, the most important dietary food sources of iodine are milk and dairy products, lean fish and eggs (21). **Table 1** gives the iodine content of selected dietary food sources in the Norwegian diet.

Table 1. Iodine content of dietary food sources in the Norwegian diet

Food item	**Iodine content** (µg/100 g) [a]	**Regular portion size** [b]	**Iodine per portion** (µg/portion)
Cod	279	200 g	558
Farmed Atlantic salmon	6	175 g	11
Mackerel in tomato sauce	13	For one slice of bread (40 g)	5
Cow's milk	16	One glass (2 dl)	32
Yoghurt	16	150 g	24
White cheese	31	For one slice of bread (15 g)	5
Brown cheese	134	For one slice of bread (16 g)	21
Goat's cheese (brown)	307	For one slice of bread (16 g)	49
Egg	34	One egg (56 g)	19
Iodised table salt	500	1 g	5

[a] Iodine content retrieved from the Norwegian Food Composition Table (30) (accessed January 17th 2022)
[b] Regular Norwegian portion size (31)

At the beginning of the 20th century, the most important iodine sources in the Norwegian diet were fish and other marine foods. Later, in the 1950s, iodine fortification of cow fodder in Norway became mandatory as a way to improve animal welfare and health (32). This resulted in an increased iodine concentration in cow's milk, and in the recent decades milk and dairy products have been the most important iodine source in the Norwegian diet (33). In the most recent national dietary survey among adults in Norway (NORKOST-3) (21), milk and dairy products contributed with ~35% of total iodine intake, fish and other seafood ~20%, eggs ~5%, and dietary supplements ~5%. However, the contribution of different iodine sources does vary somewhat between different population groups. In a recent study of pregnant Norwegian women from 2018 (34), milk and dairy products contributed with ~45% of total iodine intake, fish and other seafood ~15%, eggs ~5%, and dietary supplements ~20%.

1.3 Metabolism and the functions of iodine

1.3.1 Iodine metabolism

After ingestion, dietary iodine is reduced to iodide (I^-) by glutathione within the gastrointestinal tract (35). Iodide is further almost completely absorbed (>90%) from the stomach and duodenum (36). Following absorption, free iodide is rapidly cleared from the circulation by absorption to the thyroid gland and kidneys (37). The amount of iodide uptake to the thyroid gland varies with iodine intake and status; if iodine status is adequate, ~10% of the iodide is taken up by the thyroid, while during chronic iodine deficiency this rate may increase to >80% (38). The body of an iodine-sufficient healthy adult contains about 15–20 mg iodine, of which 70–80% is found in the thyroid gland (39). Iodine is mainly excreted through the kidneys and more than 90% of iodine is excreted through urine 24–48 hours after intake (40, 41). Small amounts are excreted through faeces and sweat and for lactating women iodine is also excreted through breast milk (42).

1.3.2 Thyroid hormone synthesis

The only known physiological function of iodine in the human body is the incorporation of iodine in the synthesis of the thyroid hormones, triiodothyronine (T3) and thyroxine (T4), in the thyroid gland (4). After absorption, iodide from the circulation is transported into the thyroid follicular cells by the active sodium iodine symporter (NIS), a transmembrane glycoprotein, at a concentration gradient 20–50 times that of plasma (43). Iodide is further transported to the colloidal follicle lumen of the thyroid. Here, iodide (I^-) is oxidised to iodine (I) and reacts with tyrosyl residues of the glycoprotein thyroglobulin (Tg), a process catalysed by the enzyme thyroid peroxidase (TPO) and hydrogen peroxide (H_2O_2) (44). This process results in the production of Tg-monoiodotyrosine (Tg-MIT) and Tg-diiodotyrosine (Tg-DIT), which are precursors for the thyroid hormones. Further, TPO catalyses the process to form the thyroid hormones T3 (Tg-MIT + Tg-DIT) and T4 (Tg-DIT + Tg-DIT) (45). Accordingly, the hormone T3 contains three iodine atoms, while T4 contains four. The thyroid hormones T3 and T4 remain bound to Tg and are stored in the colloidal follicle lumen until the hormones are needed (46). The release of thyroid hormones from the

thyroid gland is regulated through a hormonal negative feedback system (47). A decline in thyroid hormone levels stimulates the thyrotropin-releasing hormone (TRH) released from the hypothalamus to act on the pituitary gland to release thyroid-stimulating hormone (TSH). TSH further acts on the thyroid gland and stimulates it to release more T3 and T4 into the circulation (47). Here, Tg-T3 and Tg-T4 are released into the thyroid follicle cell by endocytosis and further hydrolysed by lysosomal proteases from Tg, which results in excretion of T3 and T4 into the circulation (46). About 90% of the thyroid hormone release is in the form of T4, but T3 is the most biologically active hormone (46).

1.3.3 Functions of the thyroid hormones

The thyroid hormones are crucial for human life as they are involved in a broad range of physiological and metabolic processes in the body (48). The main mechanisms of the hormones are regulated through gene expression, as the thyroid hormones bind to nuclear thyroid hormone receptors and have a subsequent effect on protein expression and gene regulation (49). This includes genes important for normal growth and development, metabolic regulation, nutrient metabolism and reproduction (48). Adequate thyroid hormone production is particularly important during pregnancy and early childhood as the thyroid hormones are involved in neurodevelopment through cell migration and differentiation, myelination, dendritic branching and synaptic plasticity (50). Thus, inadequate thyroid hormone production during pregnancy and the first years of life may lead to impaired neurodevelopment (51).

1.4 Iodine requirements and recommendations

To cover the adequate intake of iodine during an entire lifetime, less than ~5 g of iodine is needed. The body, however, cannot store iodine for long periods, and small amounts are needed regularly (12). Dietary reference values for nutrients are set by different authorities and include recommended intake values for iodine. **Table 2** gives the recommended iodine intake at different life stages from the Nordic Nutrition Recommendations (NNR) (52), the WHO (8), the European Food Safety Authority (EFSA) (53) and the Institute of Medicine (IOM) (US) (54). In the NNR, the term

'recommended intake' (RI), refers to the average daily intake that is assumed to cover the iodine requirements of nearly all healthy individuals in a population group (52). This definition corresponds to the term 'Recommended Nutrient Intake' (RNI) used by the WHO, 'Adequate Intake' (AI) used by the EFSA, and 'Recommended Dietary Allowance' (RDA) used in the US. The recommended intake of iodine for adults is set to 150 µg/day by all the above-mentioned authorities. The recommended intake is based on the amount of iodine required to maintain normal thyroid function and to prevent goitre (8, 52).

Table 2. Recommended intakes of iodine by different authorities

NNR (52)		**WHO** (8)		**EFSA** (53)		**IOM** (54)	
Recommended Intake (RI)		Recommended Nutrient Intake (RNI)		Adequate Intake (AI)		Recommended Dietary Allowance (RDA)	
Life stage	µg/day	Life stage	µg/day	Life stage	µg/day	Life stage	µg/day
Infants (6–11 m)	50	Children (0–5 y)	90	Infants (7–11 m)	70	Children (1–9 y)	90
Children (1–9 y) [1]	70–120	Children (6–12 y)	120	Children (1–17 y) [2]	90–130	Children (9–12 y)	120
Adults (≥10 y)	150	Adults (>12 y)	150	Adults (≥18 y)	150	Adults (>13 y)	150
Pregnant women	175	Pregnant women	250	Pregnant women	200	Pregnant women	220
Lactating women	200	Lactating women	250	Lactating women	200	Lactating women	290

[1] 1–2 y: 70 µg/day, 2–5 y: 90 µg/day, 6–9 y: 120 µg/day.

[2] 1–10 y: 90 µg/day, 11–14 y: 120 µg/day, 15–17 y: 130 µg/day

EFSA, European Food Safety Authority; IOM, Institute of Medicine; NNR, Nordic Nutrition Recommendations; y, years; WHO, World Health Organization

1.4.1 Pregnant and lactating women

Iodine requirements increase substantially during pregnancy and lactation due to increased thyroid hormone synthesis, transfer of iodine to the foetus, increased glomerular filtration, and secretion of iodine into breast milk during lactation (37). Hence, the recommended intakes of iodine for pregnant and lactating women are higher compared with other adults. However, there is still a lack of knowledge on what is the optimal intake level for pregnant and lactating women, and the recommendations vary between countries and different authorities (**Table 2**). In the Nordic countries (NNR),

the health authorities recommend 175 µg/day for pregnant women and 200 µg/day for lactating women (52). The WHO recommends 250 µg/day for both pregnant and lactating women (8), and EFSA recommends 200 µg/day for both groups (53). In the US, the IOM recommends 220 µg/day for pregnant women and 290 µg/day for lactating women (54).

1.4.2 Children

For infants and children, the recommended intake is lower compared to adults, however, it also varies between different authorities (**Table 2**). While the NNR recommends 50 µg/day for infants aged 6–11 months, the WHO recommends 90 µg/day for all children aged 0–5 years.

1.5 Assessment of iodine status

In order to provide recommendations and strategies for preventing iodine deficiency, accurate measurements of iodine nutrition status in a population are needed (55). The WHO recommends the following indicators for the assessment of iodine status: urinary iodine concentration (UIC), TSH and Tg concentrations in blood, and measurement of thyroid size (8). In addition, measurement of the thyroid hormones T3 and T4, breast milk iodine concentration (BMIC) and dietary assessment methods may be used to assess iodine status in a population (13).

1.5.1 Urinary iodine concentration (UIC)

More than 90% of ingested iodine is excreted through urine within 24–48 hours after intake (40). Therefore, UIC can be used as a measure of recent iodine intake (days) (56). The iodine content in urine can be measured in spot samples (µg/L) or as 24-hour urine collections (µg/day) (57). The WHO recommends median UIC from spot samples to measure iodine status in a population, and this is also the most common method for assessing iodine status (8). However, due to variation in iodine intake and hydration status, iodine excretion in urine varies both between days, and within the same day (58). Accordingly, spot urine samples are not recommended to use as an individual marker of iodine status (58). It has been suggested that ≥10 spot urine samples or 24-

hour urine samples are needed to reliably estimate individual iodine status (57). However, this is impractical and usually not feasible, either in research studies or in the clinic (57). Nevertheless, the intra- and inter-individual variation in urinary iodine excretion tends to even out in a large population and the use of median UIC provides an adequate estimate of iodine status in a population (8).

Epidemiological criteria from the WHO used for assessing iodine nutrition based on median UIC in different population groups are shown in **Table 3**. In adults and children ≥6 years of age, iodine deficiency is defined as median UIC <100 µg/L, and further categorised as mild (UIC 50–99 µg/L), moderate (UIC 20–49 µg/L), or severe (UIC <20 µg/L). In pregnant women, insufficient iodine intake is defined as median UIC <150 µg/L. There are currently no specific categories of iodine deficiency in pregnant women, but mild-to-moderate iodine deficiency is often defined as median UIC in the range of 50–149 µg/L, and severe iodine deficiency as median UIC <50 µg/L (59). For lactating women and children <2 years of age, a UIC <100 µg/L is indicated as insufficient iodine intake, while a UIC >100 µg/L is considered adequate.

Table 3. Epidemiological criteria for assessing iodine nutrition based on median UIC in different population groups (8)

Population group	Median UIC (µg/L)	Iodine intake	Iodine status
School-age children (≥6 y) and adults	<20	Insufficient	Severe iodine deficiency
	20–49	Insufficient	Moderate iodine deficiency
	50–99	Insufficient	Mild iodine deficiency
	100–199	Adequate	Adequate iodine nutrition
	200–299	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk of more than adequate intake in the overall population
	≥300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases)
Pregnant women	<150	Insufficient	-
	150–249	Adequate	-
	250–499	Above requirements	-
	≥500	Excessive	-
Children <2 y and lactating women	<100	Insufficient	-
	≥100	Adequate	-

Table reproduced from the WHO (8)

Urinary iodine-to-creatinine ratio (UIC:Cr)

To adjust for individual hydration status, UIC may also be presented as UIC:creatinine ratio (UIC:Cr) (µg/g). Creatinine excretion in urine is relatively constant (~1 g/24 h in adults) and can reduce the variability in UIC as it accounts for hydration status (60). However, creatinine excretions vary with gender, age, body mass index (BMI), ethnicity and protein intake (61). Therefore, the WHO does not recommend using UIC:Cr when assessing iodine status in a population, as it may introduce more errors in the estimates (8, 62). However, several studies have proposed that, in homogenous populations, UIC:Cr is a better measurement of iodine status compared with UIC alone (57, 63-65).

1.5.2 Breast milk iodine concentration (BMIC)

In breastfeeding women during lactation, iodine is also excreted into breast milk (66). BMIC measured in spot breast milk samples has therefore been proposed as a marker of iodine status in lactating women (67). However, similar to UIC, spot BMIC only reflects recent iodine intake and excretion varies both between days, and within the same day (68). Therefore, BMIC is not a proper marker of individual iodine status unless several repeated samples are obtained (69). Although no established cut-off value has been determined, a median BMIC of 100–200 µg/L has been suggested as adequate in a population of lactating women (69).

1.5.3 Blood markers

TSH, fT3 and fT4

In a severe iodine-deficient population, serum TSH is generally higher compared with an iodine-replete population (8). Also, serum fT4 is typically lowered, while fT3 is higher compared with normal populations (8). However, TSH, fT3 or fT4 are not sensitive biomarkers of iodine nutrition, as the intra-individual changes vary and possible alterations are often within the normal range (13, 70). Also, potential changes may only be seen under severe iodine deficiency due to tight homeostatic control of the thyroid hormones (71). However, TSH may be a sensitive indicator of iodine status in one population group; neonates (8). In iodine-deficient newborns, TSH levels are increased in the first weeks of life and may be a sensitive marker of iodine status (12).

The prevalence of neonates with elevated TSH levels can therefore be used as an indicator of the severity of iodine deficiency in a population (8).

Thyroglobulin (Tg)

Tg is a protein produced in the thyroid gland, and it is a precursor of the thyroid hormones (8). Small amounts of Tg can be detected in the blood of all healthy individuals (8). When iodine deficiency is present, serum Tg levels are elevated due to TSH hyperstimulation and thyroid hyperplasia of the thyroid gland (72). In this setting, Tg can be used as an indicator of an intermediate response of changes in iodine intake (weeks to months) (56). Use of Tg as a biomarker of iodine nutrition has shown promising results in school-age children (73-75), adults (72, 76) and pregnant women (77, 78).

1.5.4 Thyroid size

If goitre (enlargement of the thyroid gland) is present due to iodine deficiency, assessment of thyroid size by palpation or ultrasound may be a useful method to assess the severity of iodine deficiency (8). The change of goitre rate can reflect long-term iodine nutrition in a population (months to years) (56). However, the method lacks sensitivity to acute changes in intake (8), and palpation in areas of mild-to-moderate iodine deficiency has poor sensitivity and specificity (13). Also, the use of both palpation and ultrasound requires well-trained technicians with a low inter- and intra-variability (13).

1.5.5 Dietary assessment

Dietary assessment methods may be used to evaluate iodine status through estimation of dietary iodine intake and by comparing it to dietary recommendations (13). In addition, dietary assessment methods can give a better understanding of current iodine status and iodine sources in a population (79). However, estimating iodine intake poses several challenges as it requires accurate and reliable food composition data (13), and it demands a dietary method that is validated for iodine and for the specific population group (80). The major dietary assessment methods used to capture iodine intake are food frequency questionnaires (FFQs), food diaries and 24-h dietary recalls. While

food diaries and 24-h dietary recalls measure short-term iodine intake, an FFQ has the advantage that it can measure habitual longer-term intake and include food sources that are irregularly consumed (13). However, the use of dietary assessment methods is challenging in populations where iodised salt contributes significantly to total iodine intake, mainly because the contribution of iodised salt used in cooking and processed foods is difficult to quantify (81). Iodised salt is considered a negligible source of iodine in the Norwegian diet. In addition, there are few available dietary iodine sources in the diet (milk and dairy, lean fish, eggs and supplements) (33). Accordingly, the use of dietary assessment methods may be well suited to assess iodine nutrition in the Norwegian population (82).

1.6 Iodine nutrition status

1.6.1 Globally

Iodine deficiency is one of the most common nutritional disorders in the world. The first estimate of endemic goitre caused by iodine deficiency, published in 1960 by the WHO, estimated that iodine deficiency affected approximately 20–60% of the world's population (4, 83). In 2007, the WHO estimated that nearly two billion people were at risk of insufficient iodine intake (8). Nevertheless, during the last decades great progress has been made towards eliminating iodine deficiency; mainly through salt iodisation programmes and with dietary iodine supplementation (9). Because of these efforts, severe iodine deficiency has been almost completely eradicated. However, mild-to-moderate iodine deficiency is still a threat to global public health as it is still present in several population groups (83).

According to the WHO, a population is considered iodine-deficient if the median UIC in school-age children (aged 6–12 years) is <100 µg/L (8). According to this definition, the prevalence of iodine-deficient countries decreased from 54 countries in 2003 (84), to 32 countries in 2011 (85), and 21 countries in 2020 (86). However, not all population groups are covered by this definition, and studies indicate that several other population groups are at risk of iodine deficiency even when school-age children are considered iodine sufficient (87-91). Thus, even though there has been great progress in

eliminating iodine deficiency, there are still concerns for the most vulnerable groups of iodine deficiency: women of reproductive age, pregnant and lactating women and infants (92). In 2017, the Iodine Global Network (IGN) reported that 54% of the world's countries were classified as having insufficient iodine intake among pregnant women (**Figure 1**) (93, 94). In Europe, 75% of the countries had inadequate iodine intake, making Europe the region with the highest prevalence of iodine deficiency in pregnant women. Also, estimates suggest that up to 50% of infants in Europe are at risk of iodine deficiency (11). However, available studies on infant iodine status during the first year of life are scarce (69).

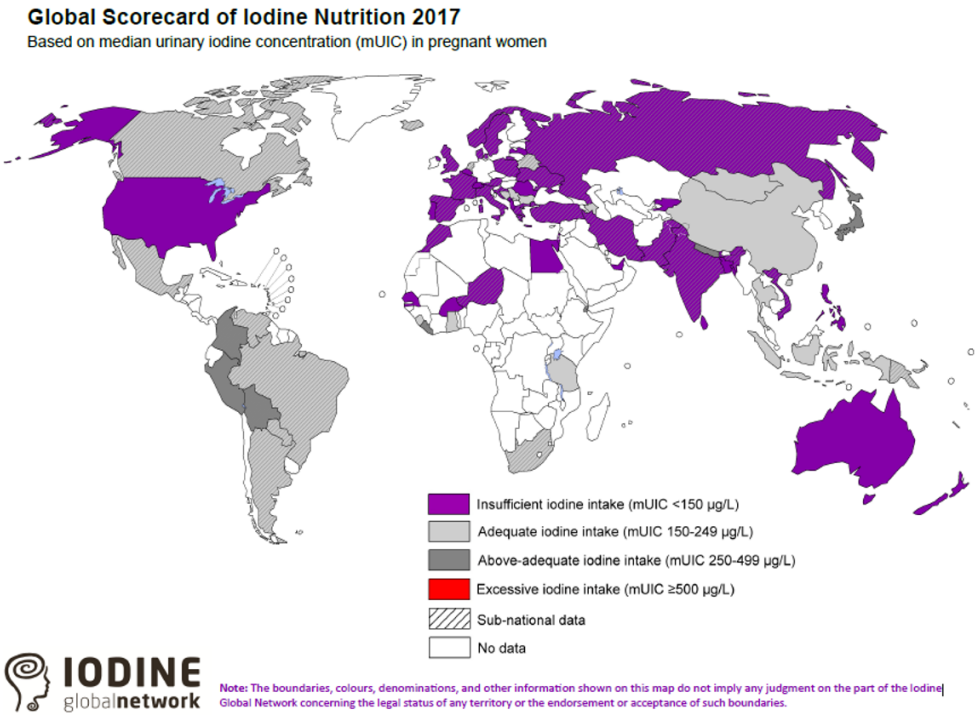

Figure 1. Global iodine status in pregnant women in 2017 based on median urinary iodine concentration (mUIC) by country (93). Figure reprinted with permission from the Iodine Global Network.

1.6.2 In Norway

Endemic goitre due to iodine deficiency was prevalent in Norway prior to the 1950s. In the inland area of Norway during the 1930s, goitre was present in up to 80% of

school-age children (95). In the 1950s, iodine fortification of cow fodder became mandatory. This resulted in an increased iodine concentration in milk, which further improved iodine intake in the population (33). During the next decades, a few publications reported sufficient iodine status among adults and children (96-99), and the Norwegian population was considered iodine-replete (33). Later, in 2013, insufficient iodine status was reported among pregnant women in the Norwegian Mother, Father and Child Cohort (MoBa) study, indicating that iodine deficiency had re-emerged in Norway (100). Moreover, in a report from 2016, the National Nutrition Council in Norway concluded that 'iodine intake is alarmingly low in parts of the population' (82). Since this report, mild-to-moderate iodine deficiency has been reported in several population groups in Norway; young women (101), pregnant women (102, 103), lactating and postpartum women (104-106), and vegans and vegetarians (34, 107). In contrast, adequate iodine status has been reported in infants (108), toddlers (109), pre-school children (110) and teenagers (111). However, these groups may also be at risk, if intake of the most important iodine sources such as milk and dairy products is low.

In the annual report from the Iodine Global Network in 2021, Norway was one of 21 countries classified as iodine-deficient (86). However, in contrast to previous decades where severe iodine deficiency was present, iodine deficiency is now present as mild-to-moderate in certain population groups in Norway (32).

1.7 Consequences of iodine deficiency

Iodine deficiency can have multiple adverse effects on human health (12). These adverse effects are collectively termed as the 'iodine deficiency disorders' (IDDs) (1). The health consequences of iodine deficiency disorders vary throughout the life cycle, but include hypo- and hyperthyroidism, goitre, cretinism, increased infant mortality, impaired growth and development, and decreased mental function (38). Compared to severe iodine deficiency, mild-to-moderate iodine deficiency results in less severe outcomes, although, the consequences of mild-to-moderate iodine deficiency are still not conclusive (12).

1.7.1 Thyroid function

The only known underlying mechanism of iodine deficiency causing adverse health effects is through disturbances of the thyroid hormones (60). The association between iodine intake and the prevalence of thyroid disorders is u-shaped, as both iodine deficiency and iodine excess could cause thyroid disorders (112). When the availability of iodine decreases, several thyroidal autoregulatory mechanisms are induced in order to maintain normal thyroid function (euthyroidism) (113). This includes increased concentrations of TSH, which increases the expression of the sodium-iodide symporter to increase thyroidal iodine uptake (12). Further, this may stimulate excessive growth of the thyroid follicular cells possibly leading to the development of goitre (38). Additionally, the production of T3 is preferred over T4 in order to save one iodine atom and to prioritise production of the most active hormone, T3 (113). Therefore, when iodine deficiency progresses, the concentrations of T3 may increase or remain normal, while concentrations of T4 are decreased (71). Lastly, when thyroidal iodine is depleted, the thyroid cannot maintain the production of thyroid hormones and concentrations of T3 and T4 fall leading to the development of hypothyroidism (71). However, these described mechanisms are mostly prominent when severe iodine deficiency is present. In populations with mild-to-moderate iodine deficiency, concentrations of TSH, T3 and T4 often remain in the normal range as the thyroid is able to compensate for the low iodine intake (7). However, less is known about the consequences of mild-to-moderate iodine deficiency on thyroid function, and it is still uncertain at which level of iodine status the thyroid hormones are affected (114).

1.7.2 In pregnancy and early childhood

Iodine deficiency can lead to various health consequences throughout life, although, the consequences are most severe in early life as iodine deficiency may result in irreversible brain damage (115). Therefore, foetuses and infants are the groups most vulnerable to iodine deficiency (6). During pregnancy, the foetus is dependent on maternal transfer of thyroid hormones until it starts its own production from ~gestational week 18-20 (116). However, the foetus is still dependent on the maternal transfer of iodine throughout pregnancy (117). After birth, fully breastfed infants rely on the maternal iodine supply through breast milk (66). Consequently, adequate

maternal iodine nutrition during pregnancy and the postpartum period is particularly important.

The consequences of severe iodine deficiency during pregnancy and early childhood are well documented, as in worst case, it may result in cretinism and mental retardation of the child (1, 118). In contrast, the effects of mild-to-moderate iodine deficiency are less certain. However, during the last decade, several observational studies have reported associations between mild-to-moderate iodine deficiency in pregnancy and reduced child language scores (119-121), reduced cognitive scores (121, 122), lower motor skills (123) and reduced educational outcomes in children (120, 124, 125). Nevertheless, not all observational studies have found associations with reduced child neurodevelopment (126-128). In addition, randomised controlled trials (RCTs) with iodine supplementation in pregnant women with mild-to-moderate iodine deficiency show no clear benefits on child neurodevelopment (129-131). However, another aspect in this discussion is that the initiation of supplementation in the mentioned RCTs might have been too late in pregnancy to document any effect on child development (132). Observational studies have also found that the foetus is particularly vulnerable to iodine deficiency in the first trimester of pregnancy and that thyroidal iodine stores should be optimised before conception of pregnancy (133-135).

Most research within iodine nutrition has focused on the effects of iodine deficiency during pregnancy, and less is known about the effects of postnatal iodine deficiency during infancy (69). In particular, the isolated postnatal effect of inadequate iodine status during infancy and early childhood is not well described in populations with mild-to-moderate iodine deficiency (12). An RCT in mildly iodine-deficient school-age children (median UIC: 63 μg/L) from New Zealand demonstrated that iodine supplementation improved iodine status and cognitive function, further proposing that even mild iodine deficiency in later childhood could prevent children from attaining their full cognitive potential (136). Consequently, adequate iodine status is also important after birth, particularly during infancy and the childhood period (6, 137).

1.8 Global efforts to prevent iodine deficiency

1.8.1 Iodised salt

Globally, salt iodisation has been recommended by the WHO as the preferred strategy for preventing iodine deficiency (8). A systematic review from 2014 concluded that salt iodisation programs have had a large effect on reducing the risk of iodine deficiency and IDD (138). In 2020, 124 countries had legislation for mandatory salt iodisation, and 88% of the global population used iodised salt (9). However, not all countries have mandatory use of iodised salt, and the permitted level of iodine in salt varies between countries (26). Currently, Europe is the region with the lowest coverage of iodised salt (139). As previously mentioned, the use of iodised salt is not mandatory in Norway, and the permitted levels of iodine in iodised salt is low (5 µg/g). In contrast, the neighbouring countries of Sweden (50 µg/g), Denmark (20 µg/g) and Finland (25 µg/g) have much higher concentrations in iodised salt (140). However, as a result of reported iodine deficiency among several population groups, in February 2021, the National Nutrition Council in Norway recommended the national authorities to introduce mandatory iodisation of table salt and industrial salt used in bread and bakery products (141). In addition, they proposed to increase the iodisation to 20 µg/g of both table and industrialised salt (141). The health authorities have not yet concluded and therefore the contribution of iodised salt may increase in the Norwegian diet in future years.

1.8.2 Iodine supplementation

The WHO recommends iodine supplementation in areas with insufficient access to iodised salt and where few dietary iodine sources are available (8). However, this recommendation only considers the most vulnerable groups: pregnant and lactating women (250 µg/day), women of reproductive age (15-49 y) (150 µg/day), and children <2 years (90 µg/day). Both the European and American Thyroid association recommend iodine supplementation for women who are planning pregnancy, and for pregnant and lactating women (142, 143). In Norway, since 2018, women of fertile age, pregnant and lactating women have been advised to take an iodine supplement if intake of the most important iodine sources (milk and dairy, and lean fish) is low (144).

The specific iodine supplement recommendations given by the Norwegian Directorate of Health are shown in **Table 4**.

Table 4. Recommendations of iodine supplement use in Norway (144)

Population group	Intake of iodine-rich food group	Recommended iodine supplement dose
Women of fertile age	<3 dl milk/yoghurt with a regular intake of lean fish *or* <5 dl milk/yoghurt with little or no intake of lean fish	100 µg/day
Pregnant and lactating women	<6 dl milk/yoghurt with a regular intake of lean fish *or* <8 dl milk/yoghurt with little or no intake of lean fish	150 µg/day

Even though iodine supplementation is recommended by several authorities and countries, the benefits of iodine supplementation in mildly-to-moderately iodine-deficient populations remain unclear (70). A Cochrane review from 2017 assessed the effects of iodine supplementation during the pre-conception, pregnancy and postpartum periods (145). They concluded that there is insufficient evidence to conclude whether iodine supplementation has an effect on thyroid function and child development in areas with mild-to-moderate iodine deficiency. This has also been the conclusion in previous systematic reviews (146-149).

1.9 Knowledge gaps and the rationale for this thesis

Whereas the adverse effects of severe iodine deficiency are well documented, the mechanisms and consequences of mild-to-moderate iodine deficiency on thyroid function are less understood (150). Furthermore, more research focusing on the effect of iodine supplementation and timing of supplement initiation during pregnancy are needed (146, 151, 152). In addition to pregnant women and foetuses, infants are the group most vulnerable to the consequences of iodine deficiency (6). However, data on infant iodine status and thyroid function in countries with mild iodine deficiency are sparse (153). Also, more data assessing the association between iodine status and thyroid function in infants are needed to refine the criteria for optimal iodine nutrition in this group (69).

2. Objectives

The main objective of this PhD project was to describe iodine nutrition and thyroid function and to explore associations between them among pregnant and postpartum women and their infants. This was investigated in a cohort study where women were followed-up during pregnancy at gestational weeks 18 and 36 and further at 3, 6 and 11 months postpartum with their infants.

Specific objectives

Paper I

Assess the validity and reproducibility of an iodine-specific FFQ (I-FFQ) developed for pregnant women.

Paper II

Explore whether iodine nutrition (UIC and iodine intake) and timing of iodine supplement initiation were associated with altered thyroid function in mildly-to-moderately iodine-deficient pregnant and postpartum women.

Paper III

Describe infant iodine status and thyroid function and further explore associations between them in the first year of life. In addition, assess the impact of maternal iodine nutrition and breastfeeding status on infant iodine status.

3. Material and methods

3.1 Study design

This PhD project is based on data from the 'Mommy's Food' study, which took place in Bergen, Norway between 2016–2018. The study was originally a two-armed RCT in pregnant women where the primary and secondary outcomes were to investigate if an increased intake of lean fish (Atlantic cod) during pregnancy (from gestational week 20-36) had an impact on i) maternal iodine status and ii) infant development. The study protocol (154) and results from the primary and secondary outcomes (155) have been published elsewhere.

A cohort is defined as 'a group of persons who are followed or traced over a period of time' (156). In the papers of the current PhD project, the data were analysed as secondary analyses with a cohort design where pregnant women were followed up at gestational weeks 18 and 36, and further at 3-, 6-, and 11 months postpartum with their infants. In the specific papers, the data were analysed in an observational design using both cross-sectional and longitudinal observational data.

3.2 Study population

The source population of the study was pregnant women who gave birth at the Women's Clinic at Haukeland University Hospital in Health Region West in Bergen, Norway (annually ~5000 births) at the time period of recruitment. The women were recruited from January 2016 until February 2017. Information regarding the study was included in the invitation to the routine ultrasound that takes place at gestational week ~18. In addition, study information was broadcasted online through social media (Facebook, Instagram and an online magazine for pregnant women in Norway) to increase the participation rate. Inclusion criteria were first-time pregnant, singleton pregnancy, gestational week ≤19, and Norwegian speaking and/or able to understand Norwegian writing (because of the questionnaires and validated tests of the child being in Norwegian). Exclusion criteria were known thyroid dysfunction diseases

(hypothyroidism, hyperthyroidism, Graves disease, thyroiditis, and thyroid nodules) and fish allergies.

A flow-chart of the study population is given in **Figure 2**. In total, 165 pregnant women showed an interest to participate, and, out of these, 137 participants were enrolled in the study. Between enrolment and follow-up 11 months postpartum, 25 participants withdrew from the study (actively or passively) and a total of 112 mothers completed follow-up with their infants.

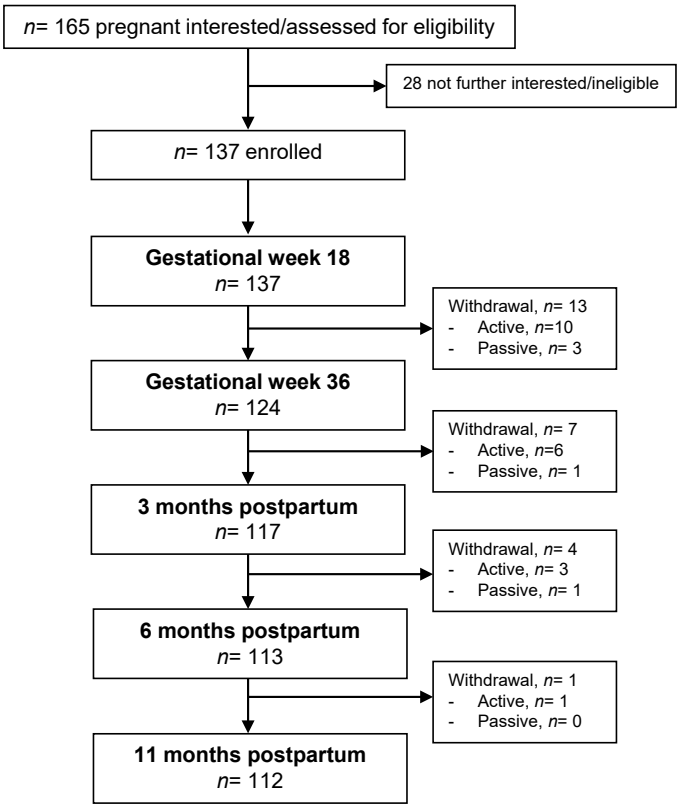

Figure 2. Flow-chart of the study population

3.3 Data collection methods

Data from the participants were collected at five time points; gestational weeks 18 and 36, and 3-, 6- and 11 months postpartum. This included biological samples (blood, urine and breast milk), dietary assessment methods (FFQ, food diary and 24-h dietary recall) and online questionnaires regarding demography and anthropometry. The type of data that are included in the specific papers and number of participants available at each time point are given in **Table 5**. Owing to loss to follow-up and missing data, the numbers of participants with completed data differed at each time point. The following sections will describe the data collection methods that have been used in the three papers included in this PhD.

Table 5. Data included in the specific papers (I, II, III) and number of participants with data

	Mother					**Infant**		
Data	**GW 18**	**GW 36**	**3 M**	**6 M**	**11 M**	**3 M**	**6 M**	**11 M**
UIC	*n*= 134 I, II, III	*n*= 122 I, II, III	*n*= 111 I, II, III	*n*= 103 I, II, III	-	*n*= 108 III	*n*= 90 III	*n*= 91 III
UIC:Cr	*n*= 134 II, III	*n*= 122 II, III	*n*= 111 II, III	*n*= 103 II, III	-	*n*= 108 III	*n*= 86 III	*n*= 87 III
Thyroid function	*n*= 137 I, II	*n*= 119 I, II	*n*= 112 I, II	*n*= 105 I, II	-	*n*= 47 III	*n*= 52 III	-
BMIC	-	-	*n*= 108 III	-	-	-	-	-
I-FFQ	*n*= 124 I, II, III	*n*= 106 I, II, III	*n*= 92 I, II, III	*n*= 86 I, II, III	*n*= 77 III	-	-	-
Food diary	*n*= 134 I	-	-	-	-	-	-	-
Breastfeeding status	-	-	-	-	-	*n*= 108 III	*n*= 90 III	*n*= 64 III

BMIC, breast milk iodine concentration; GW, gestational week; I-FFQ, iodine-specific food frequency questionnaire; M, months; UIC, urinary iodine concentration; UIC:Cr, urinary iodine-to-creatinine ratio

3.3.1 Urine samples

Spot urine samples were collected from the mothers (gestational weeks 18 and 36, and 3- and 6 months) and infants (3, 6 and 11 months). During pregnancy, six spot urine samples were collected on six consecutive days. From the six urine samples, equal amounts of urine were homogenised into one pooled composite sample. Postpartum, one spot urine sample was collected from both mother and infant. For the infants, a urine collection pad (21 cm x 7 cm, Steriset urine collection pack, Steriset Medical Products; Penafiel, Portugal) was placed in the disposable diaper one to two hours before the study visit. The urine collection pads were collected during the study visits and further extracted for urine. All urine samples were stored at -20◦C in cryo tubes (CryoTube^{TM} Vials Nunc; Thermo Fischer Scientific, Roskilde, Denmark) pending analysis for iodine and creatinine concentrations.

Urinary iodine and creatinine concentrations

Iodine concentration in the urine samples was analysed by inductively coupled plasma mass spectrometry (ICP-MS), at the IMR in Bergen, Norway. The measurement uncertainty of the method has been assessed based on internal reproducibility and analysis of standard reference material and is set at 20%. Creatinine concentration in the urine samples was analysed spectrophotometrically using a MAXMAT PL II multidisciplinary diagnostic platform with a creatinine PAP kit (ERBA Diagnostics France SARL; Montpellier, France) at the IMR. The laboratory at IMR is accredited according to ISO 17025 and regularly participates in quality programmes. The reference values from the WHO of UIC during pregnancy (150 µg/L), lactation (100 µg/L) and infancy (100 µg/L) were used to assess adequate iodine status (157).

3.3.2 Breast milk samples

Breast milk samples were collected 3 months postpartum. One sample was collected at the beginning, during and at the end of a chosen feed for two consecutive days (a total of six samples). From the six breast milk samples, equal amounts of breast milk were homogenised into one pooled composite sample and stored at -20◦C pending analysis for iodine. BMIC was analysed with ICP-MS at the IMR as described previously.

3.3.3 Blood samples

Blood samples were collected during pregnancy (gestational weeks 18 and 36) and 3- and 6 months postpartum in both mother and infants by a trained phlebotomist. Venous blood samples for serum preparation were collected in BD Vacutainer® SST™ vials II Advanced (Becton, Dickinson and Co.; NJ, US) and set to coagulate for a minimum of 30 minutes before centrifuging (1,000–3,000 × g, room temperature, 10 minutes) within 60 minutes after venepuncture. Post-separation, serum samples were stored at −80◦C for a maximum of 3 months. If venepuncture was not possible in infants, capillary blood was collected from the infant's heel or fingertip (according to age or bodyweight) and placed in a BD Microtainer® Blood Collection Tube (Becton, Dickinson and Co.; Franklin Lakes, NJ, US). A Tenderfoot ITC® heel-incision device (Accriva Diagnostics; San Diego, CA, US) was used for heel pricks and ACCU-CHEK® Safe-T-Pro Plus lancets (Roche Diagnostics; Rotkreuz, Switzerland) were used for finger pricks. Prior to capillary blood sampling, the heel or finger was warmed with a hot water balloon to ensure vasodilation to enable sufficient blood flow. The infants were given 1–2 ml of a 25% sucrose-water solution before blood sampling to reduce eventual pain-related stress.

Serum concentrations of TSH, fT3 and fT4

Serum blood samples were analysed for TSH, fT3 and fT4 at Fürst Medical Laboratory in Oslo, Norway. The laboratory is accredited according to NS-EN ISO 15189 and regularly participates in quality programmes. TSH, fT4 and fT3 were analysed using magnetic separation and detection by chemiluminescence, labelling with acridinium ester, on an Advia Centaur XPT Immunoassay system (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, US). For TSH, fT3 and fT4, the analytical coefficient of variation (CV) was 3.1%, 3.3% and 4.6%, respectively.

Reference ranges for TSH, fT3 and fT4 were used to classify participants with biochemically assessed thyroid dysfunction. The reference ranges of TSH, fT3 and fT3 that were used in Paper II and Paper III are given in **Table 6**. The American Thyroid Association (ATA) (143) recommends that TSH reference ranges for pregnant and postpartum women should be based on population-based reference ranges through

assessment of local population data. For TSH, we therefore used previously published population-specific reference ranges specifically derived from a pregnant (158) and a non-pregnant female (159) population in Norway. The ATA recommends using assay-specific reference ranges for fT3 and fT4 for the reason that laboratory differences can be large (143). For fT3 and fT4, we therefore used reference ranges for adults (specific reference ranges for pregnant or postpartum women were not available) derived from the laboratory (Fürst Medical Laboratory) (160). For infants, age-specific reference ranges for TSH, fT3 and fT4 were derived from the laboratory (160) as population-specific reference ranges were not available. The decisions regarding reference ranges were consulted with clinical endocrinologists.

Table 6. Reference ranges of TSH, fT3 and fT4 used for classifying biochemically assessed thyroid dysfunction in pregnant and postpartum women and infants

	Reference ranges		
	Pregnant women	**Postpartum women**	**Infants**
TSH (mIU/L)	0.39–2.70 [1]	0.37–3.30 [3]	1.1–8.2 [4]
fT3 (pmol/L)	3.5–6.5 [2]	3.5–6.5 [2]	4.5–8.0 [4]
fT4 (pmol/L)	11.0–23.0 [2]	11.0–23.0 [2]	11.0–23.0 [4]

[1] Population-specific reference ranges from MoBa (the Norwegian, Mother, Father and Child Cohort) (158). Derived from 2.5–97.5 percentiles in *n*= 2577 thyroid peroxidase antibody (TPOAb)-negative pregnant women (mean GW = 18.5).
[2] Assay-specific reference ranges from the Fürst Medical Laboratory (160)
[3] Population-specific reference ranges from the Norwegian Trøndelag Health Study (HUNT) (159). Derived from 2.5–97.5 percentiles in *n*= 514 TPOAb-negative females (<40 years old, non-pregnant)
[4] Age- and assay-specific reference ranges from the Fürst Medical Laboratory (160); TSH: 1–12 months; fT3: 0–9 years; fT4: 0–12 months.

Thyroid dysfunction was defined biochemically by thyroid function tests outside reference ranges (161). Overt hypothyroidism was defined as TSH above and fT4 below reference values. Overt hyperthyroidism was defined as TSH below and fT4 above reference values. Subclinical hypothyroidism and hyperthyroidism were defined as TSH above and below reference values, respectively, and normal fT4 values. Isolated hypothyroxinaemia was defined as normal TSH values and fT4 values below reference values.

3.3.4 Dietary assessment methods

There are several dietary assessment methods available to measure dietary intake in a population or in individuals. In this study, an FFQ, a food diary and 24-hour dietary recall were used to assess the maternal and infant diet.

Food frequency questionnaire (I-FFQ)

An I-FFQ (Appendix I) was developed specifically to assess iodine intake among pregnant and postpartum women in this study. Validation of the I-FFQ was assessed in Paper I and the I-FFQ was further used in Paper II and Paper III. The I-FFQ was semi-quantitative and aimed to capture the participants' habitual diet and supplement use focusing on the most important iodine sources in the Norwegian diet (milk and dairy products, fish and other seafood, eggs and dietary supplements). The I-FFQ was included in an online questionnaire (Qualtrics Survey Software) which the participants received by email. In the I-FFQ completed in gestational week 18, the participants were asked to report an estimate of their diet since they became pregnant, and the recall period aimed to be the first half of pregnancy. The I-FFQ completed in gestational week 36 covered the diet over the last 4 months (since the last time they completed the I-FFQ) and the recall period aimed to be the second half of pregnancy. In the I-FFQs completed at 3-, 6- and 11 months postpartum, the recall period aimed to be the last 3 months of the participant's habitual diet.

The I-FFQ included questions of intake frequency of a total of 60 food items; 24 questions regarding milk and dairy products (including mixed foods such as porridge, pancakes etc.), 35 questions regarding fish and other seafood products and one question regarding eggs. All questions regarding the frequency of food items had follow-up questions for portion sizes per meal. The specific portion sizes were also specified in the I-FFQ, for example: 'When you eat salmon for dinner, how big of a portion do you usually eat? One portion= 150 g'. In addition, the I-FFQ included questions regarding dietary supplement use, including type, brand and intake frequency. The I-FFQ completed at gestational week 18 also included one question regarding the use of pre-pregnancy dietary supplement use.

Food diary

A structured manual six-day food diary (Appendix II) was completed prospective by the mothers on six consecutive days at gestational week 18 (exact same days as the urine samples). The food diary was developed specifically for this study with the purpose of estimating iodine intake during pregnancy. The food diary included a total of 28 food items; 19 questions regarding milk and dairy products (including mixed foods such as porridge, pancakes etc.), 8 questions regarding fish and seafood and one question regarding eggs. Each food item included quantitative response alternatives (glasses or cups, portions, slices etc.) and the participants filled out their respective intakes from each day (e.g. 4 slices of cheese). In addition, the food diary included questions regarding dietary supplements including type, brand and intake frequency.

Breastfeeding status: 24-h dietary recall and FFQ

At the study visits 3- and 6 months postpartum, a 24-h dietary recall was conducted to obtain the infants' diet reported by the mothers. This included information regarding breastfeeding status and eventual formula use. A 24-h dietary recall was not obtained at age 11 months and, at this age, information regarding breastfeeding status (breastmilk and formula use) was retrieved from an FFQ included in the online questionnaire obtained by the mothers.

3.3.5 Data management of dietary assessment methods

Calculation of iodine intake

To calculate the intake of each food item from the I-FFQ in gram/day, firstly, the frequency of reported intake was converted to continuous data through the calculation of indexes in accordance with the methodology described by Markhus et al. (162). For fish and seafood products, when frequency of consumption was given as a range (e.g., 1-2 times per week), the lowest frequency in each range was used (*here*: 1 time per week). This was performed as the I-FFQ consisted of an extensive list of different fish and seafood species and recall is prone to overestimate low intakes when asked about several detailed food items separately (162). For the questions regarding milk and dairy products, eggs and dietary supplement use, when the frequency was given as a range (e.g. 1-2 times per day), the mean frequency consumption was used (*here*: 1.5 times

per day) as these food categories consisted of fewer questions. Secondly, the calculated index of frequency from the I-FFQ was multiplied by the reported portion sizes to estimate intake in portions/day. Thirdly, intake of portions/day was multiplied with the estimated portion sizes in grams as defined in the report 'Weights, measures and portion sizes for foods' which is developed by the Norwegian Food Safety Authority, the University of Oslo and the Norwegian Directorate of Health (31). This latter stage was also calculated from the food diary in order to estimate the intake of each food item in gram/day.

Further, to calculate the mean intake of iodine in µg/day of each food item, intake in g/day was multiplied by the iodine content of the specific food item. The iodine content of the specific foods was retrieved from the publication Nerhus et al. 2018 (18), the nutrient database *Seafood data* developed by the Institute of Marine Research (IMR) (19) and the Norwegian Food Composition Table (30). In the publication from Nerhus et al. 2018, the aim was to analyse the iodine content of the most important iodine-rich food groups consumed in the Norwegian diet (six fish species, 27 Norwegian milk and dairy products and eggs). This study was performed by the IMR so that updated analytical food composition data were available for calculation of iodine intake to the present study. Not all food items specified in the I-FFQ and the food diary were analysed in the Nerhus et al. 2018. For the remaining food items, the most relevant and analytical value of iodine content from either *Seafood data* or the Norwegian Food Composition Table was used. The iodine content of the different food items that were used for the calculation of iodine intake is given in Supplementary Data of Paper I.

For calculation of iodine intake from dietary supplements in the I-FFQ and the food diary, the iodine content of each supplement was retrieved from the product labels specified by manufacturers. The iodine content varied from 75–225 µg per recommended daily dose with most supplements containing 150–220 µg/dose. To calculate iodine intake from dietary supplements in µg/day, the reported frequency of intake was multiplied by the iodine content of the supplement specified by the participant.

Finally, to calculate the total estimated iodine intake per day (µg/day), from both the I-FFQ and the food diary, estimated iodine intake from foods and supplements was summarised. More detailed information regarding the calculation of iodine intake from the I-FFQ and food diary has been given in Paper I.

Iodine supplement use

To explore whether the timing of iodine supplement initiation was associated with thyroid function in Paper II, the reported use of iodine supplements from the I-FFQ was used. The use of iodine-containing supplements was defined as >2 times/week. Reported use of iodine-containing supplements from pre-pregnancy and until gestational week 18 were merged and categorised into the following categories:

- None: no use of supplements reported either pre-pregnancy or gestational week 0–18
- Pre-pregnancy: only reported supplement use pre-pregnancy
- Gestational week 0–18: only reported supplement use gestational week 0–18
- Pre-pregnancy and gestational week 0–18: reported supplement use, both pre-pregnancy and gestational week 0–18

Breastfeeding status

Breastfeeding status data from the 24-hour dietary recall obtained at age 3 and 6 months and the electronic questionnaire at age 11 months were used to create the following categories:

- Breastfed: no use of formula (exclusively or predominantly breastfeeding)
- Mixed-milk fed: breastfeeding and use of formula
- Formula-fed: no breastfeeding, only use of formula

No distinction was made between predominantly or exclusively breastfeeding in the 'breastfed' category, as the infants' ages varied between 3 and 11 months. Thus, the categories also included infants receiving complementary foods at age 6 and 11 months. To define infants that were exclusively breastfed, the WHO's definition of exclusively breastfeeding was used: 'breastfeeding with no other food or drink, not

even water' (163). With this definition, prescribed medication, vitamins and minerals are not counted as fluids or foods.

3.3.6 Subject characteristics and covariates

Maternal and infant characteristics were retrieved from an electronic questionnaire conducted at each study time point. The questionnaires included information regarding maternal age, education level, pre-pregnancy weight and height, current weight, nicotine use and the gestational week at birth. Also, they included information concerning infant sex, birth weight, current infant weight and height and specific infant age when measuring anthropometric variables.

Maternal and infant ferritin concentrations were analysed in serum blood samples which were collected as described in section 3.3.3. Serum ferritin was analysed at the Fürst Medical Laboratory in Oslo, Norway by an immunoturbidimetric method using an Advia Chemistry XPT system (Siemens Medical Solutions Diagnostica). The CV for serum ferritin concentration was 2.5%.

3.4 Statistical analyses

Prior to statistical analyses, a plan of analysis was made for each paper by the author of this thesis with input from the co-authors. Data management and statistical analyses were performed in Statistical Package for the Social Sciences (SPSS) for Windows, version 25 and version 26 (IBM Corporation; Armonk, NY).

Variables were tested for normality by visual inspection of Q-Q plots and histograms, and by using the Kolmogorov-Smirnov test. Descriptive results were reported as proportions (*n* and %) for categorical variables and mean, median or percentiles as appropriate for continuous variables. If the specific statistical model required normality of a variable, the variable was log2 transformed in the analyses.

In Paper I, the following statistical analyses were used to assess validity and reproducibility of the I-FFQ; Wilcoxon signed-rank test, Spearman's rank order

correlation coefficient (Spearman's rho), Bland-Altman plots, Cohen's weighted kappa (k_w) and linear regression models.

In Paper II, the associations between maternal UIC:Cr, iodine intakes and iodine supplement use with thyroid function (TSH, fT3, fT4) were estimated using multiple Generalized Estimating Equation models (GEEs).

In Paper III, the associations between infant UIC, maternal predictors of iodine status (UIC:Cr, iodine intake and BMIC) and infant thyroid hormone function (TSH, fT3, fT4) were estimated using linear mixed models.

More information regarding the statistical analyses has been published in Papers I–III.

3.5 Literature search

In order to be updated on relevant literature, a literature search was performed in PubMed before writing the specific articles. The following search strategies were performed for the specific articles:

- Paper I: (iodine) AND (food frequency questionnaire OR FFQ)
- Paper II: (iodine intake OR iodine status OR urinary iodine concentration) AND (pregnancy OR pregnant OR lactation OR lactating OR postpartum OR postpartum OR fertile)
- Paper III: (iodine intake or iodine status OR urinary iodine concentration OR UIC) AND (infant or infancy or child or childhood)

The records resulting from the literature searches were screened by title and abstract and relevant papers were imported to EndNote. In addition, to be updated on new literature, the author of this thesis subscribed to weekly email updates from PubMed from the following literature search:

- (iodine intake OR iodine status)

Additionally, relevant papers, reports and books from reference lists, newsletters from the Iodine Global Network and colleagues were used.

3.6 The PhD candidate's role in the project

The planning of this study was performed prior to the author of this thesis being included in the project. The data collection occurred between January 2016 to September 2018. The PhD candidate was included in the project as a master student in 2017–2018 and assisted with data collection from August 2017. This involved assisting the study visits and with data collection. Furthermore, the PhD candidate was responsible for data management of all the dietary assessment methods. This included extraction of data from the six-day food diary and 24-h dietary recalls and calculation of iodine intake from the I-FFQ and food diary. The PhD candidate was responsible for and conducted all the statistical analyses in Paper II and Paper III. In Paper I, the statistical analyses were conducted together with the shared first author I.A.

3.7 Ethics

Ethical approval of this study was given by the Norwegian Regional Committees for Medical and Health Research Ethics West (reference REK 2015/879). The study is also registered at ClinicalTrials.gov (NCT02610959) (registered November 15th, 2015). The study was conducted and performed according to the ethical principles in the latest version of the Declaration of Helsinki. Written informed consent was obtained from the participating pregnant women after giving both written and oral information about the study. Participation in the study was voluntary and the participants could withdraw from the study at any time without giving any reason. This was also highlighted in the declaration of informed consent. Provision of biological samples was optional and the mother consented to blood sampling of the infant at every study visit. Biological samples are stored in a research biobank at IMR that expires in 2030. All data from the participants were treated confidentially and analyses was done on de-identified data.

The study was supported by the Norwegian Seafood Research Fund (http://www.fhf.no/) (grant no. 901038). The funder had no role in the design of the study, analysis, interpretation of data or writing of the included papers. The author of this thesis and all co-authors of the papers have reported no conflicts of interest.

4. Summary of results

4.1 Paper I - Validation of an iodine-specific FFQ (I-FFQ)

Specific objective: Assess the validity and reproducibility of an I-FFQ developed for pregnant women.

4.1.1 Main results

In this paper, we assessed the validity and reproducibility of an I-FFQ that was completed by 124 pregnant women at gestational week 18. The validity of the I-FFQ was assessed against the reference methods a six-day structured food diary and the biomarker UIC (pooled sample of spot UIC from six consecutive days). There was a strong correlation between estimated total iodine intake from the I-FFQ and the food diary (r= 0.62, P< 0.001) and an acceptable correlation between the I-FFQ and UIC (r= 0.21, P= 0.018). In Cohen's weighted kappa analyses, the agreement between calculated iodine intake from the I-FFQ and the food diary was moderate-to-substantial (k_w= 0.60) and 89% of the women were classified into the same (47%) or adjacent (42%) quartile of intake. A fair agreement was seen between the I-FFQ and UIC (k_w= 0.21). The estimated iodine intake calculated from I-FFQ was slightly higher compared to the food diary (mean absolute difference: 33 µg/day). Few participants, however, fell outside the limits of agreement from the Bland-Altman plot (6.5%).

Reproducibility was assessed by comparing the I-FFQ completed in gestational week 18 with the same I-FFQ completed in gestational week 36 in a subsample of the study population (n= 47). There was no difference between the estimated total iodine intake at the two time points (mean absolute difference: 3 µg/day) and there was a strong correlation (r= 0.63, P< 0.001) between them.

In conclusion, the results indicate that the I-FFQ can be used as a valid tool to estimate and rank iodine intake among pregnant women in Norway and, possibly, in other population groups with similar dietary patterns.

4.2 Paper II - Iodine nutrition and thyroid function in pregnant and postpartum women

Specific objective: Explore whether iodine nutrition (UIC and iodine intake) and timing of iodine supplement initiation were associated with altered thyroid function in mildly-to-moderately iodine-deficient pregnant and postpartum women.

4.2.1 Main results

Associations between maternal UIC:Cr, iodine intake and iodine supplement use and thyroid hormone function (TSH, fT3 and fT4) were estimated using GEE models including data from up to four time points (gestational weeks 18 and 36 and 3- and 6 months postpartum).

UIC:Cr (per 100 μg/g) was negatively associated with fT3 (β= -0.191, 95% CI: [-0.331, -0.051]) and fT4 (β= -0.756, 95% CI: [-1.372, -0.141]) concentrations. Iodine intake (per 100 μg/day) was positively associated with TSH (β= 0.099, 95% CI: [0.022, 0.177]), and negatively associated with fT3 (β= -0.084, 95% CI: [-0.0141, -0.027]) and fT4 (β= -0.390, 95% CI [-0.599, -0.182]) concentrations.

Compared with no use of supplement, participants initiating an iodine-containing supplement before conception and continuing through pregnancy had lower concentrations of TSH (estimated means: 1.35 compared with 1.68 mIU/L, *P*= 0.021) and higher concentrations of fT3 (4.48 compared with 4.28 pmol/L, *P*= 0.035) and fT4 (15.2 compared with 14.4 pmol/L, *P*= 0.024). This association was not seen for those initiating an iodine-containing supplement after the conception of pregnancy.

In conclusion, in this mild-to-moderate iodine deficient population, the results indicate that lower iodine availability during pregnancy and postpartum was associated with lower TSH, and higher fT3 and fT4 concentrations. When comparing the timing of iodine supplement initiation, however, compared with no use of supplement, those initiating an iodine-containing supplement pre-pregnancy and continuing through pregnancy had lower TSH, and higher fT3 and fT4 concentrations, which might suggest improved thyroid function.

4.3 Paper III - Infant iodine status and thyroid function

Specific objective: Describe infant iodine status and thyroid function and explore associations between them in the first year of life. In addition, assess the impact of maternal iodine nutrition and breastfeeding status on infant iodine status.

4.3.1 Main results

Infant spot UIC was measured at ages 3, 6 and 11 months. The median UIC was below the recommended WHO cut-off (100 µg/L) at age 3 months with a median UIC of 82 µg/L, indicating insufficient iodine status at a group level. At ages 6 and 11 months the median UIC was 110 µg/L, indicating adequate iodine status. Median BMIC was 76 µg/L 3 months postpartum.

Infant thyroid function (TSH, fT3 and fT4) was measured at ages 3 and 6 months. The prevalence of thyroid dysfunction was low and no associations between infant UIC nor BMIC and infant thyroid function tests (TSH, fT3 and fT4) were found.

Infant UIC was positively associated with maternal UIC:Cr (β= 0.33, 95% CI: [0.12, 0.54], *P*= 0.002), maternal iodine intake (β= 0.30, 95% CI= [0.18, 0.42], *P*< 0.001) and BMIC (β= 0.46, 95% CI= [0.13, 0.79], *P*= 0.006).

At ages 3 and 6 months, breastfed infants had a lower median UIC (76 and 105 µg/L, respectively) compared with formula-fed infants (190 and 315 µg/L, respectively) (*P* <0.001). At age 11 months, no differences were found between the breastfeeding status categories.

In conclusion, the results indicate that breastfed infants relying on maternal iodine intake are vulnerable to insufficient iodine status in the first months of life. In contrast, weaned and formula-fed infants are less vulnerable to iodine deficiency considering that iodine intake is introduced through complementary foods and formula.

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

This thesis comprises three papers, all of which were based on data from the 'Mommy's Food' study. This was originally a two-armed RCT with dietary cod during pregnancy (from gestational weeks 20-36) where the primary outcomes were maternal UIC after the intervention (gestational week 36) and child neurodevelopment at 11 months of age (155). The papers in the current thesis were secondary analyses of the study and the data were analysed in a cohort design, as cross-sectional and longitudinal observational data. The majority of decisions regarding study design have consequently been based on the primary outcomes of the 'Mommy's Food' study and not necessarily the outcomes included in this thesis, which further is a limitation. However, the study was designed to focus on iodine status and thyroid function during pregnancy and postpartum. Hence, most of the decisions regarding the study design and data collection methods reflect the aims of this thesis. Furthermore, when conducting human studies, this demands significant resources. Thus, using secondary data from a study avoids having to collect new data and many resources are saved. For ethical reasons, one should also utilise all relevant data from a research project as the participants have dedicated a lot of time and effort to the project (164).

Cross-sectional and longitudinal observational data were used in this thesis. Observational data are used to describe associations between exposures and outcomes (165). However, observational data cannot directly establish causal relationships as the observed effect measures may be biased due to confounding (166). A confounding factor is a third variable that is associated with both the exposure and the outcome variable and further distorts the association between them (167). Bias refers to all errors that deviate the observed value from the true value causing a systematic difference of results from the truth (156). Further, this may increase the risk of an incorrect estimate of the association between the exposure and outcome (168). Both bias and confounding threaten the *internal validity* of a study; which is the extent to how accurately a study

measures what it is intended to measure (156). Observational studies are particularly susceptible to the effects of bias and confounding (168) and, accordingly, the results of observational studies should be interpreted in light of these limitations.

The participants of the current study were followed-up in in a cohort design and data were collected from five different time points during pregnancy and postpartum. This gave us the opportunity to use data from several different time points and, in Paper II and Paper III, the data were analysed in repeated measurement analyses. As opposed to cross-sectional data, the use of repeated measurements increases the precision of the estimated effects measures which further increases the power to detect potential associations (169). Furthermore, it reduces the consequences of intra-individual variability and the risk of *regression to the mean* (extreme values are followed by measurements that are closer to the mean on the next time point) (168). This is because repeated measurements provide a more realistic distribution when there is a substantial variability in the measurements and avoids overestimating the tails, further, providing a more accurate estimate of the true value (170). Accordingly, the use of repeated measurement analyses is a considerable strength of this thesis.

5.1.2 Study population

The source population of this study was pregnant women in the area of Bergen, Norway. Concurrently, the target population was considered to be all pregnant women in Norway and in countries with similar dietary patterns and iodine nutrition status. Selection bias occurs when the study population does not represent the target population and there is a systematic difference between them (168). Therefore, any factors that affect the inclusion of participants at the beginning of a study might introduce selection bias (171). For example, a well-known problem is that participants volunteering for studies tend to be healthier than the general population, also known as the *healthy volunteer effect* (168). In this study, the participants had a similar age to other primiparous women in Norway (172). On the contrary, compared with similar population groups in Norway, they had a higher level of education (173), a lower prevalence of overweight and obesity (174) and reported lower nicotine use (175, 176). Furthermore, we only recruited participants from one area in Norway. Consequently,

the study population may not be entirely representative of the target population which may limit the generalisability of the study. Cohort studies are also vulnerable to selection bias over time as a result of withdrawal and loss to follow-up (177). If a distinct group of the participants (e.g. those with lower education or those with high or low exposure status) are lost to follow-up, attrition bias may occur (171, 178). In our study, however, there were no differences between completers and non-completers of the study in either participant characteristics, measurements of iodine nutrition or thyroid function tests measured at baseline (gestational week 18) (data not shown). Hence, proposing the participants to be missing at random. Also, the follow-up rate was rather high as more than 80% of the participants completed the study, which is very good considering acceptable follow-up rates (179). Nevertheless, all the above-mentioned factors may have contributed to selection bias in our study. However, even though some selection bias is present, it does not necessarily introduce bias in the exposure-outcome associations or threaten the internal validity of the study (180).

5.1.3 Quality of data

The methods and data in a study is considered *valid* if the study measures what it is intended to measure and there are no errors in the way the data are collected, analysed or interpreted (171). The term *reliability* is used when the measures and data collected can produce consistent results over time when the measurement is repeated (181). Both random and systematic errors may occur during data collection, which is also referred to as information bias (168). These errors may threaten the validity and reliability of a study. Information bias and the quality of data used in this thesis will be discussed in the following sections.

UIC and UIC:Cr

Spot urine samples were used to measure maternal and infant UIC and UIC:Cr. The use of spot urine samples to measure iodine status poses several limitations; as iodine is excreted within 24-48 hours, one spot UIC only reflects recent iodine intake (58). Also, dietary iodine intake may vary from day to day and spot samples do not account for this variability (70). Furthermore, hydration status may also lead to day-to-day and within-day variations of UIC (182). Taken together, the mentioned limitations cause

inter- and intraindividual variations and UIC from one spot sample is not suitable to determine individual iodine status. However, in this study, we used six spot urine samples during pregnancy. This is a substantial strength because it reduces the day-to-day variation and, particularly, the intra-individual variability of UIC. However, it has been suggested that ≥10 spot urine samples are needed to reliably estimate individual iodine status (57). Owing to a potential large burden for the participants, this was not prioritised in the current study. Nevertheless, such an assessment would have been useful particularly when exploring associations between UIC and thyroid function. In Paper III, infant UIC was only measured with one spot sample, thus, the individual UIC was subjected to a large probability of measurement error. No associations were found between infant UIC with infant thyroid function. Nevertheless, as the thyroid can store iodine for ~3 months and the intrathyroidal iodine stores act as a buffer, one might only expect an association in the participants with a stable low UIC (183). Consequently, this may be one potential reason for why we did not observe any association between infant UIC and thyroid function; a result of random measurement errors (from spot UIC samples) that cause *regression dilution bias* (regression coefficient biased towards the null) (184). One strategy to cope with measurement errors and regression dilution bias is to obtain repeated measurements from an individual (184). In Paper II and Paper III, we used repeated measurement models to explore the associations between UIC and thyroid function. In Paper II, each woman had up to four repeated measurements on different time points, while in Paper III, the infant had up to two measurements of UIC and thyroid function. Two individual measurements from the infants, however, may not have been sufficient to cope with the potential regression dilution bias.

Even though spot UIC is not suitable for measuring individual iodine status, median UIC in a group provides an adequate estimate of iodine status in a population (8). It has been suggested that approximately 100 individuals are required from each subgroup to estimate iodine status in a population (65). Accordingly, our study was considered sufficient to reliably estimate iodine status in pregnant and postpartum women and infants at a group level by using median UIC.

In Paper II and Paper III, urinary iodine was expressed as both UIC and UIC:Cr. Creatinine excretion in urine is relatively constant (~1 g/24 h in adults) and using UIC:Cr can reduce the variability in UIC as it accounts for hydration status (60). However, creatinine excretions have also been found to vary with gender, age, BMI, ethnicity and protein intake (61) and use of creatine adjusted UIC may introduce another source of error in the estimation (62). However, in our study, the population was a rather homogenous population according to age, BMI and nutritional status. We therefore decided to present maternal iodine status as both UIC and UIC:Cr in Paper II and Paper III. In Paper I, when assessing the validity of the I-FFQ, only UIC was presented and not UIC:Cr. This decision was based on previous validation studies (185-187) where none of them used UIC:Cr. In hindsight, it would have been a strength to use both UIC and UIC:Cr in Paper I. **Table 7** gives the correlation coefficient between UIC, UIC:Cr with estimated iodine intake calculated from the I-FFQ and the food diary. The correlation coefficients were considerably higher when using UIC:Cr compared with only UIC. Furthermore, the coefficients of associations in Paper II and Paper III were also greater when using UIC:Cr compared with only UIC. Thus, suggesting that the use of maternal UIC:Cr was a better measure compared with only UIC in this study group. This has also been confirmed in other populations (57, 63-65). In Paper III, UIC:Cr in infants was presented only in Supplementary Data because infant urinary creatinine concentrations can be highly variable and no standardised reference values are available (188).

Table 7. Spearman's rho correlation coefficient between UIC, UIC:Cr and iodine intake calculated from the I-FFQ and the food diary during pregnancy and postpartum

Iodine intake	UIC	UIC:Cr
I-FFQ - GW 18	0.213 (*P*= 0.018)	0.394 (*P*< 0.001)
I-FFQ - GW 36	0.229 (*P*= 0.018)	0.323 (*P*= 0.001)
I-FFQ - 3 M	0.319 (*P*= 0.002)	0.423 (*P*< 0.001)
I-FFQ - 6 M	0.324 (*P*= 0.005)	0.424 (*P*< 0.001)
Food diary - GW 18	0.408 (*P*< 0.001)	0.560 (*P*< 0.001)

I-FFQ, iodine-specific food frequency questionnaire, GW, gestational week, M, months; UIC, urinary iodine concentration, UIC:Cr, urinary iodine-to-creatinine ratio

UIC was analysed with ICP-MS. There are several analytical methods available for analysing UIC, however, ICP-MS is considered to be the 'gold standard' for the measurement of UIC and it has a high degree of accuracy (60). The urine samples were analysed at the IMR, which is an accredited laboratory that regularly participates in quality programmes.

BMIC

BMIC was assessed at 3 months postpartum and included in Paper III. The breastmilk was collected as spot samples, though, similar to UIC, the BMIC is prone to vary from day-to-day and within days (68). The BMIC in our study was assessed by including three spot samples (before, during and after feeding) from two consecutive days (a total of six samples). This may have reduced some of the intra- and inter-variability, however, it is not certain if this was sufficient to assess individual BMIC.

Thyroid function

To assess maternal and infant thyroid function, TSH, fT3 and fT4 were analysed in blood samples. Unfortunately, we did not have the capability to measure thyroid size, Tg, TPOAb or thyroglobulin antibody (TgAb). Compared with TSH, fT3 and fT4, Tg has been shown to be a more sensitive marker of iodine status and it can also reflect longer-term iodine intake (77). Also, some studies have reported that lower iodine status during pregnancy is associated with an increased prevalence of TPOAb or TgAb positivity (189-191). Consequently, the use of Tg, TPOAb and TgAb could have gained a better understanding of the associations between thyroid function and iodine nutrition in this study.

Misclassification bias might have occurred when using reference ranges to classify participants with biochemically-assessed thyroid dysfunction as there is a risk of participants being distributed to an incorrect category (168). For example, the reference range for TSH in pregnancy, derived from the Norwegian MoBa study, was lower than most other reference ranges (161). This may have led to an overestimation of reported overt and subclinical hypothyroidism among the pregnant women in this study. However, this reference range was the most appropriate available, as it is recommended

to use population-, trimester-, and assay-specific reference ranges when these are available (143). Also, in general, the study population had a low prevalence of thyroid dysfunction, and it is not believed that the associations between thyroid dysfunction and measurements of iodine nutrition would have been altered if other reference ranges were available. Individual variations of serum thyroid function tests may have also contributed to a possible misclassification bias (192-194). Furthermore, the thyroid function tests were measured using serum immunoassays and may potentially have under- or overestimated the true concentration due to immunoassay interference (195, 196). However, all samples were measured at the same laboratory, which is an accredited medical laboratory that regularly participates in quality programmes.

Dietary assessment methods

Several methods for dietary assessment are available, all with different strengths and limitations. Though, as stated by George H. Beaton: 'There will always be error in dietary assessments. The challenge is to understand, estimate, and make use of the error structure during analysis' (197).

In this study, an I-FFQ was developed to assess maternal iodine intake during pregnancy and the postpartum period. In Paper I, the validity of the I-FFQ were assessed against a six-day iodine-specific food diary and UIC from the same six consecutive days. *Validity* of a dietary method describes the degree to which the dietary method (e.g., a FFQ) measures what it is intended to measure (e.g., iodine intake) (198). All dietary assessment methods are prone to systematic and random errors, which further may reduce the validity of the methods (197). FFQs are particularly prone to systematic errors related to misreporting (recall bias) (198). The I-FFQ in this study aimed to capture iodine intake retrospectively over a time period of approximately 3-4 months. In a self-administered FFQ that measures long-term dietary intake retrospectively, the participants are challenged with memory, their ability to correctly estimate frequency of consumption and portion sizes, in addition to their competence to consider variations of intake during the past months (199). All of these factors have increased the risk of recall bias when completing the I-FFQ in this study. Additionally, the I-FFQ assessed dietary intake during pregnancy and the postpartum period. This is

often a period where eating habits change (200), which further may increase recall bias when completing an FFQ retrospectively. Another limitation with an FFQ is that people tend to overreport their consumption of healthy food items, a phenomenon known as social desirability bias (201). In addition, recall is also prone to the overestimation of low intakes when asked about several detailed food items separately (162). Even though the total number of food items in the current I-FFQ was lower compared with most other FFQs, the number of questions regarding fish and seafood was substantial (in total 35 detailed questions). Consequently, both social desirability bias and the high number of food items related to fish and seafood in the current I-FFQ may have increased the risk of overestimating iodine intake. This has also been shown in another study estimating iodine intake from an FFQ (202).

In light of the mentioned limitations of FFQs, validation studies are required to evaluate if the dietary method measures what it is intended to measure (e.g., iodine intake) (198). Ideally, the FFQ should be validated for the specific nutrient in the specific population the questionnaire is aimed for (e.g. pregnant women). Generally, validation studies of FFQs assess the extent to which the method agrees with the 'gold standard' or other dietary assessment method, a so-called 'reference method' (80). The most commonly used reference methods are alternative dietary assessment methods known to have less error, e.g., food diary, weighted food record, or 24-hour dietary recall (80). However, no method can measure dietary intake without error (197). Therefore, when using a dietary reference method to evaluate the validity of an FFQ, the relative validity is being assessed rather than the absolute validity (198, 203). In this study, a six-day structured food diary was used as the dietary reference method. Food diaries or weighted food records are generally preferred as reference methods when validating FFQs (80, 198). The strength of a food diary include its prospective design, which reduces the risk of recall bias as it does not rely on memory. Nevertheless, as with all dietary methods, food diaries also pose limitations. Food diaries measure short-term intake over a limited time period (in our study: six days) and are generally more susceptible to day-to-day and seasonal variations compared to FFQs (204). Ideally, the time period of assessment should be the same for both the test method and the reference

method (80). This was not prioritised in our study due to a potentially high participant burden. In most settings, however, a six-day food diary is considered sufficient when validating an FFQ (205).

A common error that is present when calculating dietary intake from both an FFQ and a food diary, is the use of food composition data. Accurate and reliable food composition data is essential for estimating nutrient intake in a population (206). This is particularly challenging when calculating iodine intake, since the iodine content of foods can be highly variable, especially in seafood and milk and dairy products (18, 207). For instance, in a Norwegian study from 2018, the iodine content of Atlantic cod (*n*= 121 samples) varied from 22 to 720 µg/100 g (18). Another challenge is that representative national databases on the iodine content in foods are lacking in many countries (79). In this study, when estimating iodine intake from the I-FFQ and the food diary, we used up-to-date chemical analyses of most food items (18), which further is a considerable strength. Although, the use of fixed values for the iodine content of different food items may have introduced errors when calculating iodine intake.

Another limitation when estimating iodine intake from dietary assessment methods, is that it is difficult to identify all the potential sources of iodine and it is challenging to estimate the amount of iodised salt consumed (13). In the Norwegian diet, however, the contribution of iodised salt is considered insignificant, as the permitted level of iodine is low (5 µg/g). Additionally, there are few available iodine sources in the diet (milk and dairy, fish, eggs, and supplements), which reduces the errors when calculating iodine intake. Thus, the use of dietary assessment methods may be well suited to assess iodine nutrition in the Norwegian population (77).

Even though the agreement between an FFQ and a food diary is acceptable, it does not necessarily indicate validity as both methods are prone to errors (198). The errors present in the FFQ and the reference method should ideally be independent of each other (198). However, this is difficult to ensure, and the errors present in both methods are often correlated. To overcome this problem, the use of a biomarker as an

independent variable may be applied to assess the relative validity of the dietary assessment methods (198). Compared to self-reported dietary data, a biomarker can provide an objective estimate of dietary intake and it is naturally less prone to errors related to misreporting and memory (80). In addition to the food diary, the biomarker UIC (six spot samples from six consecutive days) was used to assess the validity of the I-FFQ. Due to the intra- and inter-variability in UIC, six spot samples may not have been sufficient to capture the habitual iodine intake the I-FFQ intended to cover (3-4 months). Nevertheless, the use of both a biomarker and a dietary reference method to assess the validity of the FFQ is an important strength in this study.

In validation studies of FFQs, reproducibility of the method should always be assessed. The term *reproducibility* refers to whether the method gives the same result in repeated measurements over time (198). We assessed reproducibility by comparing the completed I-FFQ at two different time points during pregnancy (gestational week 18 vs. gestational week 36). In retrospect, we could have assessed the reproducibility during the postpartum period, as maternal iodine intake from the I-FFQ also was assessed 3, 6 and 11 months postpartum. The correlation was acceptable or good when comparing iodine intake from the I-FFQ at gestational week 36 vs. 3 months postpartum (r= 0.33, P= 0.041), 3 months vs. 6 months postpartum (r= 0.59, P< 0.001) and 6 months vs. 11 months postpartum (r= 0.45, P= 0.012). In addition, the I-FFQ showed a similar or better correlation with UIC in the postpartum period vs. pregnancy (**Table 7**). Accordingly, we believe the I-FFQ can be used as a valid and reliable dietary method in the postpartum period as well.

Information regarding breastfeeding status in Paper III was retrieved from 24-h dietary recalls at ages 3 and 6 months. This is also the recommended method to assess breastfeeding rates by the WHO (163). At age 11 months, data of breastfeeding status was obtained from the electronic FFQ. The use of two different dietary assessment methods to assess breastfeeding status may obscure the comparison between the different time points. However, we did not have the possibility to obtain a 24-h dietary recall at age 11 months and the use of an electronic FFQ was considered the subsequent option.

Covariates

Potential covariates associated with the exposure and the outcomes were adjusted for in the statistical analyses to reduce the risk of confounding. However, despite adjusting for potential confounding factors, the risk of *residual confounding* (measurement errors of covariates) or *unmeasured confounding* (potential covariates not included) cannot be excluded (208). For example, we did not measure selenium status in the current study, which also is an essential trace element important for optimal thyroid function (209). An association between selenium and iodine in thyroid hormone synthesis has also been proposed (210) and low selenium status has been associated with increased risk of thyroid dysfunction in iodine deficient postpartum women (211).

5.1.4 Data management and statistical considerations

In Paper I, several statistical approaches were used to assess validity of the I-FFQ. This is considered a strength in validation studies, as it gives a more comprehensive insight into the various aspects of validity (80, 212). A statistical approach we did not use was 'the methods of triads' (213). In this method, there is a triangular comparison between the test method (e.g. I-FFQ), another dietary method considered the reference method (e.g. food diary) and a biomarker (e.g. UIC) where an estimated validity coefficient is calculated. Calculating this later using the methods of triads, the validity coefficient for the I-FFQ was 0.56 (food diary and UIC) and 0.66 (food diary and UIC:Cr). This is in accordance with the other statistical analyses from Paper I and also comparable to other validation studies estimating iodine intake from an FFQ using the methods of triads (186, 187). In retrospect, it would have been favourable to apply these results to Paper I. However, it would not have changed the conclusion of the paper as it only confirmed the previous results.

During data management, continuous variables may be converted to categorical variables as this makes the results easier to interpret and it enables comparisons of groups. However, categorisation of continuous data cause methodological issues as there is a loss of power and a risk of misclassification (214). Because of these limitations, it is in general recommended to keep the continuous exposure variables as

continuous in statistical analyses (215). However, it might be relevant to categorise the outcome variable when established cut-off points are established (216). As previously mentioned, some of the exposure variables (e.g. UIC and iodine intake) in our study are particularly prone to measurement errors and potentially large intra-individual variations. Consequently, categorisation would have increased the risk of misclassification bias. We therefore decided to analyse the continuous exposure variables as continuous data in the statistical analyses.

In Paper II and Paper III, the data were analysed using longitudinal models including data from several time points. Here, the associations between the variables are analysed concurrently at different time points and the dependency of the repeated observations within each subject is accounted for. One of the advantages of these methods is that all available data are analysed and the subject does not have to contribute with data for all time points to be included in analyses (217). In Paper II, the associations were analysed using GEE models, while in Paper III, linear mixed models were used. In linear longitudinal regression analyses, both GEE and linear mixed models produce almost identical results (217). However, if the outcome variable is dichotomous the GEE analysis might be more appropriate to use (217). Paper II also included a dichotomous outcome variable and we therefore decided to use the GEE models in this paper. For continuous outcome variables, even though they produce almost identical results, linear mixed models may be slightly more flexible compared to GEE analysis (217). In Paper III, we therefore decided to analyse data i linear mixed models.

The papers of the current thesis were secondary analyses of data and multiple associations were explored in the different papers. When performing multiple statistical tests from a data set, this increases the probability of detecting false positive results (type I error) (218). Therefore, some argue that multiple comparisons should be adjusted for; for example by decreasing the statistical significance rate. However, adjustments for multiple comparisons will also increase the risk of false negative results (type II error) and reduce the power of the associations (218). Accordingly, we decided to not correct for multiple comparisons.

5.1.5 External validity

External validity refers to the extent that the results can be generalised to the general or target population of the study (171). For a study to be externally valid, it must also be internally valid. However, good internal validity does not necessarily guarantee external validity or generalisability of the study (171). As discussed in section 5.1.2, some selection bias have occurred in the study population. This for the reason that data were only collected from one geographical area and the study population tended to be more educated and healthier compared with the general population in Norway. Nevertheless, previous studies from Norway have not found an association between socioeconomic status and iodine status in pregnant and postpartum women (102-104, 119). Also, previous studies have reported minimal differences in iodine status between different geographical areas of Norway (103, 109). Thus, we believe our results apply to the general population of pregnant and postpartum women and infants in Norway. Furthermore, we believe the results are also relevant and generalisable to other populations with similar dietary patterns and iodine nutrition status.

5.2 Discussion of main findings

5.2.1 Use of an I-FFQ to assess maternal iodine nutrition

In Paper I, we assessed the validity and reproducibility of an I-FFQ developed specifically for estimating iodine intake in pregnant women. **Table 8** gives an overview of the published studies that have previously assessed the validity of iodine intake estimated from an FFQ in pregnant, postpartum and young women of fertile age. To our knowledge, there is only one previous study that has assessed the validity of an I-FFQ that is developed specifically for pregnant women (185). Other validation studies have mainly focused on fertile women (186, 202, 219) or have used a general or full FFQ (220-223). Furthermore, to the best of our knowledge, in addition to the Australian study from Condo et al. (185), Paper I is the only validation study that also has assessed reproducibility of the FFQ and included both a dietary method (food diary) and a biomarker (UIC) as reference methods (**Table 8**).

There was a strong correlation between estimated iodine intake from the I-FFQ and the six-day food diary (r= 0.62). This was mostly higher or comparable to other validation studies (**Table 8**). In addition, the kappa analyses showed substantial agreement between the two methods (k_w= 0.60). However, the estimated iodine intake was slightly higher from the I-FFQ compared to the food diary (mean absolute difference: 33 µg/day). In addition, the Bland-Altman plot showed that there seemed to be a systematic increase in difference between the two methods with an increasing iodine intake. This has also been shown in other studies validating iodine intake from an FFQ (202, 219). Thus, indicating that estimating iodine intake from an FFQ is more challenging when intake is increasing. However, the I-FFQ and the six-day food diary covered different time periods; the I-FFQ was completed retrospectively to give an estimate of the diet over the past 3-4 months, while the food diary was completed day-by-day for a total of six days. Also, the I-FFQ may have covered rarely consumed food items which the food diary did not cover. Accordingly, the difference in intake between the two methods could also indicate a real difference in iodine intake.

Table 8. Studies assessing the validity of iodine intake estimated from an FFQ in pregnant, postpartum and fertile women

Study	Study population	FFQ	Dietary reference method	Biomarker	Reproducibility
Paper I 2019, Norway (224)	Pregnant women, GW 18, *n*= 124	Semi-quantitative iodine-specific FFQ (60 food items)	6-day structured iodine specific food diary • *r*= 0.62 (*P*< 0.001)	UIC (pooled sample of six spot urine samples) • UIC: *r*= 0.21 (*P*= 0.018) • UIC:Cr: *r*= 0.39 (*P*< 0.001)	FFQ GW 36 • *r*= 0.63 (*P*< 0.001)
Glabska 2017, Poland (219)	Women, 20–35 y, *n*= 90	Iodine-specific FFQ (44 food items)	3-day dietary record • *r*= 0.26 (*P*= 0.001)	-	FFQ 6 weeks later • *r*= 0.82 (*P*< 0.001)
Condo 2015, Australia (185)	Pregnant women, GW 28, *n*= 96	Iodine-specific FFQ (44 food items)	4-day weighed food record • *r*= 0.88 (*P*< 0.001)	24-h urinary iodine excretion (UIE) • Iodised salt users: *r*= 0.331 (*P*= 0.028) • Non-iodised salt users: *r*= 0.605 (*P*< 0.001)	FFQ < GW 20 • *r*= 0.62 (*P*< 0.001)
Zhang 2015, China (225)	Pregnant women, GW 12, *n*= 123	Semi-quantitative FFQ (61 food items)	24-h dietary recall x3 • *r*= 0.15 (*P*> 0.05)	-	FFQ 3-4 weeks later • *r*= 0.24 (*P*= 0.01)
Combet & Lean 2014, UK (186)	Women, 19–49 y, *n*= 43	Iodine-specific FFQ (short, ~1 page)	4-day food diary x2 days • *r*= 0.45 (*P*= 0.002)	24-h urinary iodine excretion (UIE) x2 days • *r*= 0.34 (*P*= 0.025)	-
McGowan 2014, Ireland (222)	Pregnant women, GW 12–34, *n*= 130	Full FFQ (170 food items)	3-day food diaries x3 • *r*= 0.33 (*P*= 0.006)	-	-
Brantsæter 2008, Norway (187, 226)	Pregnant women, ~GW 15, *n*= 119	Full FFQ (255 food items)	4-day weighed food record • *r*= 0.48 (*P*< 0.001)	24-h urinary iodine excretion (UIE) • *r*= 0.42 (*P*< 0.001)	-
Mouratidou 2006, UK (223)	Pregnant women, <GW 14, *n*= 123	FFQ (62 food items)	24-h dietary recall x2 • *r*= -0.03 (*P*> 0.05)	-	-
Rasmussen 2002, Denmark (23)	Women, 25–30 y and 60–65 y *n*= 254	Semi-quantitative iodine specific FFQ (53 food items)	4-day weighed food record • *r*= 0.52 (*P*< 0.001)	24-h urinary iodine excretion (UIE) • *r*= 0.66 (*P*< 0.001)	-

r= Spearman rho or Pearson correlation coefficient. FFQ, food frequency questionnaire; GW, gestational week; UIC, urinary iodine concentration

Because of the previous mentioned limitations (section 5.1.3 of dietary assessment methods), an FFQ is not considered appropriate for estimating absolute intake (227). However, an FFQ is suitable for ranking individuals, so that individuals with low intakes can be separated from those with high intakes (227). Also, when studying diet-outcome associations, the ranking of individuals according to their dietary intake is more important than estimating absolute intake (228). Accordingly, the results from Paper I suggest that the I-FFQ can be used as a valid tool to estimate and rank iodine intake in this population group.

Although seldom considered, an estimate of iodine intake using a validated I-FFQ can be used in epidemiological studies investigating associations with relevant outcomes such as thyroid function and neurodevelopment (27). Along with UIC, estimated maternal iodine intake from the I-FFQ was further used in Paper II and Paper III when studying associations with relevant maternal and infant outcomes. The coefficients of associations were fairly similar for both UIC and iodine intake, further suggesting that iodine intake calculated from an I-FFQ can be used as a marker of maternal iodine nutrition. Few previous studies have combined the use of both UIC and dietary iodine intake (229). Iodine intake can complement the use of UIC and using both methods to assess iodine nutrition in pregnant and postpartum population studies has been proposed by others (79, 146, 229). In a recent published systematic review from Monaghan et al. (229), they used both maternal UIC and dietary iodine intake in pregnancy when investigating associations with child neurodevelopmental outcomes. They concluded that dietary intake data may have a stronger association with cognitive outcomes than UIC alone. They further concluded that future studies should place a greater emphasis on the use of both UIC and dietary data as it provides a more robust identification of iodine status. Consequently, the use of both UIC and dietary iodine intake in our study is a considerable strength.

5.2.2 Maternal and infant iodine status

Figure 3 gives maternal and infant UIC during pregnancy and the postpartum period in this study. Among the women, the median UIC was 94 µg/L at gestational week 18, 85 µg/L at gestational week 36, 74 µg/L 3 months postpartum and 84 µg/L 6 months postpartum. The WHO defines insufficient iodine intake in pregnant and lactating women as median UIC <150 and 100 µg/L, respectively (8). Also, even though it is not an established cut-off, a median UIC <100 µg/L can be defined as mild-to-moderate iodine deficiency (59). Median UIC among the women in this study was below 100 µg/L throughout pregnancy and the postpartum period. Accordingly, the women in this study had a median UIC corresponding to mild-to-moderate iodine deficiency. This is comparable to previous studies of pregnant (102, 103) and postpartum women (104, 105) in Norway, confirming iodine deficiency among these population groups.

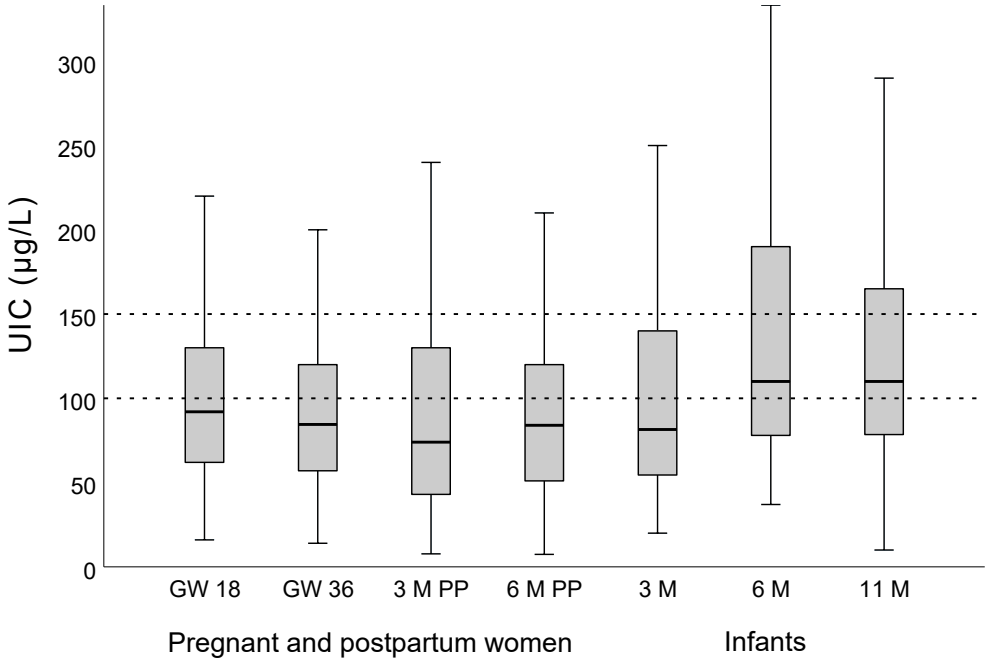

Figure 3. Box plot of maternal and infant urinary iodine concentration (UIC) during the study. The boxes indicate the upper (75th percentile) and lower (25th percentile) quartile, with the thick black line as the median (50th percentile). The dotted lines show UIC= 100 and 150 µg/L.
GW, gestational week; M, months; PP, postpartum

During lactation, iodine is excreted in both urine and breast milk and an assessment of iodine status based only on UIC can be misleading. Thus, BMIC should be measured along with UIC (69). Although no established cut-off value has been determined, a median BMIC of 100-200 µg/L has been suggested as adequate (69). Median BMIC among the lactating women was 76 µg/L at 3 months postpartum, confirming insufficient iodine status in this group.

Median infant UIC was 82 µg/L at age 3 months and below the recommended cut-off from the WHO of 100 µg/L in children <2 years, indicating insufficient iodine status in the first months of life (**Figure 3**). Infant median UIC increased during the first year of life and was 110 µg/L at ages 6 and 11 months, suggesting adequate iodine status at a group level. While several countries lack data on iodine status in the general population and among pregnant women (83), data on infant iodine status in the first year of life are even more sparse (69, 153). **Table 9** gives an overview of studies assessing infant iodine status in the first year of life published after 2010. Most of the studies reported higher infant UIC compared with our study and, except for one study (230), all studies reported adequate infant iodine status (median UIC> 100 µg/L). The reason for the lower infant UIC observed in our study is probably related to lower maternal UIC and BMIC and higher breastfeeding rates. Consequently, we show here that insufficient maternal iodine status postpartum results in insufficient iodine status among breastfed infants in the first months of life. In contrast to our study, a recent study from Norway found that infants (median age 5 months, range 0-12 months) had adequate iodine status with a median UIC of 146 µg/L (108), which also is substantially higher than in our study. Higher iodine status has also been reported in Norwegian toddlers at age 18 months (median UIC 129 µg/L) (109). However, a higher mean age, lower breastfeeding rates and higher iodine intake from complementary foods in the two studies may explain the differences compared with our results.

Table 9. Studies assessing infant and maternal iodine status (median UIC and/or BMIC) in the first year of life

Study	**Age** [a] (months)	**n** [b]	**Infant UIC** (µg/L) [c]	**Maternal UIC/BMIC** (µg/L) [d]
Paper III 2022, Norway	3, 6, 11	108, 90, 91	82, 110, 110	UIC, 3M: 74; 6M: 84 BMIC, 3M: 76
Stråvik 2021, Sweden (231)	4	369	114	BMIC: 77
Prpić 2021, Croatia (232)	3	101	234	UIC: 75 BMIC: 121
Jin 2021, New Zealand (233)	3, 6, 11	67, 43, 33	115, 120, 118	UIC: 82, 85, 95 BMIC: 69, 59, 35
Bakken 2021, Norway (108)	5.5	130	146	UIC: 90 BMIC: 71
Petersen 2020, Iceland (234)	5.5	60	152	BMIC: 84
Wang 2018, China (235)	1, 2, 3	77, 56, 61	251, 183, 164	UIC: 152, 112, 109 BMIC: 222, 175, 148
Nazeri 2018, Iran (236)	2	124	BF: 183 FF: 140	UIC: BF: 78 UIC: FF: 87
Dumrongwongsiri 2018, Thailand (237)	5	48	282	UIC: 149 BMIC: 255
Huynh 2017, Australia (238)	3	628	198	UIC: 125 BMIC: 127
Osei 2016, South Africa (239)	3	100	373	UIC: 118
Gordon 2014, US (240)	2	95	198	Not measured
Andersson 2010, Switzerland (230)	6, 12	279, 228	91, 103	UIC: 75 BMIC (6 M): 51

[a] Mean or median age in months

[b] Number of participants with available data on infant UIC

[c] Median infant UIC

[d] Median maternal UIC or BMIC

BF, breastfed; BMIC, breast milk iodine concentration; FF, formula-fed; UIC, urinary iodine concentration

The WHO recommends exclusively breastfeeding for infants in the first six months of life (241). In this period, the infant is entirely dependent on maternal dietary intake to ensure adequate iodine nutrition and thyroid hormone production (66). In Paper III, we demonstrated that infant UIC was strongly associated with all markers of maternal iodine nutrition, including BMIC, UIC and dietary iodine intake. This is also comparable with other studies (233, 236, 237, 239). Subsequently, our study confirms that maternal iodine nutrition is the most important factor for providing sufficient

iodine status in breastfed infants. However, the coefficients of associations decreased during the first year of life, demonstrating that maternal iodine nutrition is less important when the infant is introduced to other iodine sources than breast milk. We also found that breastfed infants had substantially lower median UIC compared with formula-fed infants at ages 3 months (76 vs. 190 µg/L) and 6 months (105 vs. 315 µg/L). No difference between breastfed and formula-fed infants were seen at age 11 months. This implies that weaned and formula-fed infants are at a lower risk of insufficient iodine status, probably because complementary foods and infant formula seem to secure an adequate intake of iodine. Lower iodine status among breastfed infants compared with formula-fed infants has also been reported in other Norwegian studies (108, 242), in addition to international studies (230, 231, 233, 243).

Measurement of UIC in school-age children (aged 6-12 years) has been the main indicator of assessing iodine status in a country and it has been considered an adequate estimate for the general population (8). In Norway, there are currently no data on this age group, but adequate iodine status has been reported in pre-school children (median age 5 years, median UIC: 132 µg/L) (110) and teenagers (median age 15 years, median UIC: 123 µg/L) (111). Accordingly, also indicating that iodine status is most likely adequate in Norwegian school-age children aged 6-12 years. As we in this study report iodine deficiency among pregnant and postpartum women and infants in the first months of life, we show here that monitoring of iodine status should be performed in the specific population groups considering that several groups are at risk of iodine deficiency even if school-age children have an adequate status. This has also been documented in several other countries (87-91). Furthermore, it should also be noted that the UIC cut-offs from the WHO to assess iodine status in pregnant and lactating women and infants have been debated (60, 69). In addition, the dietary recommendations of iodine intake for pregnant and lactating women and infants vary considerably between organisations and countries (**Table 2**). In order to correctly assess iodine status in a population, current reference ranges and dietary intake recommendations should be coherent and further internationally harmonised.

5.2.3 Iodine nutrition and thyroid function

The effects of mild-to-moderate iodine deficiency are less well documented than those of severe deficiency. The RCTs with iodine supplementation in pregnant women with mild-to-moderate iodine deficiency show no clear evidence on either thyroid function or child development (129-131). However, several observational studies have reported impaired development of the child when mild-to-moderate iodine deficiency is present during pregnancy (119-121, 124, 125). The only known underlying mechanism of iodine deficiency causing impaired development of the child is through inadequate thyroid hormone production (60). When severe iodine deficiency is present in pregnancy and childhood, there is consistent evidence that the cause of impaired neurodevelopment is trough decreased availability of thyroid hormones (60). If mild-to-moderate iodine deficiency also causes impaired development of the child, it would be expected that alterations in thyroid hormone function are also present. However, the observational studies reporting an association between mild-to-moderate iodine deficiency during pregnancy and impaired child development do not report any data on thyroid function (119-121, 124, 125). Furthermore, the findings from observational studies investigating the association between iodine nutrition and thyroid function in mild-to-moderate iodine deficient populations are not consistent. Of the few published studies, some have found an association between mild-to-moderate iodine deficiency and thyroid function in pregnant and postpartum women (158, 189, 244), whereas others have not (245-249). Consequently, the biological mechanism of mild-to-moderate iodine deficiency causing potential neurodevelopmental impairment of the child is not fully explained.

In Paper II, lower maternal iodine availability (measured by dietary iodine intake and UIC:Cr) was associated with lower TSH and higher fT3 and fT4 concentrations. This was rather unexpected, because based on physiological mechanisms one would assume that lower iodine status was associated with lower fT4 and higher TSH concentrations, as this is documented when severe iodine deficiency is present (250). However, the effect on thyroid function during mild-to-moderate iodine deficiency might also differ from severe iodine deficiency. In mild-to-moderate iodine deficiency, the thyroid gland could be able to compensate for the low iodine intake by increasing thyroid activity

(71). This maintains euthyroidism and TSH, fT3 and fT4 often remain in the normal range. In some individuals, however, the increased thyroid activity can lead to thyroid nodularity and autonomy (71). As a result, decreased TSH concentrations may occur in populations with mild-to-moderate iodine deficiency owing to an increase in thyroid nodularity and autonomy which further lowers TSH (251, 252). This may explain why we observed a positive association between iodine intake and TSH concentrations and further a negative association with fT4 concentrations due to the inverse correlation between TSH and fT4. A positive association between iodine status and TSH has also been reported in other pregnant populations (189, 253, 254). In addition, a negative association between iodine status with fT4 has also been found in birth cohorts from Sweden (189) and Norway (158). The two latter studies proposed that this association may be a result of a 'stunning effect' on thyroid hormone production, similar to the Wolff-Chaikoff effect, caused by a rapidly increased iodine intake in pregnancy (255). However, none of the mentioned studies measured pre-pregnancy iodine status or intake, and nor did we. Consequently, we cannot conclude whether it was an abrupt increase in iodine intake when becoming pregnant that caused the inverse association with fT4. However, in our study, the reported use of an iodine-containing supplement increased from 25% pre-pregnancy until 41% in the first part of pregnancy. Accordingly, several of the women in the study most likely increased their total iodine intake when becoming pregnant. The 'stunning effect' on thyroid hormone production has been proposed to be a result of an abrupt increase in iodine intake during pregnancy, for example, after initiation of an iodine supplement during pregnancy (140, 256). This effect is proposed to cause inadequate production of the thyroid hormones (T3 and T4), which additionally results in higher TSH concentrations. The previous mentioned Norwegian birth cohort MoBa also found that initiating iodine supplement use after conception of pregnancy was associated with lower fT4 concentrations, which further may have negative consequences for the developing child (158). Also, other studies have shown that women who started taking iodine-containing supplements in pregnancy had higher TSH concentrations (245, 257, 258). In our study, we found no effect on thyroid function, either beneficial or harmful, if initiating an iodine supplement in pregnancy. However, compared to no use of supplements, use of iodine-

containing supplements before conception and continuing through pregnancy was associated with lower concentrations of TSH and higher concentrations of fT4 and fT3. This result might suggest improved thyroid function when iodine supplementation is initiated before the conception of pregnancy. The prior RCTs with iodine supplementation in mildly-to-moderately iodine-deficient pregnant women found mostly no effect on thyroid function (114, 129, 130, 259, 260). There may be several reasons for the null-findings in the mentioned studies. One reason is that initiation of iodine supplementation after conception of pregnancy may be too late in order to cope with the increased demand of thyroid hormone synthesis. In addition, securement of thyroidal iodine stores prior to pregnancy has been proposed as particularly important (132). Our findings support this notion; however, further studies are warranted.

Another important aspect when studying iodine nutrition and thyroid function in pregnancy is that what we are actually interested in studying, namely foetal thyroid hormone function, is not possible to measure directly. Accordingly, even if previous studies have found inconsistent results between maternal iodine status and thyroid function, the foetal supply of thyroid hormones could be affected (183). The foetal thyroid hormone production begins around gestational week 18-20 (261). However, the transfer of maternal thyroid hormones continues until birth and the foetus is dependent on maternal iodine transfer during the whole pregnancy (261). Additionally, after birth, fully breastfed infants rely on maternal iodine intake for a sufficient production of thyroid hormones (66). In our study, infant thyroid function was measured at ages 3 and 6 months. No associations were found between infant UIC nor BMIC with either TSH, fT3 or fT4. However, thyroid function data were available from only half the infants, further providing low power to detect any potential associations. In addition, UIC was measured with only one spot sample at each time point. As previously mentioned, spot UIC has high intra-individual variation and may not be representative of longer-term iodine intake. Thus, an association with thyroid function may not either be expected. It should also be noted that the prevalence of both maternal and infant biochemically-assessed thyroid dysfunction was rather low and few participants had thyroid function tests outside the reference ranges. Also, no

association between maternal iodine nutrition with thyroid dysfunction was found. Accordingly, we do not know the clinical implications of the observed associations between maternal iodine nutrition and thyroid function. However, in previous observational studies, reduced maternal fT4 concentrations during pregnancy have been associated with reduced child development, lower child IQ and lower child grey matter and cortex volume (133, 262-266). Consequently, our findings may also have importance for child development.

5.2.4 Maternal iodine supplement use

Even though iodine supplementation is recommended in several parts of the world, the benefits of iodine supplementation in mildly-to-moderately iodine-deficient populations of pregnant and lactating women and infants remain unclear (70). A Cochrane review from 2017 assessed the effects of iodine supplementation during the pre-conception, pregnancy and postpartum periods (145). They stated that there is insufficient evidence to conclude whether iodine supplementation has an effect on thyroid function and child development in areas with mild-to-moderate iodine deficiency. This has also been the conclusion in previous systematic reviews (146-149). The currently largest RCT with iodine supplementation in pregnant women with mild-to-moderate iodine deficiency was conducted in India and Thailand from 2018-2011 (130). Supplementing 200 μg iodine/day had no effect on maternal thyroid function or child development. However, the study has been criticised for several limitations; the group of Indian pregnant women were not classified as mild-to-moderate iodine-deficient (median UIC 188 μg/L); the iodine status in the placebo group increased to the lower end of the adequate range; the dose of iodine in the intervention group was relatively high compared to what is considered beneficial in epidemiological studies (200 μg); and the initiation of supplementation may have been too late (> gestational week 11) (132). As previously mentioned, our findings in Paper II support the notion that iodine supplementation should start prior to pregnancy. This has also been supported by other observational studies (158, 258, 267). However, more research is needed to make any conclusion. Optimally, an RCT starting with iodine supplementation pre-conception should be conducted, however, owing to both ethical and feasible considerations this may not be possible. Consequently, cohort studies

starting before conception may be the best available option for filling this knowledge gap.

Even though the benefits of iodine supplementation on thyroid function and child development are unclear, there is indisputable evidence that use of iodine supplementation increases iodine status (130, 136, 259, 268). This was also evident in our study and participants reporting iodine supplement use had higher maternal median UIC at all time points (**Figure 4**). The largest difference was seen at 3 months postpartum where women reporting iodine supplement use had a median UIC of 130 µg/L compared with only 67 µg/L in women reporting no use of supplements (P= 0.002). Maternal iodine supplement use was also associated with higher infant iodine status at age 3 months (**Figure 5**). Here, infants of mothers reporting use of iodine containing supplements had a median UIC of 110 µg/L compared with a median of 71 µg/L in non-users, indicating insufficient iodine status among the non-users (P= 0.008).

In Norway, iodine supplementation is recommended in pregnant and lactating women if intake of dairy products and lean fish is low (< 6 dl milk/yoghurt with a regular intake of lean fish) (144). Consequently, this recommendation will apply to large parts of the pregnant and postpartum population in Norway. The proportion of women taking an iodine-containing supplement was highest in the first part of pregnancy where 41% reported use. This proportion decreased to 28% in the latter part of pregnancy, to 30% at 3 months postpartum and was only 17% at 6 months postpartum. However, the current study was completed before the current recommendation of supplementation in Norway published in 2018. No studies have assessed the use of iodine supplementation in Norway after this recommendation and current use during pregnancy and the postpartum period is not known. Previous studies have reported a low knowledge of iodine among young, pregnant and lactating women in Norway (101, 106, 269). Furthermore, in a recent Norwegian study of lactating women, only 16% of the women reported receiving information from health care professionals about iodine (106). In addition, the guidelines for iodine supplementation in Norway are not well promoted. Consequently, awareness of the current iodine supplementation recommendations is expected to be low in the country.

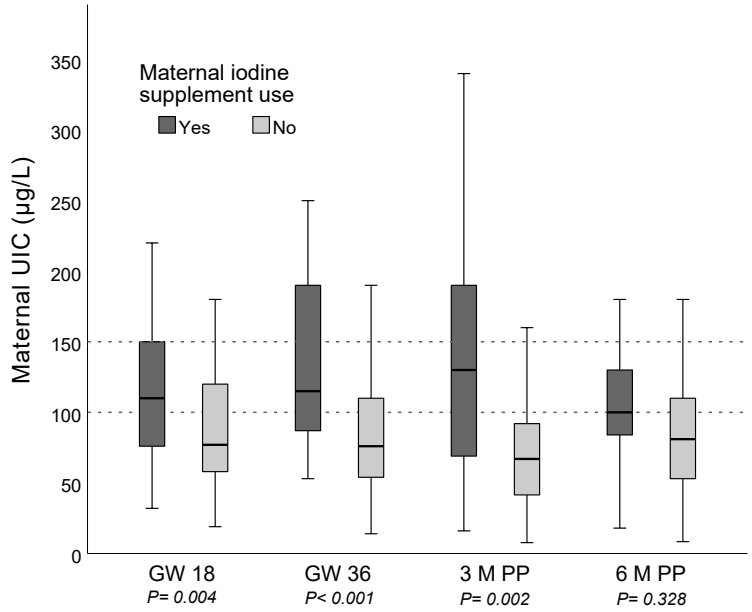

Figure 4. Box plot of maternal UIC by categories of maternal iodine supplement use at gestational week 18 and 36 and 3- and 6 months postpartum.
The dotted lines show UIC= 100 and 150 µg/L. *P*-values indicate differences between groups assessed by independent samples T-test.

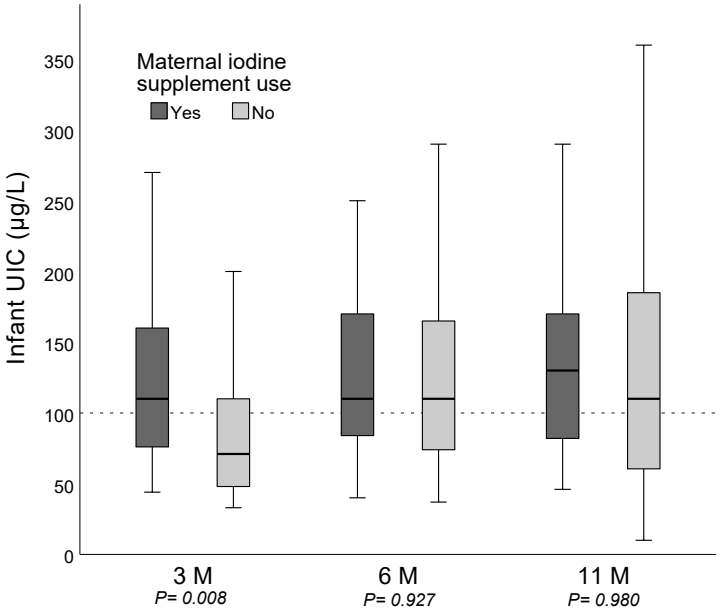

Figure 5. Box plot of infant UIC by categories of maternal iodine supplement use at ages 3, 6 and 11 months.
The dotted line show UIC= 100 µg/L. *P*-values indicate differences between groups assessed by independent samples T-test.

6. Conclusion

This thesis indicates that mild-to-moderate iodine deficiency is prevalent among pregnant and postpartum women in Norway. Furthermore, as a consequence of maternal iodine deficiency, breastfed infants are vulnerable to insufficient iodine intake in the first months of life because they rely on adequate maternal iodine status and sufficient iodine concentration in breastmilk. The results also suggest that, along with UIC, maternal iodine intake estimated from an I-FFQ can be used as a suitable measure of iodine nutrition during pregnancy and in the postpartum period.

Even though iodine deficiency was present, the prevalence of both maternal and infant thyroid dysfunction was low. No associations were found between infant iodine status and thyroid function. However, maternal iodine nutrition was associated with thyroid function during pregnancy and postpartum as lower maternal iodine nutrition was associated with lower TSH, and higher fT3 and fT4 concentrations. This was rather unexpected, nevertheless, similar results have also been found in other pregnancy cohorts with mild-to-moderate iodine deficiency. When comparing the timing of iodine supplement initiation, however, those initiating an iodine-containing supplement pre-pregnancy and continuing through pregnancy had lower TSH, and higher fT3 and fT4 concentrations, compared with non-supplement users. This latter finding suggests improved thyroid function when iodine supplementation begins pre-pregnancy. The results further support the notion that optimisation of iodine intake should start before conception of pregnancy. However, the clinical implications of these findings are not known. Additionally, the study design limits the possibilities of making any causal assumptions.

Overall, to ensure normal thyroid function in the developing foetus and future child, maternal iodine nutrition should be optimised before conception and continued through pregnancy and the postpartum period. Awareness of promoting adequate iodine nutrition for these vulnerable population groups should be prioritised to secure sufficient iodine intake for mothers and, subsequently, their infants.

7. Future perspectives

This thesis provides new knowledge in the field of iodine nutrition and thyroid function during pregnancy, the postpartum period and in infancy. However, the consequences of mild-to-moderate iodine deficiency in these population groups are still not clear and more research is needed. In addition, it is still uncertain evidence whether iodine supplementation among these groups is beneficial, even though this is recommended by several authorities and countries. Optimally, a double-blinded RCT with iodine supplementation during pregnancy, starting before conception, in a group with a median UIC of 50-100 µg/L, should be performed. However, given the current public health recommendations of iodine supplementation this may not be possible owing to ethical considerations and the principle of clinical equipoise. If RCTs are not achievable, well-designed cohort studies in a population with mild-to-moderate iodine deficiency could be considered. Ideally, the study should be initiated before conception and continue through pregnancy and the postpartum period. In addition to measuring possible confounding variables, such a study should include appropriate measurements of iodine nutrition, including repeated measurements of UIC and UIC:Cr, BMIC, dietary iodine intake, supplement use and serum Tg. Furthermore, suitable measurements of thyroid function, including TSH, fT3, fT4, TPOAb and TgAb should be included. After birth, the children should be followed-up with measurements of iodine status, thyroid function (including newborn TSH), and an appropriate assessment of neurodevelopment and other birth outcomes.

Finally, in addition to longitudinal studies, cross-sectional studies measuring iodine status in pregnant and postpartum women and infants are important in order to monitor the iodine status of a population and further to evaluate which recommendations and policies the health authorities should prioritise. Current recommendations of iodine supplementation and salt iodisation programmes may change and monitoring iodine status and thyroid function in populations is therefore important. Also, if recommendations are not followed, efforts to promote knowledge about iodine nutrition for both the population and health workers should be enforced.

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Appendix I

Hei! Takk for at du har valgt å være med i prosjektet "Mammas mat".

I denne undersøkelsen vil vi spørre deg blant annet om kostholdet ditt og hvordan du har hatt det siden du ble gravid.

Vi setter veldig stor pris på din deltakelse!

Sjømat

Sjømat

Her vil vi gjerne få informasjon om deler av kostholdet ditt. Ha den **tiden siden du ble gravid** i bakhodet når du fyller ut skjemaet. Vi er klar over at kostholdet varierer fra dag til dag. Prøv likevel så godt du kan å gi et "gjennomsnitt" av ditt matinntak når det spørres om det.

I de første spørsmålene ønsker vi informasjon om ditt inntak av fisk, fiskeprodukter og annen sjømat.

Hvor ofte har du spist fisk, fiskeprodukter eller annen sjømat som varmt måltid siden du ble gravid (gjelder ikke pålegg)?

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/måned	1 gang/uke	2-3 ganger/uke	4 ganger eller mer/uke
Middag	○	○	○	○	○	○
Lunsj	○	○	○	○	○	○

Hvis du spiser fisk, fiskeprodukter eller annen sjømat til middag/varm lunsj, hvor mye spiser du vanligvis?

1 porsjon tilsvarer 150 gram laks, 200 gram torsk, 12 sushibiter, tre fiskekaker, seks fiskeboller, syv fiskepinner eller 2 dl reker u/skall

Vennligst sett 1 kryss per linje.

	½ porsjon eller mindre	1 porsjon	1 ½ porsjon	2 porsjoner	3 porsjoner eller mer
Middag	○	○	○	○	○
Lunsj	○	○	○	○	○

Hvor ofte har du spist følgende sjømat som middag og som varm lunsj siden du ble gravid?

NB Sushi og fiskemat (fiskekaker, fiskeboller o.l.) er egne spørsmål og kommer senere.

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke
Laks, ørret - middag	○	○	○	○	○
Laks, ørret – lunsj	○	○	○	○	○
Torsk - middag	○	○	○	○	○
Torsk - lunsj	○	○	○	○	○
Sei - middag	○	○	○	○	○
Sei - lunsj	○	○	○	○	○
Makrell – middag	○	○	○	○	○
Makrell - lunsj	○	○	○	○	○
Sild - middag	○	○	○	○	○
Sild - lunsj	○	○	○	○	○
Lyr - middag	○	○	○	○	○
Lyr – lunsj	○	○	○	○	○

Du har svart at du spiser laks/ørret til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ○ ½ porsjon eller mindre
- ○ 1 porsjon
- ○ 1 ½ porsjon
- ○ 2 porsjoner
- ○ 3 porsjoner

Du har svart at du spiser laks/ørret til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ○ ½ porsjon eller mindre
- ○ 1 porsjon
- ○ 1 ½ porsjon
- ○ 2 porsjoner
- ○ 3 porsjoner

Du har svart at du spiser torsk til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser torsk til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sei til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sei til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser makrell til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser makrell til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sild til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sild til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser lyr til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser lyr til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke
Lange - middag	○	○	○	○	○
Lange - lunsj	○	○	○	○	○
Kveite - middag	○	○	○	○	○
Kveite - lunsj	○	○	○	○	○
Steinbit - middag	○	○	○	○	○
Steinbit - lunsj	○	○	○	○	○

Du har svart at du spiser lange til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner

- 3 porsjoner

Du har svart at du spiser lange til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser kveite til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser kveite til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser steinbit til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
-

- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser steinbit til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 200 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Sushi og fiskemat (fiskekaker, fiskeboller o.l.)

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke
Sushi - middag	○	○	○	○	○
Sushi - lunsj	○	○	○	○	○
Fiskekaker/-boller/-pudding - middag	○	○	○	○	○
Fiskekaker/-boller/-pudding - lunsj	○	○	○	○	○
Fiskegrateng	○	○	○	○	○
Fiskepinner	○	○	○	○	○
Fiskesuppe	○	○	○	○	○
Klippfisk	○	○	○	○	○

Du har svart at du spiser sushi til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 12 biter.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sushi til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 12 biter.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser fiskekaker/-boller/-pudding til middag. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 3 fiskekaker, 6 fiskeboller eller 3 skiver fiskepudding.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser fiskekaker/-boller/-pudding til lunsj. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 3 fiskekaker, 6 fiskeboller eller 3 skiver fiskepudding.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser fiskegrateng. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 275 gram**.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser fiskepinner. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 7 biter.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser fiskesuppe. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 350 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser klippfisk. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke
Reker	○	○	○	○	○
Krabbe, klokjøtt	○	○	○	○	○
Krabbe, brunmat	○	○	○	○	○
Hummer	○	○	○	○	○
Blåskjell	○	○	○	○	○
Kamskjell	○	○	○	○	○

Du har svart at du spiser reker. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 250 gram reker med skall.**

- ½ porsjon eller mindre

- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser klokjøtt av krabbe. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser brunmat av krabbe. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser hummer. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 150 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser blåskjell. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 115 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon

- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser kamskjell. Hvor stor porsjon spiser du vanligvis? **Én porsjon = 115 gram.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Har du spist annen sjømat som middag eller varm lunsj siden du ble gravid?

- Nei
- Ja

Vennligst oppgi hva slags fisk du har spist som middag og som varm lunsj siden du ble gravid

1 porsjon tilsvarer 150 gram laks, 200 gram torsk, 12 sushibiter, tre fiskekaker, seks fiskeboller, syv fiskepinner eller 2 dl reker u/skall

	Sjeldnere enn 1 gang/måned	1-3 ganger/måned	1-2 ganger/uke	3 ganger eller mer/uke	½ porsjon eller mindre	1 porsjon	1 ½ porsjon	2 porsjoner	3 porsjoner
1.									
2.									
3.									

Hvor ofte bruker du fisk, fiskeprodukter eller annen sjømat som pålegg, i salat, mellommåltid, snacks eller lignende?

- Aldri
- Sjelden
- 1-3 ganger/måned
- 1-2 ganger/uke
-

- 3-5 ganger/uke
- Mer enn 5 ganger/uke

Hvis du bruker fisk, fiskeprodukter eller annen sjømat som pålegg, i salat, mellommåltid, snacks eller lignende, hvor mye spiser du vanligvis?

1 porsjon tilsvarer for eksempel èn skive røkelaks, makrell i tomat til èn skive, kaviar til èn skive, èn fiskekake eller 2 dl reker u/skall

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Hvor ofte har du spist følgende fisk, fiskeprodukter eller annen sjømat som pålegg, i salat, mellommåltid, snacks eller lignende siden du ble gravid?

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke
Makrell på boks (alle typer)	○	○	○	○	○
Laks på boks	○	○	○	○	○
Tunfisk på boks	○	○	○	○	○
Røkt laks, ørret	○	○	○	○	○
Gravet laks, ørret	○	○	○	○	○
Sild (sursild, rømmesild, kryddersild el.lign.)	○	○	○	○	○
Kaviar	○	○	○	○	○
Peppermakrell	○	○	○	○	○
Reker (ikke rekesalat)	○	○	○	○	○
Sardin på boks	○	○	○	○	○
Ansjos	○	○	○	○	○
Crabsticks	○	○	○	○	○
Svolværpostei	○	○	○	○	○
Lofotpostei	○	○	○	○	○

Du har svart at du spiser makrell på boks. Hvor stor porsjon spiser du vanligvis? **Én porsjon = makrell på boks til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser laks på boks. Hvor stor porsjon spiser du vanligvis? **Én porsjon = laks på boks til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser tunfisk på boks. Hvor stor porsjon spiser du vanligvis? **Én porsjon = én spiseskje tunfisk.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser røkt laks/ørret. Hvor stor porsjon spiser du vanligvis? **Én porsjon = én oppskåret skive laks/ørret.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser gravet laks/ørret. Hvor stor porsjon spiser du vanligvis? **Én porsjon = én skive gravet laks/ørret.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sild. Hvor stor porsjon spiser du vanligvis? **Én porsjon = sild til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser kaviar. Hvor stor porsjon spiser du vanligvis? **Én porsjon = kaviar til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser peppermakrell. Hvor stor porsjon spiser du vanligvis? **Én porsjon = pepper-/kaldrøkt/varmrøkt makrell til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser reker som pålegg. Hvor stor porsjon spiser du vanligvis? **Én porsjon = reker til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser sardiner på boks. Hvor stor porsjon spiser du vanligvis? **Én porsjon brisling = brisling til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser ansjos. Hvor stor porsjon spiser du vanligvis? **Én porsjon ansjos = ansjos til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser crabsticks. Hvor stor porsjon spiser du vanligvis? **Én porsjon crabsticks = 4 stk crabsticks.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
-

- 3 porsjoner

Du har svart at du spiser svolværpostei. Hvor stor porsjon spiser du vanligvis? **Én porsjon = postei til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har svart at du spiser lofotpostei. Hvor stor porsjon spiser du vanligvis? **Én porsjon = postei til én brødskive.**

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Er det andre typer fisk, fiskeprodukter eller sjømat som du har spist som pålegg, i salat, mellommåltid, snacks eller lignende siden du ble gravid?

- Nei
- Ja

Vennligst spesifiser hvilke typer fisk du har spist hvor ofte og hvor mye

1 Porsjon tilsvarer for eksempel èn skive røkelaks, makrell i tomat til èn skive, kaviar til èn skive, èn fiskekake

	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke	½ porsjon eller mindre	1 porsjon	1 ½ porsjon	2 porsjoner	3 porsjoner
1.	○	○	○	○	○	○	○	○	○

	Sjeldnere enn 1 gang/måned	1-3 ganger/ måned	1-2 ganger/uke	3 ganger eller mer/uke	½ porsjon eller mindre	1 porsjon	1 ½ porsjon	2 porsjoner	3 porsjoner
2.	○	○	○	○	○	○	○	○	○
3.	○	○	○	○	○	○	○	○	○

Spiser du fiskerogn eller fiskelever?

- ○ Nei
- ○ Ja

Hvor mange ganger per år spiser du fiskeinnmat?

Vennligst sett 1 kryss per linje.

	Aldri	1-3 ganger/år	4-6 ganger/år	7-9 ganger/år	≥ 10 ganger/år
Fiskerogn	○	○	○	○	○
Fiskelever	○	○	○	○	○

Eventuelle kommentarer til spørsmålene om fisk, fiskeprodukter og sjømat

Melk og Meieriprodukter

Melk og meieriprodukter

I de neste spørsmålene ønsker vi informasjon om ditt inntak av melk og meieriprodukter. Vi minner om at du skal ha **tiden fra du ble gravid** i tankene når du svarer på spørsmålene.

Hvor ofte har du spist og/eller drukket meieriprodukter (melk, yoghurt, ost e.l.) siden du ble gravid? Ikke ta med melk du eventuelt bruker i kaffe/te.

- Aldri
- Sjeldnere enn 1 gang/uke
- 1-3 ganger/uke
- 4-6 ganger/uke
- 1 gang hver dag
- 2 ganger/dag
- 3-4 ganger eller mer/dag

Hvor mange ganger har du drukket følgende melke- og meieriprodukter og/eller brukt det i frokostblandinger/grøt siden du ble gravid?

Ta med laktosefri og laktosereduserte produkter.

NB Ikke ta med bruk av melk i kaffedrikker (kommer som eget spørsmål).

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/uke	1-3 ganger/uke	4-6 ganger/uke	1 gang/dag	2 ganger/dag	3-4 ganger eller mer/dag
Helmelk	○	○	○	○	○	○	○
Lettmelk	○	○	○	○	○	○	○
Ekstra lett melk	○	○	○	○	○	○	○
Skummet melk	○	○	○	○	○	○	○
Melk med smak (f.eks sjokomelk, jordbærmelk)	○	○	○	○	○	○	○
Syrnet melk naturell	○	○	○	○	○	○	○
Syrnet melk med smak	○	○	○	○	○	○	○
Yoghurt (alle typer)	○	○	○	○	○	○	○
Drikkeyoghurt	○	○	○	○	○	○	○
Smoothie med melk	○	○	○	○	○	○	○
Geitemelk	○	○	○	○	○	○	○

Du har krysset av for at du har drukket helmelk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer f.eks. 1,5 dl (lite glass) eller et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner

- 3 porsjoner

Du har krysset av for at du har drukket lettmelk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket ekstra lett melk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket skummet melk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket melk med smak. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket syrnet melk naturell. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket syrnet melk med smak. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist yoghurt. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket drikkeyoghurt. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket smoothie med melk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har drukket geitemelk. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Har du drukket eller brukt andre typer melke- og meieriprodukter i frokostblandingen/grøt siden du ble gravid (f.eks. melk fra ris, havre, soya)?

- Nei
- Ja

Vennligst spesifiser

1 porsjon tilsvarer 1,5 dl (lite glass), et lite beger yoghurt. Ta med laktosefri og laktosereduserte produkter.

NB Ikke ta med bruk av melk i kaffedrikker (kommer som eget spørsmål).

	Sjeldnere enn 1 gang/uke	1-3 ganger/uke	4-6 ganger/uke	1 gang/dag	2 ganger/dag	3-4 ganger eller mer/dag	½ porsjon eller mindre	1 porsjon	1 ½ porsjon	2 porsjoner	3 porsjoner
1.	○	○	○	○	○	○	○	○	○	○	○
2.	○	○	○	○	○	○	○	○	○	○	○
3.	○	○	○	○	○	○	○	○	○	○	○

Hvor ofte har du vanligvis drukket kaffe siden du ble gravid?

- ○ Aldri
- ○ Sjeldnere enn 1 gang/uke
- ○ 1-3 ganger/uke
- ○ 4-6 ganger/uke
- ○ 1 gang/dag
- ○ 2 ganger/dag
- ○ 3-4 ganger eller mer/dag

Hvor ofte har du vanligvis drukket te siden du ble gravid?

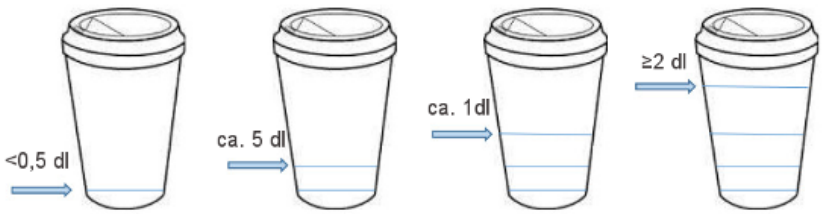
- ○ Aldri
- ○ Sjeldnere enn 1 gang/uke
- ○ 1-3 ganger/uke
- ○ 4-6 ganger/uke
- ○ 1 gang/dag
- ○ 2 ganger/dag
- ○ 3-4 ganger eller mer/dag

Bruker du melk i kaffe/te (gjelder kun kumelk)?

- ○ Nei
- ○ Ja

Hvor mye melk bruker du vanligvis i hver kopp kaffe/te?

	Drikker ikke	< 0,5dl	ca 0,5dl	ca 1dl	≥ 2dl
Kaffe	○	○	○	○	○
Te	○	○	○	○	○



Hvor ofte spiser du følgende meieriprodukter? Gjelder også økologiske og laktosefri og/eller – reduserte varianter. Ta med det du bruker i taco, i lasagne, på pizza og i annen matlaging.

Vi minner om at du skal ha **tiden fra du ble gravid** i tankene når du svarer på spørsmålene.

Vennligst sett 1 kryss per linje.

	Aldri	Sjeldnere enn 1 gang/uke	1-3 ganger/uke	4-6 ganger/uke	1 gang/dag	2 ganger/dag	3-4 ganger eller mer/dag
Hvitost (f.eks. Jarlsberg, Norvegia, Synnøve Finden gulost)	○	○	○	○	○	○	○
Hvit geitost (f.eks Chevre, Ekte hvit geitost, Snøfrisk)	○	○	○	○	○	○	○
Brunost (f.eks Gudbrandsdals-, Fløtemys-, Millom, Heidalsost)	○	○	○	○	○	○	○
Brun geitost (Ekte Geitost)	○	○	○	○	○	○	○
Myke oster (f.eks Brie, Camberbert)	○	○	○	○	○	○	○

	Aldri	Sjeldnere enn 1 gang/uke	1-3 ganger/uke	4-6 ganger/uke	1 gang/dag	2 ganger/dag	3-4 ganger eller mer/dag
Smøreoster (f.eks Kremost, Tubeost, Philadelphia)	○	○	○	○	○	○	○
Osteprodukter på boks (f.eks Cottage cheese, Kesam/Kvarg)	○	○	○	○	○	○	○
Meieriprodukter på boks (rømme, crème fraiche)	○	○	○	○	○	○	○
Melkebasert mat som saus, suppe, gryte el.	○	○	○	○	○	○	○
Melkebasert mat som pannekaker, vafler, sveler el.	○	○	○	○	○	○	○
Is, vaniljesaus e.l (fløte/yoghurt/melkebasert)	○	○	○	○	○	○	○

Du har krysset av for at du har spist hvitost. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer skivet ost til én brødskive.

- ○ ½ porsjon eller mindre
- ○ 1 porsjon
- ○ 1 ½ porsjon
- ○ 2 porsjoner
- ○ 3 porsjoner

Du har krysset av for at du har spist hvit geitost. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer skivet ost til én brødskive eller smøreost til én brødskive.

- ○ ½ porsjon eller mindre
- ○ 1 porsjon
- ○ 1 ½ porsjon
- ○ 2 porsjoner
- ○ 3 porsjoner

Du har krysset av for at du har spist brunost. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer skivet ost til én brødskive eller smøreost til én brødskive.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist brun geitost. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer skivet ost til én brødskive eller smøreost til én brødskive.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist myke oster. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer skivet ost til én brødskive, smøreost til én brødskive, én mozerella.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist smøreoster. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer smøreost til én brødskive.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist osteprodukter på boks. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer én dl cottage cheese/kesam.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist meieriprodukter på boks. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer én spiseskje rømme / crème fraiche.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist melkebasert mat som saus, suppe, gryte el.. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer én dl melkebasert saus/suppe/gryte.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist melkebasert mat som pannekaker, vafler, sveler el.. Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer én pannekake eller én vaffel.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Du har krysset av for at du har spist is, vaniljesaus e.l (fløte/yoghurt/melkebasert). Hvor stor er porsjonen vanligvis?

1 porsjon tilsvarer én dl melkebasert saus/suppe/gryte eller én kule is.

- ½ porsjon eller mindre
- 1 porsjon
- 1 ½ porsjon
- 2 porsjoner
- 3 porsjoner

Hvor mange egg spiser du per uke? (Stekt, kokt, eggerøre, omelett)

Egg i bakverk skal ikke tas med.

- Mindre enn 1 egg/uke
- 1 egg/uke
- 2-3 egg/uke
- 4-5 egg /uke
- 6-7 egg/uke
- 8 eller flere egg/uke

Kosttilskudd

Kosttilskudd

I den siste delen av spørsmål om kostholdet ønsker vi informasjon om eventuelle kosttilskudd. Vi minner om at du skal ha **tiden fra du ble gravid** i tankene når du svarer på spørsmålene.

Tar du et komplett tilskudd for gravide (med omega-3, vitaminer og mineraler)**?**

- ○ Nei
- ○ Ja

Hvor ofte tar du kosttilskudd for gravide?

	Bruker ikke	1-3 ganger/uke	4-6 ganger/uke	Daglig
Lifeline Care Gravid	○	○	○	○
Nycoplus Care Gravid	○	○	○	○
Annet, spesifiser:	○	○	○	○

Bruker du annet kosttilskudd?

Kryss av på aktuelle alternativer (maks. 1 kryss per linje)

	Bruker ikke	1-3 ganger/måned	1-3 ganger/uke	4-6 ganger/uke	Daglig
Tran/flytende fiskeolje	○	○	○	○	○
Omega-3-kapsler	○	○	○	○	○
Jern (tilskudd med kun jern)	○	○	○	○	○
B-vitaminer (inkl. folsyre)	○	○	○	○	○
Multivitamin og mineral	○	○	○	○	○

Bruker du annet kosttilskudd som ikke ble nevnt?

- Nei
- Ja

Vennligst spesifiser:

		1-3 ganger/måned	1-3 ganger/uke	4-6 ganger/uke	Daglig
1.					
2.					
3.					

Brukte du kosttilskudd FØR du ble gravid?

- Ja
- Nei

Kryss av på aktuelle alternativer

	Brukte ikke	1-3 ganger/uke	4-6 ganger/uke	Daglig
Tran/flytende fiskeolje				
Omega-3-kapsler				
Jern (tilskudd med kun jern)				
B-vitaminer (inkl. folsyre)				
Multivitamin og mineral				

Brukte du annet kosttilskudd FØR du ble gravid som ikke ble nevnt?

- Ja
- Nei

Vennligst spesifiser:

	1-3 ganger/måned	1-3 ganger/uke	4-6 ganger/uke	Daglig
1.				
2.				
3.				

Appendix II

KOSTDAGBOK FOR DELTAKERE I «MAMMAS MAT»

ID nummer_____
Dato _____
Ukedag _____
Klokkeslett urinprøve _____

HUSK:

- Kostdagboken skal fylles ut seks dager på rad, ett skjema per dag
- Du vil sikkert oppleve å ikke finne alle rettene du spiser og/eller drikker. Vi er kun ute etter det vi har spurt om, det vil si at alt du spiser og drikker av det som er nevnt i dette skjemaet, skal registreres så nøyaktig som mulig
- Vær ærlig, all informasjon er viktig for prosjektet
- Dersom du spiser et sted hvor du ikke har dagboken med deg, noter det (f.eks. på en lapp eller mobilen), og før det inn på kvelden
- Kostdagboken skal leveres ved ditt «Mammas mat» -møte i svangerskapsuke 19

Var denne dagen en vanlig dag?

Ja ☐ Nei ☐

Hvis denne dagen ikke var vanlig, vennligst beskriv hvorfor: _____
(f.eks. pølsefest, julebord)

DRIKKE

Skriv inn antall glass/kopper av følgende drikker i listen:

1 glass = 2 dl
1 kopp = 1,7 dl

Type drikke	Antall	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Vann (med eller uten kullsyre)	Glass					
Melk/sjokolademelk/kakao (kumelk)	Glass					
Soya-, havre-, mandelmelk osv	Glass					
Juice, alle typer	Glass					
Smoothie m/kumelk eller yoghurt	Glass					
Kaffe (svart kaffe)	Kopp					
Kaffe latte / Cappuchino / Chai latte	Kopp					
Cortado / Macchiato o.l.	Kopp					

PÅLEGG

Type	Beskrivelse	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Hvitost	Antall oppskåret skiver av ost					
Brunost (Fløtemysost, Gudbrandsdalsost)	Antall oppskåret skiver av ost					
Geitost (brun eller hvit)	Antall oppskåret skiver av ost					
Røkt laks/ørret	Antall oppskåret skiver av laks/ørret					

PÅLEGG

Én brødskive tilsvarer ½ rundstykke, 1 knekkebrød, 2 vaffelhjerter, 2 kjeks eller ½ ciabatta

Type	Beskrivelse	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Smøreost (philadelphia, tubeost, snøfrisk o.l)	Skriv **antall** brødskiver e.l. du spiser **med** dette pålegget					
Rekesalat	Skriv **antall** brødskiver e.l. du spiser **med** dette pålegget					
Reker	Skriv **antall** brødskiver e.l. du spiser **med** dette pålegget					
Makrell i tomat, annet fiskepålegg på hermetikk	Skriv **antall** brødskiver e.l. du spiser **med** dette pålegget					
Sild/sardiner/brisling/ansjos	Skriv **antall** brødskiver e.l. du spiser **med** dette pålegget					
Egg (kalde/varme; omelett/kokte/speilegg)	Antall egg					

LUNSJ / MELLOMMÅLTID / MIDDAG

1 porsjon tilsvarer for eksempel 200 gram torsk/sei/hyse, 150 gram laks/ørret/kveite, 150 gram kjøtt, 195 gram kylling/kalkun, 200 gram potetmos

Type mat	**Porsjoner**	**Kl. 06-10**	**Kl.10-14**	**Kl.14-18**	**Kl.18-22**	**Kl.22-06**
Pannekaker/vafler/sveler	Antall					
Fiskekaker/fiskepudding	Antall					
Torsk, sei, hyse, lyr o.l.	Porsjoner					
Laks, ørret, kveite	Porsjoner					
Kjøttmåltid (alle typer, inkludert taco, pizza, lasagne, wok etc.)	Porsjoner					
Kylling/kalkun-måltid (alle typer, inkludert taco, pai, wok etc.)	Porsjoner					
Vegetarmåltid (alle typer, inkludert taco, lasagne, wok etc.)	Porsjoner					
Potetmos laget på melk	Porsjoner					
Suppe med melk/creme fraiche e.l.						
Saus med melk/creme fraiche e.l.	Porsjoner					

MEIERIPRODUKTER brukt i matlaging eller alene

Produkt	Oppgis i	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Hvitost (f.eks i taco, på pizza, i salat etc)	Osteskiver (ca antall)					
Chevre	Osteskiver					
Fetaost (f.eks i salat)	ss					
Cottage cheese	ss					
Kesam/rømme/crème fraiche (f.eks i taco, på pizza, i salat etc)	ss					
Yoghurt, alle typer	dl					
Gryn, frokostblandinger eller grøt laget på kumelk	Porsjoner					

KOSTTILSKUDD

Type	Antall	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Multivitaminer og/eller mineraltilskudd **Navn / merke:**	stk					
Folat	stk					
Flytende omega-3	ss					
Omega-3-kapsler	stk					
Annet, **beskriv**:	stk					

FRUKT OG GRØNT

En porsjon tilsvarer 100 gram; for eksempel en gulrot, en middels stor frukt, en håndfull bær. Ikke ta med poteter.
Ta med det du spiser gjennom hele dagen, også som en del av måltider (f.eks til taco).

Mat	Antall	Kl. 06-10	Kl.10-14	Kl.14-18	Kl.18-22	Kl.22-06
Frukt	Porsjon					
Grønnsaker	Porsjon					

KOMMENTARER:

Dersom du har spørsmål underveis, ta kontakt på

mammasmat@nifes.no eller på tlf 95783682

HUSK Å TA MED KOSTDAGBOKEN TIL «MAMMAS MAT»-PRØVETAKING I SVANGERSKAPSUKE 19

TAKK FOR INNSATSEN!

Paper I

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Nutrition Journal

RESEARCH Open Access

Validation and reproducibility of a new iodine specific food frequency questionnaire for assessing iodine intake in Norwegian pregnant women

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Abstract

Background: Iodized salt is not mandatory in Norway, and the permitted level of iodine in table salt is low (5 μg/g). Thus, milk and dairy products, fish and eggs are the main dietary sources of iodine in Norway. Mild-to-moderate iodine deficiency in pregnant women has been described in several European countries, including Norway. There are few validated tools available to assess iodine intake in an efficient manner. The aim of the current study was to assess the validity and reproducibility of a new iodine-specific food frequency questionnaire (I-FFQ) in Norwegian pregnant women.

Methods: An I-FFQ consisting of a total of 60 food items and the use of supplements was developed to assess iodine intake and was administrated to 137 pregnant women at gestational week 18–19. Reference methods were a structured 6-days iodine specific food diary, urinary iodine concentration (UIC) (pooled sample of spot UIC from six consecutive days), and thyroid function tests. Correlation analyses, Cohen's weighted kappa, Bland-Altman plots, and linear regression analyses were used to assess validity. Reproducibility of the I-FFQ was assessed in a subgroup ($n = 47$) at gestational week 35–36.

Results: There was a strong correlation between estimated iodine intake from the I-FFQ and food diary ($r = 0.62$, $P < 0.001$) and an acceptable correlation between the I-FFQ and UIC ($r = 0.21$, $P = 0.018$). There was no significant association between the I-FFQ and thyroid function tests. The I-FFQ estimated higher iodine intake compared to the food diary with a mean absolute difference 33 μg/day. The limits of agreement from the Bland-Altman plots were large, however few participants fell outside the limits of agreement (5.2–6.5%). There was no difference between the estimated iodine intake from the I-FFQ assessed at gestational week 18–19, and gestational week 35–36 ($P = 0.866$), and there was a strong correlation between the two time points ($r = 0.63$, $P < 0.001$).

Conclusion: In summary, this study suggests that the I-FFQ can be used as a valid tool to estimate and rank iodine intake among Norwegian pregnant women. We further suggest that this I-FFQ may also be valid in other populations with similarly dietary patterns and where salt is not iodized.

Trial registration: The study is registered in ClinicalTrials.gov (NCT02610959).

Keywords: Iodine, FFQ, Validation, Pregnancy, Dietary assessment

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Introduction

Iodine is an essential micronutrient which is crucial for the synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) [1]. The thyroid hormones regulates a wide range of physiological functions in the body and are essential for normal growth, development and metabolic regulation [2]. Although great progress have been made towards eliminating iodine deficiency, it is still present in many European countries [3]. Furthermore, pregnant women are a particularly vulnerable group regarding iodine deficiency, as the fetus is dependent on supply of thyroid hormones and iodine from the mother [4]. Mild- to moderate iodine deficiency has been described in several studies of Norwegian pregnant women [5–8]. Iodized salt is not mandatory in Norway, and the permitted level of iodine in table salt is low (5 μg/g), therefore the main dietary sources of iodine in the Norwegian diet are milk and dairy products, fish and eggs [9, 10]. Since 2018, women of childbearing age in Norway with a low intake of milk and fish have been advised by the Norwegian Directorate of Health to take iodine containing supplements in order to secure sufficient iodine intake (supplement of 150 μg/day for pregnant and lactating women and supplement of 100 μg/day for women in fertile age) [11]. This recommendation was introduced after the current study was conducted.

Urinary iodine concentration (UIC) is the most common method for assessing iodine status [1]. However, as iodine excretion in urine varies considerable in individuals both between days, and within the same day, spot urine is not recommended to assess individual iodine status [12]. The day-to-day variation will neither be accounted for in one 24-h urine sample [12, 13]. Other biomarkers such as thyroid stimulating hormone (TSH) and thyroglobulin may also be used to assess iodine status, but all current methods poses limitations [1, 12]. Dietary assessment methods may be used to estimate iodine intake, to identify the major dietary iodine sources, and evaluate the iodine status through dietary recommendations [12]. However, all dietary assessment methods poses several challenges, as many tools are time consuming for the participants and rely on memory and accurate frequency, or portion estimations [13]. Further, dietary methods are highly dependent on accurate and reliable food composition data [12]. This may pose an extra challenge for assessment of iodine intake, since iodine content of food may vary considerably, e.g. between similar products [14] or between the same species of fish [15]. Food frequency questionnaires (FFQs) are one of the most common dietary methods used to measure dietary intake in nutrition research [16]. FFQs are particularly useful for assessing food items which are not frequently consumed, or foods consumed by less than 50% of the population that contain high levels of nutrients [17]. FFQs can further be used to assess habitual iodine intake [12], however all FFQs developed should be validated for the specific nutrient and population [18].

The Mommy's Food study is a randomized controlled trial (RCT), designed to explore whether cod intake during pregnancy could affect iodine status and subsequently infant development [19]. An iodine-specific FFQ (I-FFQ) was developed for the RCT in order to assess the habitual iodine intake from iodine-rich food groups (milk and dairy products, seafood, eggs) and supplements in pregnant Norwegian women [19]. The I-FFQ was based on a short validated seafood FFQ for pregnant and post-partum women [20]. A full FFQ has previously been used and validated to assess iodine intake in pregnant women in Norway [21, 22]. However, a full FFQ may be very comprehensive and time consuming for the participants. An I-FFQ has the advantage to measure long-term dietary iodine intake in a simple, cost- and time-efficient manner, in a large sample size that is geographically widespread [16]. It can also be useful in identifying the most important sources of iodine in the diet [23]. Continuously monitoring of iodine intake in a population is important, especially in groups where deficiency already has been ascertained, such as pregnant women in Norway and in Europe.

As iodine deficiency is re-emerging in Norway, an I-FFQ to assess and evaluate iodine intake may be a useful tool. The aim of the present paper is to assess the validity and reproducibility of a new I-FFQ against the following: (1), a 6-days iodine specific food diary (2), urinary iodine concentration (UIC) (3), thyroid function tests (thyroid stimulating hormone (TSH), free T3 (fT3), free T4 (fT4)).

Methods

Study design and subjects

This paper used data from the Mommy's Food study, a two-armed RCT in Norwegian pregnant women. The primary and secondary outcomes of the study were to investigate if an increased intake of cod during pregnancy has an impact on i) maternal iodine status and ii) infant development. The overall study design, including enrolment, randomization, study procedure and ethics are further described in detail by Markhus et al. [19]. An overview of methods used in the validation of this I-FFQ is shown in Figure S1, listed in Additional file 1. This current paper used data from baseline (pre-intervention) at gestational week 18–19 for assessing validity of the I-FFQ. A total of 137 pregnant women from Bergen, Norway were enrolled in the study. The participants were recruited between January 2016 to February 2017. Data from the I-FFQ were available from 124 participants, food diary from 134 participants and UIC from 134 participants. The sample size was considered adequate in according to validate an FFQ in a population group, where of at least 50–100 subjects is recommended [18]. To assess reproducibility of the I-FFQ,

data from the control group post-intervention (gestational week 35–36) were used. Due to the design of the study (RCT) we were only able to use the control group ($n = 47$) for assessing reproducibility as the intervention group was intended to increase their iodine intake. Thus, including the intervention group would not be suitable for assessing reproducibility.

The study was conducted and performed according to the Declaration of Helsinki. The study was approved by the Regional Committees for Medical and Health Research Ethics West (REK 2015/879) and is registered in ClinicalTrials.gov (NCT02610959).

Data collection methods

The participants received an electronic online questionnaire in gestational week 18–19 and gestational week 35–36. The questionnaire included questions of baseline characteristics such as age, gestational age, education level, nicotine use, pre-pregnancy weight, current weight and height. Pre-pregnancy body mass index (BMI) was calculated as pre-pregnancy weight in kilograms (kg) divided by the square of the height in meters (kg/m^2).

I-FFQ

A semi-quantitative I-FFQ were included in the online questionnaire to acquire information about the participants' habitual diet and supplement use with focus on iodine rich food groups. In the I-FFQ completed in gestational week 18–19, the participants were asked to report an estimate of their diet since they became pregnant. In the I-FFQ completed in gestational week 35–36, the participants were asked to report an estimate of their diet the last 16 weeks (since the last time they completed the I-FFQ).

The number of food items listed in the I-FFQ and the number of responses of frequencies for each food items are listed in Additional file 1: Table S1. The I-FFQ included 21 food items regarding frequency of seafood intake as dinner and warm lunch, and 14 food items regarding frequency of seafood intake as spread. All questions included type of seafood species or products consumed. The frequency intervals ranged from *"never"* to *"three times a week or more"* (five frequency alternatives in total). Further, there were 24 food items regarding intake of milk and dairy products (including mixed foods with milk such as pancakes, waffles and porridge) with frequency intervals ranging from *"never"* to *"three to four times per day"* (seven frequency alternatives in total). All food items of seafood, milk and dairy products had follow-up questions concerning portion sizes per meal, ranging from *"half a portion or less"* to *"three portions"* (five portion alternatives in total). There was in addition one food item regarding weekly intake of eggs ranging from *"less than one egg per week"* to *"eight or more per week"* (six alternatives in total). Thus, a total of 60 food items, regarding iodine rich foods (fish and seafood, milk and dairy products and eggs), were included when calculating total iodine intake from the diet from the I-FFQ. In addition, the I-FFQ also included questions regarding dietary supplements including type, brand and intake frequency.

Data from the I-FFQ were converted to numerical continuous data through calculation of indexes in accordance to the methodology described in Markhus et al. [20]. For seafood intake, when frequency of consumption was given as a range (e.g. 1–2 times per week), the lowest frequency in each range was used (*here*: 1 time per week). This was due to recall is prone to overestimate low intakes when asked about several detailed food items separately [20]. For milk, dairy products, eggs and dietary supplements, when frequency consumption was given as a range (e.g. 1–2 times per day), the mean frequency consumption was used (*here*: 1.5 times per day) as these food categories consisted of fewer detailed questions. The calculated frequency indexes of each question were further multiplied by the reported portion sizes of intake to estimate weekly intake.

Food diary

A structured manual 6-days food diary was handed out, and instructions from the researcher were given to the participants at the first visit in gestational week 18. The food diary was filled out on six consecutive days between gestational week 18–19 (exact same days as the spot urinary samples). The food diary was developed specifically for this study with the purpose to estimate iodine intake during pregnancy. The number of food items listed in the food diary is given in Additional file 1: Table S1**.** The food diary included eight questions regarding seafood intake (as lunch/dinner and as spread), 19 questions regarding milk and dairy products, including foods made with milk, such as pancakes, waffles and other mixed dished with milk, and one question about intake of eggs. Thus, a total of 28 food items, regarding iodine rich foods (fish and seafood, milk and dairy products and eggs), were included when calculating total iodine intake from the diet from the food diary. The food diary also included questions regarding use of dietary supplements including type, brand and intake frequency. Each question included quantitative response alternatives (portions, glasses or cups, slices etc.) and the participants filled out their respective intakes from each day (e.g. *4* glasses of milk).

Estimation of iodine intake from the I-FFQ and food diary

In order to calculate consumption of the different food items from the I-FFQ and the food diary in grams per week, intake in portions per week were multiplied by estimated portion sizes in gram as defined in the report "Weights, measures and portion sizes for foods" from the Norwegian Food Safety Authority, University of Oslo

and the Norwegian Directorate of Health [24]. These portion sizes were also defined in the I-FFQ and the food diary. To calculate the mean daily iodine intake from the I-FFQ and food diary, intake of the different food groups in gram per day was multiplied by the average iodine content of the specific food and further summarized. The iodine content of the specific food groups were retrieved from Nerhus et al. 2018 [15], the database *Seafood data* from the Institute of Marine Research (IMR) [25] and the Norwegian Food Composition Table [26]. The most relevant and recent analytical value of iodine was used. Information of iodine content of the specific food groups are specified in Additional file 2: Table S2 and S3. Regarding dietary supplements, the specific iodine content of each supplement was retrieved from the manufacturers, and the mean daily iodine intake from supplements were calculated from both the I-FFQ and the food diary. Total estimated iodine intake per day from both the I-FFQ and the food diary were further calculated by summarizing the estimated iodine from foods and estimated iodine intake from supplements.

Urinary iodine concentration and thyroid function tests

The participants collected one spot urine samples on six consecutive days between gestational week 18–19 (same days as the structured 6-days food diary). The participants were instructed to collect the spot urine sample between 4 PM and midnight. The participants stored the urine samples in their home freezer until the next visit in gestational week 19. The urine samples were then transferred to cryo tubes and stored at minus 20 °C pending analysis by inductively coupled plasma mass spectrometry (ICP-MS), at the Institute of Marine Research, Norway. Equally amounts of urine from the six spot urine samples were homogenized into one composite sample of 1 ml before determination of iodine concentration. Description of the analytical method to determine UIC (μg/L) has previously been described by others [7, 27]. Estimated iodine intake from UIC was calculated by the following formula: UIC (μg/L) × 0.0235 x body weight (kg) [28], using current pregnancy weight in kg as body weight (self-reported body weight from gestational week 18–19).

Blood samples were drawn at gestational week 18. Venous blood samples for serum preparation were collected in BD Vacutainer® SST™ vials II *Advanced* and set to coagulate for minimum 30 min before centrifuging (1000–3000 G, room temperature, 10 min) within 60 min after extraction. Post separation, serum samples were stored at minus 80 °C pending analysis at Fürst Medical Laboratories in Bergen, Norway. The serum samples were stored for maximum three months before analysis. TSH, fT4 and fT3 were analysed in serum using magnetic separation and detection by chemiluminescence, labelled with acridinium ester, on an Advia Centaur XPT Immunoassay system (Siemens Healthcare diagnostics Inc., Tarrytown, USA). For all blood constitutes the CV was < 6%.

Statistics

Statistical analyses were performed using Statistical Package for Social Sciences version 25, IBM Corporation (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Two-sided statistical tests were performed. *P*-values < 0.05 were considered statistically significant. Variables were tested for normality by using the Kolmogorov-Smirnov test and by visual inspection of Q-Q plots and histograms. Descriptive results are reported as frequency (%) for categorical variables. For continuous variables mean (SD), median (p25-p75) or p5-p95 are reported as appropriate. Difference between estimated iodine intake from the I-FFQ, food diary and UIC were assessed using Wilcoxon signed-rank test. Correlation between the methods were assessed using Spearman's rank order correlation coefficient (Spearman's rho). The correlation coefficients strength (effect size) was considered poor if the Spearman's rho was < 0.20, acceptable if 0.20–0.49 and good/strong if ≥0.50 in according to previously used dietary methods [29].

The agreement between methods was analyzed using Bland-Altman plots [30], using a plot of the mean difference of iodine intake between the two methods against the mean iodine intake of the two methods, also showing 95% limits of agreement (LOA). This was conducted to graphically assess the presence of bias or disagreement.

Agreement of quartile membership was assessed between estimated iodine intake from the I-FFQ and the food diary, estimated iodine intake from the I-FFQ and UIC, and estimated iodine intake from the food diary and UIC, using Cohen's weighted kappa (k_w), which takes the squared concordance of position among groups into account [31]. The weighted kappa was calculated using crosstab analysis and the script "Weighted Kappa, Kappa for ordered categories" available from the IBM website [32]. Stability between methods are presented as numbers and percentage of participants remaining in their quartile (stable quartile), in adjacent quartile, or in opposite quartile (two or more quartiles between, e.g. from first, to third or fourth quartile), compared to the other method selected. The criteria's from Landis and Koch [33] were used to assess agreement, where a k_w of 0.01–0.20 represents slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement.

Linear regression analyses were used to assess the relationship between estimated iodine intake (including supplements) from the I-FFQ and thyroid markers: TSH, fT3 and fT4. Simple and adjusted (adjusted for BMI, age, nicotine use, and education) analyses are presented. Residual plots were examined and standardized residuals

±3 were excluded from the model (1 excluded from TSH, 2 excluded from fT4).

To assess the reproducibility of the I-FFQ we compared the estimated iodine intake from the I-FFQ completed at gestational week 18–19 with the I-FFQ completed at gestational week 35–36. The correlation of iodine intake from the I-FFQ were evaluated between the two time points, in addition to Bland-Altman plots.

Results

Characteristics of the pregnant women (gestational week 19) enrolled in the study are shown in Table 1.

Estimated iodine intake from the I-FFQ and food diary, and UIC and estimated iodine intake from UIC in the pregnant women are shown in Table 2. Median estimated iodine from the I-FFQ was 202 μg/day, which was significantly higher compared to estimated iodine intake from the food diary (151 μg/day) ($P = 0.002$). This was also higher compared to the estimated iodine intake from UIC (median 147 μg/day) ($P = 0.001$). The median estimated iodine intake from UIC (147 μg/day) was similar to the median total estimated iodine intake from the iodine specific food diary (151 μg/day) (same time period as urine spot samples) ($P = 0.882$).

Correlations coefficients between estimated iodine intake from the I-FFQ, the food diary and UIC are presented in Table 3. There was a significant strong correlation between estimated iodine intake (including diet and supplements) from the I-FFQ and the food diary ($r = 0.62$, $P < 0.001$). Further, there was a significant acceptable correlation between estimated iodine intake from I-FFQ and UIC ($r = 0.21$, $P = 0.018$) and a significant acceptable correlation between estimated iodine intake from the food diary and UIC ($r = 0.41$, $P < 0.001$).

Table 1 Baseline characteristics of pregnant women enrolled in Mommy's Food

Characteristic	N	
Age (years), mean (SD)	135	29.3 (3.4)
Gestational weeks, mean (SD)	127	19.0 (1.3)
Pre-pregnancy BMI (kg/m^2), median (p25-p75)	132	22.2 (20.6–24.3)
Marital status, n (%)	133	
Married		43 (32)
Cohabiting		85 (64)
Other		5 (4)
Education level, n (%)	133	
Elementary school		2 (1.5)
High school		17 (13)
≤ 4 years university/college		33 (25)
> 4 years university/college		81 (61)
Nicotine use in pregnancy [a], yes, n (%)	132	
≤ gestational week 8		12 (9)
> gestational week 8		0

[a]No participants reported use of nicotine after gestational week 8. BMI, body mass index; SD, standard deviation

Table 4 presents the stability of quartile membership between the different methods. The stability was highest between the estimated iodine intake from I-FFQ and the food diary, where respectively 89% were classified into the same (47%) or adjacent (42%) quartile, showing a moderate to substantial agreement ($k_w = 0.60$). A fair agreement was seen between the I-FFQ and UIC ($k_w = 0.21$), and between the food diary and UIC ($k_w = 0.40$).

The Bland-Altman plot comparing estimated iodine intake from I-FFQ and food diary (including diet and supplements) is presented in Fig. 1. The mean absolute difference (bias) in iodine intake between the methods was observed to 33 μg/day, with a LOA ranging from − 150 (lower LOA) to 216 (upper LOA) μg/day. The number of individuals observed to be beyond the LOA was 8 of 123, which corresponds to 6.5%.

The Bland-Altman plot comparing iodine intake estimated from the I-FFQ (including diet and supplements) and estimated iodine intake from UIC is presented in Fig. 2. The mean absolute difference (bias) in iodine intake between the methods was observed to 38 μg/day, with a LOA ranging from − 206 (lower LOA) to 281 (upper LOA) μg/day. The number of individuals observed to be beyond the LOA was 7 of 123, which corresponds to 5.7%.

The Bland-Altman plot comparing iodine intake estimated from the food diary (including diet and supplements) and estimated iodine intake from UIC is presented in Fig. 3. The mean absolute difference (bias) in iodine intake between the methods was observed to 3 μg/day, with a LOA ranging from − 197 (lower LOA) to 203 (upper LOA) μg/day. The number of individuals observed to be beyond the (LOA) was 7 of 134, which corresponds to 5.2%.

Estimated iodine intake from the I-FFQ was positively associated with TSH, and negatively associated with fT3 and fT4, however neither of the associations were statistically significant after adjustments (Table 5).

There was no difference between the estimated iodine intake from the I-FFQ at gestational week 18–19 and gestational week 35–36 (median (p25-p75) iodine intake: 145 (90–267) vs. 152 (115–258), $P = 0.866$, n = 47). In addition, there was a strong correlation between estimated iodine intake from the I-FFQ between these two time points ($r = 0.63$, $P < 0.001$, n = 47). The mean absolute difference (bias) in iodine intake between the methods was observed to − 5 μg/day, with a LOA ranging from − 177 (lower limit of agreement) to 167 (upper LOA) μg/day. The number of

Table 2 Descriptive of estimated iodine intake from the I-FFQ and food diary (μg/day), and urinary iodine concentration (UIC, μg/L) and estimated iodine intake from UIC (μg/day) in pregnant women (gestational week 18-19) enrolled in the Mommy's Food study

	N	Mean (SD) [f]	Median (p25-p75)	p5-p95
Estimated iodine intake, I-FFQ, μg/day [a]				
Diet	124	134 (73)	123 (89–157)	51, 309
Diet and supplements	124	202 (108)	202 (106–275)	60, 377
Estimated iodine intake, food diary, μg/day [b]				
Diet	134	116 (51)	105 (80–153)	42, 203
Diet and supplements	134	171 (99)	151 (87–262)	47, 342
Urinary iodine concentration (UIC), μg/L [c]				
All participants	134	103 (56)	94 (62–130)	36, 210
Non-supplement users [d]	87	89 (49)	77 (58–120)	31, 172
Supplements users [d]	47	129 (58)	130 (77–160)	49–270
Estimated iodine intake from UIC, μg/day [e]				
All participants	117	166 (93)	147 (104–206)	61, 404
Non-supplement users [d]	75	135 (69)	119 (83–169)	46, 273
Supplement users [d]	42	220 (105)	202 (143–262)	73, 439

[a] Iodine specific food frequency questionnaire (I-FFQ)
[b] Iodine specific food diary from six consecutive days
[c] Pooled sample of spot urinary samples from six consecutive days
[d] Reported use of iodine containing supplement in the food diary
[e] Estimated from the equation: Urinary iodine concentration (μg/L) × 0.0235 × body weight (kg) (IOM 2001) [28]. Self-reported current body weight used for estimation (data of n = 17 missing)
[f] Differences between the different methods were tested by Wilcoxon's signed-rank test. Difference between estimated iodine intake from I-FFQ and food diary (without supplements): $P = 0.030$; estimated iodine intake from I-FFQ and food diary (with supplements): $P = 0.002$; estimated iodine intake from UIC and food diary: $P = 0.882$; estimated iodine intake from UIC and I-FFQ: $P = 0.001$

individuals observed to be beyond the LOA was 5 of 47 (5.2%).

Discussion

This study suggests that the I-FFQ can be used as a valid tool to estimate and rank iodine intake among Norwegian pregnant women, because of its association with estimated iodine intake from a 6-days structured food diary and UIC from six spot urine samples. The I-FFQ further showed strong reproducibility. To the best of our knowledge, there is only one previously validated I-FFQ for pregnant women, which was developed in Australia [34]. A comprehensive FFQ has previously been used and validated for iodine intake in the Norwegian Mother and Child Cohort study [21, 22], however, this is a full FFQ consisting of 255 food items [22]. Therefore, this I-FFQ could be a useful tool, as it presents a lower burden for the participants. There are few validated tools available to asses iodine intake in an efficient manner. UIC is the most common method for assessing iodine status [1]. However, an I-FFQ has the advantage to measure long-term dietary intake in a simple, cost- and time-efficient manner in a large sample size that is geographically widespread [16]. As iodine is present in few foods, and iodized salt is used in negligible amounts in Norway, dietary assessment tools may be a promising method to evaluate iodine intake through dietary reference intakes in a population. An I-FFQ along with the use of UIC in a population, can also give a better understanding of current iodine status and iodine sources in population studies [23].

Weighed food- or diet records are considered the gold standard in dietary research, and is the first methods of choice for validation of FFQ data [18]. According to Gibson, a 7-days weighted food record is considered the

Table 3 Spearman's rho correlation coefficient [a] between estimated iodine intake from I-FFQ (μg/day), estimated iodine intake from food diary (μg/day) and urinary iodine concentration (UIC) (μg/L)

Iodine intake from	I-FFQ[b] vs. Food diary[c] (n = 123)	I-FFQ[b] vs. UIC[d] (n = 123)	Food diary[c] vs. UIC[d] (n = 134)
Diet	0.36 ($P < 0.001$)	0.06 ($P = 0.488$)	0.18 ($P = 0.042$)
Diet and supplements	0.62 ($P < 0.001$)	0.21 ($P = 0.018$)	0.41 ($P < 0.001$)

[a] Spearman's rank order correlation coefficient. The correlation coefficients strength (effect size) was considered poor if < 0.20, acceptable if 0.20–0.49 and strong if ≥0.50 in according to previously used dietary methods [30]
[b] Iodine specific food frequency questionnaire (I-FFQ)
[c] Iodine specific food diary from six consecutive days
[d] Urinary iodine concentration (UIC): Pooled sample of spot urinary samples from six consecutive days

Table 4 Agreement of quartile membership between estimated iodine intake from the iodine-specific food frequency questionnaire (I-FFQ) and the food diary, and urinary iodine concentration (UIC)

	I-FFQ[a] vs. Food diary[b] (n = 122)	I-FFQ[a] vs. UIC[c] (n = 123)	Food diary[b] vs. UIC[c] (n = 133)
Stable quartile, *n* (%)	57 (47%)	41 (33%)	53 (40%)
Adjacent quartile, *n* (%)	51 (42%)	51 (42%)	50 (38%)
Opposite quartile, *n* (%)	14 (11%)	31 (25%)	30 (23%)
Weighted kappa, k_w [d]	0.60	0.21	0.40

[a]Iodine specific food frequency questionnaire (I-FFQ)
[b]Iodine specific food diary from six consecutive days
[c]Urinary iodine concentration (UIC): Pooled sample of spot urinary samples from six consecutive days
[d]Tracking coefficient of Cohen's weighted kappa. A k_w of 0.01–0.20 represents slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement [33]

best reference method [35]. We only used a 6-days structured food diary including 28 food items of iodine rich food groups as the dietary reference method. Though, in most settings, using more than four to five observations (days) of the reference methods per subject has also been considered sufficient [36]. The agreement between the I-FFQ and the food diary was moderate to substantial ($k = 0.60$). When assessing validation of specific nutrients from an FFQ, a weighted kappa value above 0.4 has been considered as acceptable [29, 37]. The kappa value was in accordance with the correlation coefficients as there was a strong correlation between estimated total iodine intake from the I-FFQ and food diary ($r = 0.62$, $P < 0.001$). This was mostly higher or comparable to what is reported in other studies comparing iodine intake from an FFQ against a food diary or food record (correlation coefficients ranging from 0.26–0.88) [21, 34, 38–41].

The mean absolute difference between the methods showed that the estimated iodine intake was highser from the I-FFQ, compared to the food diary and estimated iodine intake from UIC. A higher iodine intake

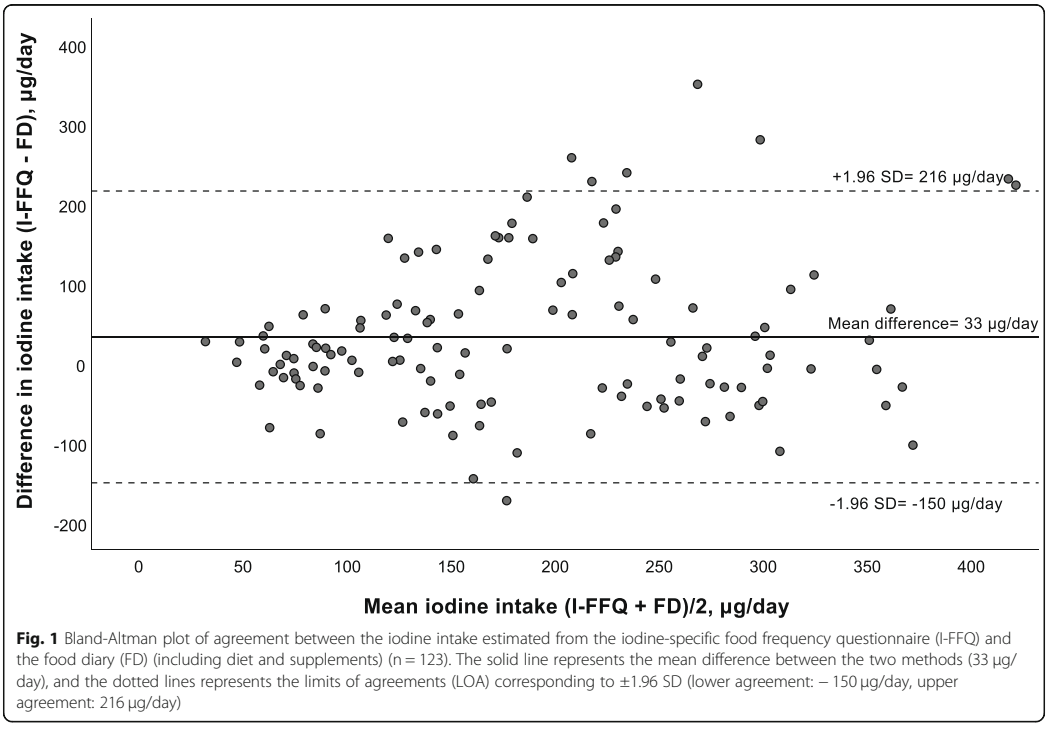

Fig. 1 Bland-Altman plot of agreement between the iodine intake estimated from the iodine-specific food frequency questionnaire (I-FFQ) and the food diary (FD) (including diet and supplements) (n = 123). The solid line represents the mean difference between the two methods (33 µg/day), and the dotted lines represents the limits of agreements (LOA) corresponding to ±1.96 SD (lower agreement: − 150 µg/day, upper agreement: 216 µg/day)

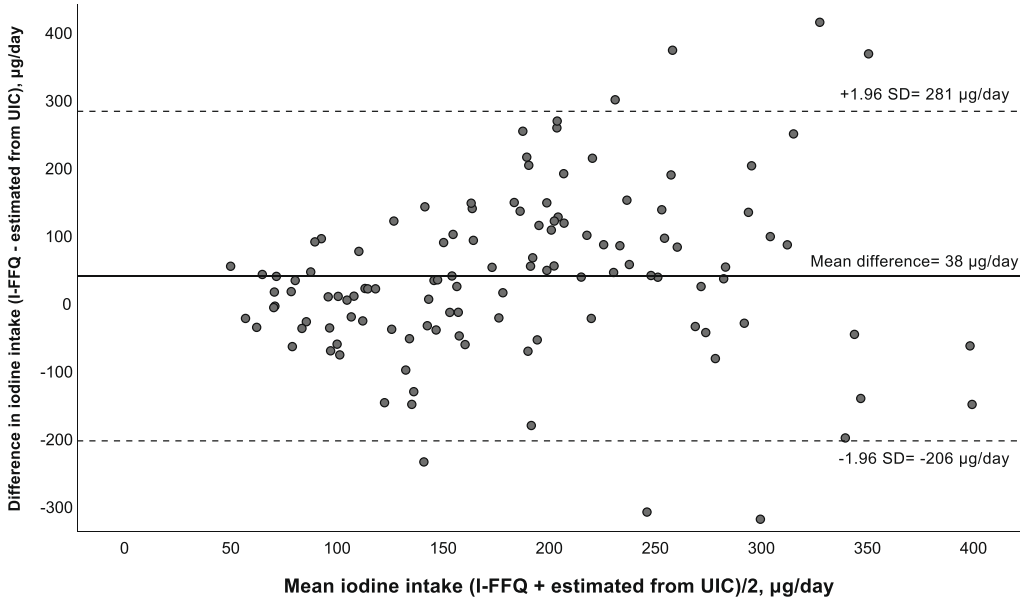

Fig. 2 Bland-Altman plot of agreement between the iodine intake estimated the iodine-specific food frequency questionnaire (I-FFQ) and iodine intake estimated from UIC (n = 123). The solid line represents the mean difference between the two methods (38 µg/day), and the dotted lines represents the limits of agreements (LOA) corresponding to ±1.96 SD (lower agreement: − 206 µg/day, upper agreement: 281 µg/day)

estimated from an FFQ compared to other dietary reference methods has also been found in other studies [39, 42, 43], while in some studies FFQ have not been found to overestimate [22, 34, 40]. There could be several reasons of why the I-FFQ estimated a higher iodine intake compared to the food diary. The records of the I-FFQ and the food diary was from different time periods (approximately four months vs. six days) and the I-FFQ was completed retrospective while the food diary was completed day-by-day. In addition, the I-FFQ assessed long-term habitual iodine intake, included more food items and covered rarely consumed food items such as several seafood species and items (e.g. reporting of an intake 1–3 times/months) which the food diary may not has covered. The time period of pregnancy have also been shown to be a period where there is a potential for dietary changes [44–47]. Thus, we cannot conclude whether the estimated higher iodine intake from the I-FFQ compared to the food diary was caused by an overestimation from the I-FFQ, reporting of rarely consumed food items which the food diary did not cover, or if it was an actual difference in intake between the two time periods. It should also be noted that we did not adjust for energy intake when calculating iodine intake, as we did not complete a full FFQ or food diary, which further is a limitation in our study. In both the I-FFQ and food diary, we only included iodine intake from milk and dairy products, seafood, eggs and supplements. These are the most important food groups of iodine intake in Norway, however other food groups (such as e.g. bread, cereals, snack, vegetables) may also contribute with some iodine [10], and the exclusion of these food groups may on the other hand contributed to an underestimation of iodine intake.

There was a significantly higher estimated iodine intake from the I-FFQ and food diary when supplements was added to the summarization. In addition, the correlations coefficients were strengthened. This is also found in other studies [21, 34] and highlights the importance of including supplements in dietary research studies of iodine as it contributes with a significant amount of intake.

Correlation between methods only assess the degree of the association between them, and not the agreement between them. In contrast, the Bland-Altman plot is a preferred method to assess agreement between two dietary reference methods across the range of intakes [18]. From the Bland-Altman plots (Figs. 1, 2 and 3), the LOA were large and for all plots there seemed to be a systematic increase in the difference between the two methods with increasing iodine intake. This may indicate that estimating iodine intake is more difficult when intake is higher. This may also be explained by the fact that when several

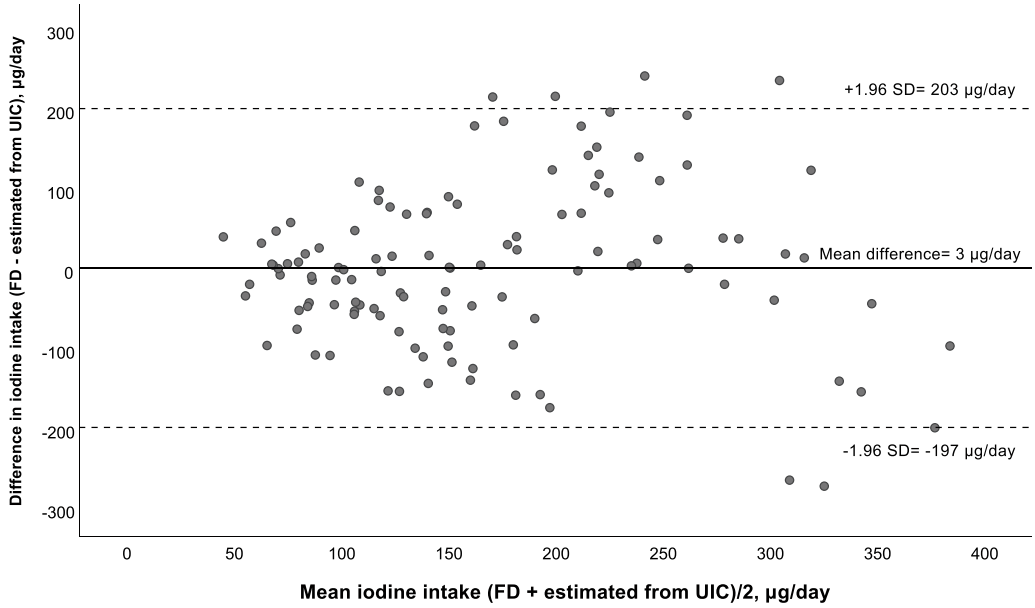

Fig. 3 Bland-Altman plot of agreement between the iodine intake estimated from the food diary (FD) and iodine intake estimated from UIC (n = 134). The solid line represents the mean difference between the two methods (3 µg/day), and the dotted lines represents the limits of agreements (LOA) corresponding to ±1.96 SD (lower agreement: − 197 µg/day, upper agreement: 203 µg/day)

sources of intake are included, the accuracy of the dietary intake estimations decrease as an increased number of potential errors are introduced, e.g. inaccurate portion estimations or food composition data. This have also been confirmed by other studies validating FFQs [38, 39]. However, few participants (5.3–6.5%) fell outside the LOA (± 1.96 SD) which is indicated as the accepted level of agreement [30, 48].

A biomarker can provide an estimate of dietary intake that is objective and independent of the subject's reported dietary intake [18, 49]. We found a fair agreement between UIC and iodine intake from the I-FFQ ($k = 0.205$) and the food diary ($k = 0.399$). In addition, there was an acceptable correlation between UIC and iodine intake from the I-FFQ ($r = 0.213$, $P = 0.018$) and the food diary ($r = 0.408$, $P < 0.001$). The use of spot urine samples to measure UIC as a marker of iodine status has its limitations owing to large inter- and intra-individual variations. A strength to this study is that the participants collected six spot urinary samples on consecutive days, and not a single spot urine sample. However, it has been suggested that at least ten spot urine samples or 24-h urine collections, is needed to account for intra- and inter individual variability [50]. Nonetheless, this is demanding for the participants and was not prioritized in this study. Consequently, we cannot exclude that the UIC has limitations regarding within day, and day-to-day variation. The iodine intake from the food diary had the highest relative validity, as it showed the highest correlation and agreement with the UIC. This was also expected as the sampling of spot urine samples was collected of the same

Table 5 Association between estimated iodine intake from the I-FFQ and thyroid biomarkers[a]

	Unadjusted coefficients (95% CI)			Adjusted coefficients (95% CI)[b]		
		P	R^2		*P*	R^2
TSH (mIU/L)	22.2 (−3.2, 47.6)	*0.087*	0.024	12.5 (−12.0, 37.1)	*0.312*	0.107
fT3 (pmol/L)	−11.5 (− 54.2, 31.2)	*0.595*	0.002	−11.6 (−51.7, 28.5)	*0.567*	0.101
fT4 (pmol/L)	−5.0 (−16.2, 6.3)	*0.382*	0.006	−5.6 (−16.5, 5.3)	*0.314*	0.107

fT3, free triiodothyronine; fT4, free thyroxine, TSH, thyroid stimulating hormone

[a]n = 123 for TSH; n = 124 for fT3; n = 122 for fT4

[b]Adjusted for BMI, age, nicotine use while pregnant and education. Categories for nicotine use: 0 = no, 1 = yes; categories for education 0 ≤ high school, 1 ≥ university/ university college

days as the food diary was conducted (six consecutive days).

We also assessed the association between thyroid function tests (TSH, fT3, fT4) with estimated iodine intake from the I-FFQ. The direction of the associations were similar to what was reported in another study of Norwegian pregnant women, where an inverse association was seen between UIC and fT3, and fT4, and a positive association between UIC and TSH [51]. However, we did not find any significant associations, similarly as reported by others [34, 51]. TSH and thyroid hormones are not considered sensitive markers of iodine status and may only be affected if severe iodine deficiency is present [1]. Thus, a significant association was not be expected.

To determine whether an FFQ shows reproducible results, reproducibility should always be assessed [18]. There was a strong association between estimated iodine intake from the I-FFQ at gestational week 18–19 with gestational week 35–36. Further, no significant differences in estimated iodine intake from the I-FFQ between the two time points were found. However, as this paper was part of an RCT we were only able to assess reproducibility in the control group of the study ($n = 47$). Thus, the reduced number of participants assessing the reproducibility of the I-FFQ is a limitation.

The strengths in this study are the use of both a dietary method (food diary) and biomarkers (UIC and thyroid function tests) to validate the I-FFQ, as using more than one approach to validate an FFQ gives further credibility to the results [18]. We also used multiple statistical tests, which is considered a strength when evaluating validity of dietary methods [29]. In addition, we used up to date chemical analyses of most food items to estimate iodine intake [15]. We included portion sizes in the I-FFQ which is recommended when calculating nutrient intake [18]. Further, the sample size was considered adequate for validation of an FFQ [18]. However, the study group may not be a representative sample of pregnant women in Norway as this was a group with high socioeconomic status. Still, the study group has a broad range of iodine intakes (Table 2), and we believe that this I-FFQ may also be valid in other populations with similarly dietary patterns where salt is not iodized, such as the general adult population in Norway.

Conclusion

In summary, this study suggests that the I-FFQ can be used as a valid tool to estimate and rank iodine intake among Norwegian pregnant women, because of its acceptable correlation and agreement with estimated iodine intake from a 6-days structured food diary and UIC. The I-FFQ further showed strong reproducibility. Thus, this I-FFQ can be used as a tool to evaluate and monitor iodine intake in this population. As iodine deficiency is re-emerging in Norway and Europe, there is a need for validated tools that are non-invasive, simple, cost- and time-efficient to evaluate iodine intake and to identify women at risk of inadequate intake.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12937-019-0489-4.

Additional file 1: Figure S1. Overview of methods used in validation of the I-FFQ in Norwegian pregnant women. **Table S1.** Number of food items specified in the I-FFQ and the food diary, and number of frequency alternatives in the I-FFQ.

Additional file 2: Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ. **Table S3.** Iodine content in food items used for calculation of iodine intake from the food diary.

Abbreviations

BMI: Body mass index; FFQ: Food frequency questionnaire; fT3: Free triiodothyronine; fT4: Free thyroxine; ICP-MS: Inductively coupled plasma mass spectrometry; I-FFQ: Iodine-specific food frequency questionnaire; IMR: Institute of Marine Research;; RCT: Randomized controlled trial; SD: Standard deviation; TSH: Thyroid stimulating hormone; UIC: Urinary iodine concentration; WHO: World Health Organization

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Author's contributions

MWM, MK, LD, LKM and IN conceptualized and designed the trial. LKM and IN were the main investigators in managing the acquisition and collection of data. SN and IA interpreted the data, performed the statistical analyses and drafted the manuscript. All authors revised, read and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Regional Committees for Medical and Health Research Ethics West (REK 2015/879) and is registered in ClinicalTrials.gov (NCT02610959). The study was conducted and performed according to the Declaration of Helsinki. Participation in the study was voluntary and written informed consent was obtained from the participants after giving both written and oral information about the study. The participants could withdraw from the study at any time without giving any reason and this was highlighted in the declaration of informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Supplementary information

Figure S1. Overview of methods used in validation of the I-FFQ in Norwegian pregnant women

Table S1. Number of food items specified in the iodine specific food frequency questionnaire (I-FFQ) and the food diary, and number of frequency alternatives in the I-FFQ.

Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ

Table S3. Iodine content in food items used for calculation of iodine intake from the food diary

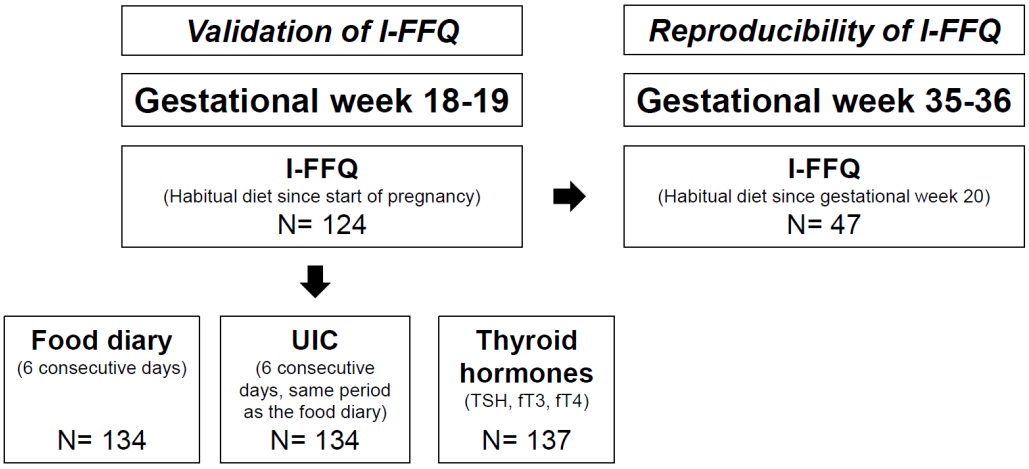

Figure S1. Overview of methods used in validation of the I-FFQ in Norwegian pregnant women

I-FFQ, iodine specific food frequency questionnaire; TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine

Table S1. Number of food items specified in the iodine specific food frequency questionnaire (I-FFQ) and the food diary, and number of frequency alternatives in the I-FFQ.

Food item	Food diary - Number of food items	I-FFQ - Number of food items	Frequency response in I-FFQ
Seafood as dinner or warm lunch	5	21	5 frequency alternatives: - Never - Less than 1/month - 1-3 times/month - 1-2 times/week - 3 times or more/week
Seafood as spread	4	14	5 frequency alternatives: - Never - Less than 1/month - 1-3 times/month - 1-2 times/week - 3 times or more/week
Milk, yoghurt and other milk containing drinks	6	13	7 frequency alternatives: - Never - Less than 1/week - 1-3 times/week - 4-6 times/week - 1 time/day - 2 times/day - 3-4 times or more/day
Cheese and cheese products	8	7	7 frequency alternatives: - Never - Less than 1/week - 1-3 times/week - 4-6 times/week - 1 time/day - 2 times/day - 3-4 times or more/day
Other foods made with milk and dairy products	5	4	7 frequency alternatives: - Never - Less than 1/week - 1-3 times/week - 4-6 times/week - 1 time/day - 2 times/day - 3-4 times or more/day
Eggs	1	1	6 frequency alternatives: - Less than 1 egg/week - 2-3 eggs/week - 4-5 eggs/week - 6-7 eggs/week - 8 or more eggs/week
Total food items	28	60	

In addition, the I-FFQ and the food diary included questions regarding dietary supplements including type, brand and intake frequency.

Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ

Food item specified in the I-FFQ	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Seafood				
Fatty fish (>5% fat)				
Salmon/trout	4	Atlantic salmon fillet *(Salmo salar)* , farmed fish	Seafood data (1)	Samples from 2017 (n= 124). Median iodine content used.
Mackerel	19	Atlantic mackerel fillet *(Scomber scombrus)* , wild fish	Seafood data (1)	Samples from 2012 (n= 71). Median iodine content used.
Halibut	21	Atlantic halibut fillet *(Hippoglossus hippoglossus)* , wild fish	Nerhus et al. 2018 (2)	Samples from 2014 (n= 20). Mean iodine content used.
Herring	17	Atlantic herring fillet *(Clupea harengus)* , wild fish	Seafood data (1)	Samples from 2012 (n= 96). Median iodine content used.
Lean fish (≤5% fat)				
Cod	81	Atlantic cod fillet *(Gadus morhua)* , wild fish	Analyzed specific for this project	Samples from 2015 (n= 30). Mean iodine content used.
Saithe	280	Saithe fillet *(Pollachius virens)* , wild fish	Nerhus et al. 2018 (2)	Samples from 2013-2015 (n= 61). Mean iodine content used.
Pollock	790	Pollock fillet *(Pollachius pollachius)* , wild fish	Nerhus et al. 2018 (2)	Samples from 2014 (n= 41). Mean iodine content used.
Ling	20	Common ling fillet *(Molva molva)* , wild fish	Seafood data (1)	Samples from 2008 (n= 50). Median iodine content used.
Wolffish	90	Wolffish *(Anarhichas lupus)* , raw	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018
Processed seafood and sushi				
Sushi	13	Atlantic salmon fillet *(Salmo salar)* , farmed fish and Atlantic halibut fillet (Hippoglossus hippoglossus), wild fish	Seafood data (1) and Nerhus et al. 2018 (2)	Iodine content of sushi not available. Used mean iodine content of two typically fish species used in sushi: Salmon fillet (4 µg/100 g) and halibut fillet (21 µg/100 g).
Fish cakes/burgers, fish balls, fish pudding	49	Fish cakes, bought	The Norwegian Food Composition Table (3)	Reference 223a: Estimated average from the report: Analyse av fiskeprodukter - Næringsstoff- og tungmetallanalyser (2016). Mattilsynet [In Norwegian].
Fish au gratin	31	Fish au gratin, bought	The Norwegian Food Composition Table (3)	Reference 223a: Estimated average from the report: Analyse av fiskeprodukter - Næringsstoff- og tungmetallanalyser (2016). Mattilsynet [In Norwegian].
Fish fingers	94	Fish fingers, Findus	The Norwegian Food Composition Table (3)	Reference 223a: Estimated average from the report: Analyse av fiskeprodukter - Næringsstoff- og tungmetallanalyser (2016). Mattilsynet [In Norwegian].
Fish soup	37	Fish soup	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018. Used mean content of four available fish soups.
Dried and salted cod	132	Dried and salted cod	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Shellfish				
Shrimps unpeeled	31	Shrimp (*Pandalus borealis*), wild	Seafood data (1)	Samples from 2017 (n= 14). Median iodine content used.
Browncrab claw meat	111	Brown crab claw meat *(Cancer pagurus)* , shellfish wild	Seafood data (1)	Samples from 2011 (n= 11). Median iodine content used.
Browncrab innards	310	Brown crab *(Cancer pagurus)* , shellfish wild	Seafood data (1)	Samples from 2011 (n= 11). Median iodine content used.

Continued Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ

Food item specified in the I-FFQ	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Lobster	560	Lobster white meat *(Homarus spp)* , shellfish wild	Seafood data (1)	Samples from 2017 (n= 25). Median iodine content used.
Blue mussel	270	Blue mussel, raw	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Scallop	11	Scallop, raw	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Seafood as spread				
Canned mackerel	15	Canned mackerel, 70% mackerel	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Canned salmon	5	Canned salmon	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Canned tuna	8	Canned tuna	Nerhus et al. 2018 (2)	Samples from 2015 (n= 30). Mean iodine content used.
Smoked salmon, trout	8	Smoked salmon	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cured salmon, trout	8	Cured salmon	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Pickled herring	13	Pickled herring	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018. Used mean content of three available pickled herring.
Caviar	85	Caviar of cod roe	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Peppered mackerel	19	Atlantic mackerel fillet *(Scomber scombrus)* , wild fish	Seafood data (1)	Samples from 2012 (n= 71). Median iodine content used.
Shrimps	31	Shrimp (*Pandalus borealis*), wild	Seafood data (1)	Samples from 2017 (n= 14). Median iodine content used.
Canned sardines	9	Canned sardines in oil	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Anchovy	16	Canned anchovy	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Crabsticks	195	Crabsticks, freezed	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cod roe and liver pate ("Svolværpostei" and "Lofotpostei")	245	Cod roe and liver pate ("Svolværpostei"/"Lofotpostei")	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Milk and dairy products				
Milk and yoghurt				
Cow milk, whole-fat ('helmelk'), 3.5-3.9% fat	15	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cow milk, low-fat ('lettmelk'), 1.0-1.2% fat	14	Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q')	Nerhus et al. 2018 (2)	Samples from 2015-2016. Mean of samples of Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'). Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items).
Cow milk, low-fat ('lettmelk'), 0.7% fat	15	Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q')	Nerhus et al. 2018 (2)	Samples from 2015-2016. Mean of samples of Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE') and cow milk, low-fat ('lettmelk'), 0.7% fat ('Q'). Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items).

Continued Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ

Food item specified in the I-FFQ	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Cow milk, skimmed ('skummet melk'), 0.1% fat	15	Cow milk, skimmed ('skummet melk'), 0.1% fat	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cow milk, flavored (e.g. chocolate, strawberry)	17	Chocolate-flavoured low-fat cow milk, 'Q'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Sour cow milk/probiotic milk (natural)	14	Sour cow milk/probiotic milk (natural)	The Norwegian Food Composition Table (3)	Reference 325: Universitetet i Oslo (2018). Jodprosjekt 2017-2018. Mean of iodine content of three different types available.
Sour cow milk/probiotic milk (with flavor)	14	Biola, with blueberry flavour, 'TINE'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers)
Yoghurt (all types)	16	Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'	Nerhus et al. 2018 (2)	Mean of samples of Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'. Mean based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers)
Drinking yoghurt	16	Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'	Nerhus et al. 2018 (2)	Mean of samples of Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'. Mean based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers)
Smoothie (with milk)	8	Smoothie with yoghurt, juice, berries and banana.	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Goat milk	49	Goat milk	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Milk from coffee/tea	15	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of all types of cow milk used.
Cheese and other dairy				
White-coloured solid cheese ('hvitost')	16	White-coloured solid cheese ('hvitost'): 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'.	Nerhus et al. 2018 (2)	Samples from 2015-2016. Mean of 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers).
Goat cheese (white)	46	Goat cheese (white): 'Snøfrisk, TINE'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Whey cheese ('brunost')	120	Whey cheese ('brunost'): 'Gudbrandsdalost, TINE' and 'Fløtemysost, TINE'	Nerhus et al. 2018 (2)	Mean of 'Gudbrandsdalost, TINE' and 'Fløtemysost, TINE'Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).

Continued Table S2. Iodine content in food items used for calculation of iodine intake from the I-FFQ

Food item specified in the I-FFQ	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Goat cheese (brown)	450	Goat cheese (brown): 'Ekte geitost, TINE'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Soft cheeses ('Brie, Camembert')	16	Soft cheeses ('Brie, Camembert'): 'Brie, Arla Foods' and 'Camembert, TINE'	Nerhus et al. 2018 (2)	Mean of 'Brie, Arla Foods' and 'Camembert, TINE'. Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Cream cheese	14	Cream cheese: 'Philadelphia, Mondalez'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Curd cheese (cottage cheese, curd/'kesam')	16	Curd cheese (cottage cheese, curd/'kesam'): 'Cottage cheese, TINE' and 'Curd with natural flavour (Kesam), TINE'	Nerhus et al. 2018 (2)	Mean of 'Cottage cheese, TINE' and 'Curd with natural flavour (Kesam), TINE'. Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Sour cream, crème fraiche	10	Sour cream, crème fraiche: 'Creme fraiche, TINE' and 'Sour creme, TINE'	Nerhus et al. 2018 (2)	Mean of 'Creme fraiche, TINE' and 'Sour creme, TINE'. Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Milk-based food as soups, sauce, casserole	8	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items).
Milk-based food as pancakes, waffles	15	Pancakes with milk, pancakes with eggs and milk, vaffles with eggs and whole-fat milk, and vaffles, 'Toro'	The Norwegian Food Composition Table (3)	Referanse 325. Universitetet i Oslo (2018). Jodprosjekt 2017-2018. Mean of iodine content of four different types available.
Ice cream, custard etc.	11	Ice cream (cream milk), ice cream (yoghurt), custard ('Piano'), custard ('Powder')	The Norwegian Food Composition Table (3)	Referanse 325. Universitetet i Oslo (2018). Jodprosjekt 2017-2018. Mean of iodine content of four different types available.
Other				
Egg	37	Egg, raw (whole egg)	Nerhus et al. 2018 (2)	Samples from 2016-2017 (n= 8). Mean iodine content of all samples used. Each sample consisted of 18 (n= 4) or 36 (n= 4) eggs.

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Table S3 Iodine content in food items used for calculation of iodine intake from the food diary

Food item specified in the food diary	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Drinks and beverages				
Cow milk (regular, flavored, soured etc.)	15	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of all types of cow milk used.
Smoothie with cow milk, yoghurt	8	Smoothie with yoghurt, juice, berries and banana.	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Caffè latte, cappuchino, chai latte	9	Caffè latte and cappuchino	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018. Mean of iodine content in caffè latte and cappuchino used.
Cortado, macchiato etc.	8	Cortado and macchiato	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018. Mean of iodine content in cortado and macchiato used.
Spreads				
White/yellow-coloured solid cheese ('hvitost')	16	White-coloured solid cheese ('hvitost'): 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'.	Nerhus et al. 2018 (2)	Samples from 2015-2016. Mean of 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers).
Whey cheese ('brunost')	120	Whey cheese ('brunost'): 'Gudbrandsdalost, TINE' and 'Fløtemysost, TINE'	Nerhus et al. 2018 (2)	Mean of 'Gudbrandsdalost, TINE' and 'Fløtemysost, TINE'. Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Goat cheese (brown or white)	238	Goat cheese ('Ekte geitost, TINE') and goat cheese, white	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of Goat cheese ('Ekte geitost, TINE') (2) and goat cheese, white (3).
Smoked salmon/trout	8	Smoked salmon	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cream cheese	30	Cream cheese: 'Philadelphia, Mondalez' and Cream cheese: 'Snøfrisk'	Nerhus et al. 2018 (2)	Mean of Cream cheese: 'Philadelphia, Mondalez' and Cream cheese: 'Snøfrisk'. Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).

Continued Table S3 Iodine content in food items used for calculation of iodine intake from the food diary

Food item specified in the food diary	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Shrimps salad (creamed)	41	Shrimps salad (creamed)	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Shrimps	31	Shrimp (*Pandalus borealis*), wild	Seafood data (1)	Samples from 2017 (n= 14). Median iodine content used.
Canned mackerel	15	Canned mackerel, 70% mackerel	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Herring, anchovy, sardines etc.	13	Herring, anchovy and canned sardines	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018. Mean of herring, anchovy and canned sardines used.
Egg	37	Egg, raw (whole egg)	Nerhus et al. 2018 (2)	Samples from 2016-2017 (n= 8). Mean iodine content of all samples used. Each sample consisted of 18 (n= 4) or 36 (n= 4) eggs.
Dinner/lunch				
Pancakes, waffles	15	Pancakes with milk,	The Norwegian Food	Referanse 325. Universitetet i Oslo
Fish cakes/burgers, fish pudding	49	Fish cakes, bought	The Norwegian Food Composition Table (3)	Reference 223a: Estimated average from the report: Analyse av fiskeprodukter - Næringsstoff- og tungmetallanalyser (2016). Mattilsynet [In Norwegian].
Lean fish: Cod, saithe, pollock, haddock etc.	142	Cod, saithe, pollock, ling, wolfish, dried and salted cod.	Seafood data (1), Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Iodine content based on mean from of of all types of lean fish species reported in the I-FFQ (Supplemental Table 1). Iodine content weightet according to intake of the specific species reported from the participants in the I-FFQ.
Fatty fish: Salmon, trout, halibut, mackerel etc.	7	Salmon, mackerel, herring and halibut.	Seafood data (1), Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Iodine content based on mean from of of all types of fatty fish species reported in the I-FFQ (Supplemental Table 1). Iodine content weightet according to intake of the specific species reported from the participants in the I-FFQ.
Mashed potatoes (with milk)	6	Mashed potatoes of powder, with milk	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Soup with milk/creme fraiche etc.	8	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items).

Continued Table S3 Iodine content in food items used for calculation of iodine intake from the food diary

Food item specified in the food diary	Iodine content (µg/100 g)	Food item retrieved for iodine content	Reference	Extended information about reference and iodine content
Sauce with milk/creme fraiche etc.	8	Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat	Nerhus et al. 2018 (2) and The Norwegian Food Composition Table (3)	Mean of Cow milk, whole-fat ('helmelk'), 3.5 and 3.9% fat, Cow milk, low-fat ('lettmelk'), 1.2% fat ('TINE') and cow milk, low-fat ('lettmelk'), 1.0% fat ('Q'), Cow milk, low-fat ('lettmelk'), 0.7% fat ('TINE' and 'Q'), Cow milk, skimmed ('skummet melk'), 0.1% fat. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items).
Other dairy products and cheese				
Solid cheese used in cooking (e.g. tacos, pizza, salads etc.)	16	White-coloured solid cheese ('hvitost'): 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'.	Nerhus et al. 2018 (2)	Samples from 2015-2016. Mean of 'Norvegia', 'Jarlsberg', and 'Synnøve Finden'. Mean of each sample is based based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers).
Chevre	80	Chevre, goat cheese, natural	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Feta cheese (e.g. used in salads)	10	Feta cheese	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.
Cottage cheese	15	Curd cheese (cottage cheese): 'Cottage cheese, TINE'	Nerhus et al. 2018 (2)	Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Sour creme, creme fraiche, curd/'kesam'	12	Curd with natural flavour (Kesam), 'TINE', Creme fraiche, 'TINE' and Sour creme, 'TINE'	Nerhus et al. 2018 (2)	Mean of Curd with natural flavour (Kesam), 'TINE', Creme fraiche, 'TINE' and Sour creme, 'TINE Mean based on two replicates per pooled sample (one pooled sample consists of three items of three different batch numbers).
Yoghurt	16	Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'	Nerhus et al. 2018 (2)	Mean of samples of Yoghurt with natural flavour, 'TINE' and 'Go' morgen' with flavour, 'TINE'. Mean based on two replicates per pooled samples (one pooled samples consists of three items of three different batch numbers)
Porridge, cereals with milk	13	Porridge of oats, with milk	The Norwegian Food Composition Table (3)	Reference 325: University of Oslo (2018): Iodine project 2017-2018.

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Paper II

The Journal of Nutrition
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Iodine Nutrition and Iodine Supplement Initiation in Association with Thyroid Function in Mildly-to-Moderately Iodine-Deficient Pregnant and Postpartum Women

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ABSTRACT

Background: Whereas the adverse effects of severe iodine deficiency during pregnancy are well documented, the effects of mild-to-moderate deficiency are not well established.

Objectives: We aimed to explore whether iodine nutrition and timing of iodine supplement initiation are associated with thyroid function in pregnant and postpartum women.

Methods: In this cohort study, 137 pregnant women were enrolled and followed up at gestational weeks (GWs) 18 and 36, and 3 and 6 mo postpartum. Thyroid function tests [thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4)], urinary iodine and creatinine concentration (UIC:Cr), and iodine intake (including iodine supplement use) were measured at each time point. The associations between thyroid hormone concentrations and UIC:Cr, iodine intakes, and iodine supplement use were estimated using multiple generalized estimating equation models.

Results: The median UIC at GW18 was 94 μg/L, indicating mild-to-moderate iodine deficiency. UIC:Cr (β; 95% CI) per 100 μg/g was negatively associated with fT3 (−0.191; −0.331, −0.051) and fT4 (−0.756; −1.372, −0.141) concentrations. Iodine intake (β; 95% CI) per 100 μg/d was positively associated with TSH (0.099; 0.022, 0.177), and negatively associated with fT3 (−0.084; −0.0141, −0.027) and fT4 (−0.390; −0.599, −0.182) concentrations. Compared with no use of supplement, those initiating an iodine-containing supplement prepregnancy and continuing through pregnancy had lower TSH (estimated means) (1.35 compared with 1.68 mIU/L, $P = 0.021$), and higher fT3 (4.48 compared with 4.28 pmol/L, $P = 0.035$) and fT4 (15.2 compared with 14.4 pmol/L, $P = 0.024$) concentrations.

Conclusions: Lower iodine availability during pregnancy and postpartum was associated with lower TSH, and higher fT3 and fT4 concentrations. The use of an iodine-containing supplement that was initiated prepregnancy and continuing through pregnancy was associated with lower TSH, and higher fT3 and fT4 concentrations, which may suggest improved thyroid function. These findings support the notion that optimization of iodine intake should start before pregnancy. This trial was registered at clinicaltrials.gov as NCT02610959. *J Nutr* 2021;00:1–10.

Keywords: iodine, thyroid hormones, pregnancy, iodine supplementation, iodine deficiency

Introduction

Sufficient iodine intake is vital for normal thyroid function through its incorporation in the thyroid hormones, triiodothyronine (T3) and thyroxine (T4), which further are important for fetal neurodevelopment (1). Iodine requirements increase during pregnancy and postpartum owing to increased thyroid hormone synthesis, transfer of iodine to the fetus, increased glomerular filtration and urinary iodine losses, and secretion into breast milk during lactation (2). Thus, pregnant and lactating women are groups vulnerable to iodine deficiency and further disturbances of thyroid function (3).

The WHO defines insufficient iodine intake in pregnant and lactating women as median urinary iodine concentration (UIC) <150 and 100 μg/L (4). Mild-to-moderate iodine deficiency in pregnant women can be defined as median UIC in the range of 50–149 μg/L, and severe iodine deficiency as median UIC <50 μg/L (5). Whereas the adverse effects of severe iodine deficiency during pregnancy are well documented (1),

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the consequences of mild-to-moderate iodine deficiency are less clear and it is uncertain at which level of iodine status the thyroid hormones are affected (6). Several observational studies have reported an association between mild-to-moderate iodine deficiency during pregnancy and impaired child development (7–11). However, these studies do not report data on maternal thyroid function; thus, the mechanisms between mild-to-moderate iodine deficiency and disturbed thyroid function, and, further, impaired child development are not fully explained (12). Of the few published studies, some have found an association between mild-to-moderate iodine deficiency and thyroid function in pregnant and postpartum women (13–15), whereas others have not (16–20).

The benefits of iodine supplementation in mildly-to-moderately iodine-deficient pregnant women remain unclear, even though it is recommended in several parts of the world. A recent systematic review and meta-analysis concluded that there was inconsistent evidence that iodine supplementation improved maternal thyroid function in this group (21). This was also the conclusion in 2 previous systematic reviews (22, 23) and a Cochrane review from 2017 (24). In addition, some studies indicate that initiating an iodine supplement after conception may be too late, and that an abrupt increase in iodine intake might have negative effects on thyroid function which further may harm the developing fetus (14, 25).

The main aims of this article were to explore whether iodine nutrition (UIC and iodine intake) and timing of iodine supplement initiation were associated with altered thyroid function in mildly-to-moderately iodine-deficient pregnant and postpartum women.

Methods

Study design

This was a cohort study where a total of 137 pregnant women were enrolled and followed up at gestational weeks (GWs) 18 and 36, and 3 and 6 mo postpartum. The current investigation is a secondary analysis from the study "Mommy's Food" (NCT02610959), which is a 2-armed randomized controlled trial (RCT) where pregnant women were randomly assigned to either receive dietary Atlantic cod (*Gadus morhua*) or continue with their habitual diet during the second and third trimesters of pregnancy (GWs 20–36) (26). The intervention increased the median UIC in the intervention group but had no effects on thyroid function (27). Therefore, in the current article, we wanted to explore potential associations between markers of iodine nutrition (UIC and iodine intake) and thyroid function tests in an observational design. Thus, participants from both the intervention and the control arms of the study were included in a secondary analysis of the data. The number of participants recruited to the study was based on the power calculation for the primary outcome of the study (UIC after the intervention) (26). Because this article was a secondary analysis of the data we did not perform a post hoc power analysis, because this is not recommended (28, 29).

The study visits during pregnancy (GWs 18 and 36) and postpartum (3 and 6 mo) included the collection of biological samples (blood and urine samples) and questionnaires regarding demography, dietary intake, and supplement use. Further information about the study, including study design, power calculation, enrolment, and study procedures, has been published elsewhere (26, 27).

Participants and recruitment

Participants were recruited through the Women's Clinic at Haukeland University Hospital in Health Region West in Norway from January 2016 to February 2017. In addition, study information was broadcast online through social media and an online magazine for pregnant women in Norway. Inclusion criteria were first-time pregnant, singleton pregnancy, GW ≤19, and Norwegian speaking and/or able to understand Norwegian writing (because of the questionnaires and validated tests of the child being in Norwegian). Exclusion criteria were diseases known to affect iodine status (hypothyroidism, hyperthyroidism, Graves disease, thyroiditis, and thyroid nodules) and fish allergies.

Outcomes

Thyroid function tests.

TSH, free triiodothyronine (fT3), and free thyroxine (fT4) were measured in serum samples collected in GWs 18 and 36, and 3 and 6 mo postpartum. Venous blood samples for serum preparation were collected in BD Vacutainer® SST™ vials II Advanced (Becton, Dickinson and Co.) and set to coagulate for a minimum of 30 min before centrifuging (1000–3000 × *g*, room temperature, 10 min) within 60 min after venipuncture. Postseparation, serum samples were stored at −80°C pending analysis at Fürst Medical Laboratory in Oslo, Norway. The serum samples were stored for a maximum of 3 mo before analysis. TSH, fT4, and fT3 were analyzed in serum using magnetic separation and detection by chemiluminescence, labeled with acridinium ester, on an Advia Centaur XPT Immunoassay system (Siemens Healthcare Diagnostics Inc.). For TSH, fT3, and fT4 the analytical CV was 3.1%, 3.3%, and 4.6%, respectively.

For TSH, reference values from MoBa (the Norwegian Mother, Father and Child Cohort Study) were used for pregnant women (GWs 18 and 36) [2.5–97.5 percentiles in $n = 2577$ thyroid peroxidase antibody (TPOAb)-negative pregnant women (mean GW = 18.5): 0.39–2.70 mIU/L] (14). Postpartum, reference values from the Norwegian HUNT Study (The Trøndelag Health Study) were used (2.5–97.5 percentiles in $n = 514$ TPOAb-negative females <40 y old: 0.37–3.30 mIU/L) (30). The total reference population in the HUNT Study consisted of $n = 17{,}824$ TPOAb-negative women (2.5–97.5 percentile: 0.48–3.60 mIU/L). For fT3 and fT4, the reference values for adults from Fürst Medical Laboratory were used because pregnancy or trimester-specific reference ranges were not available (fT3: 3.5–6.5 pmol/L; fT4: 11.0–23.0 pmol/L) (31).

Thyroid dysfunction was defined by thyroid function tests outside reference ranges (32). Overt hypothyroidism was defined as TSH above and fT4 below reference values. Overt hyperthyroidism was defined as TSH below and fT4 above reference values. Subclinical hypothyroidism and hyperthyroidism were defined as TSH above and below reference values, respectively, and normal fT4 values. Isolated hypothyroxinemia was defined as normal TSH values and fT4 values below reference values.

UIC and urinary creatinine concentrations.

In GWs 18 and 36, the participants collected spot urine samples for 6 consecutive days (6 spot urine samples). Equal amounts of urine from the 6 spot urine samples were homogenized into 1 pooled composite sample of 1 mL. At 3 and 6 mo postpartum 1 spot urine sample was collected from the participants. The participants were instructed to collect the spot urine sample between 16:00 and midnight, to reduce the within-day variation between samples. Urine samples were stored at −20°C in cryotubes (CryoTube™ Vials Nunc; Thermo Fischer

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Supplemental Tables 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
Address correspondence to SN (e-mail: synnoeve.naess@hi.no).
Abbreviations used: BMIC, breast milk iodine concentration; fT3, free triiodothyronine; fT4, free thyroxine; GEE, generalized estimating equation; GW, gestational week; HUNT Study, The Trøndelag Health Study; ICP-MS, inductively coupled plasma mass spectrometry; IMR, Institute of Marine Research; MoBa, the Norwegian Mother, Father and Child Cohort Study; RCT, randomized controlled trial; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; UIC, urinary iodine concentration; UIC:Cr, urinary iodine concentration:creatinine ratio.

Scientific) pending analysis. Iodine concentration in the urine samples was determined by inductively coupled plasma mass spectrometry (ICP-MS). Before analysis, the urine samples were defrosted in a refrigerator, diluted with 1% tetramethylammonium hydroxide, and filtered using a sterile membrane filter with a 0.45-μg pore size and single-use syringe. Samples were analyzed by an Agilent 7500 via ICP-MS at the Institute of Marine Research (IMR), Bergen, Norway. Samples were analyzed against a urine calibration curve (standard addition curve). Certified reference material was used to check the internal validity of the method: Seronorm Trace Elements Urine (Nycomed Pharma) [iodine content: 84 μg/L (range: 72–96 μg/L) and 304 μg/L (range: 260–348 μg/L)]. The measurement uncertainty of the method has been assessed based on internal reproducibility and analysis of standard reference material, and is set at 20% in the entire range (2–297 μg/L).

Urinary creatinine concentration was analyzed using a MAXMAT PL II multidisciplinary diagnostic platform with a creatinine PAP kit (ERBA Diagnostics). The urine samples were defrosted at room temperature and centrifuged in an Eppendorf (5810R) centrifuge (15 min, 2000 × *g*, and 4°C). An aliquot of 200 μL was transferred to the test tube and placed in the MAXMAT carousel for analysis. The method was calibrated with 1 standard and further controlled with 2 independent controls.

The reference values from the WHO of UIC during pregnancy (150 μg/L) and lactation (100 μg/L) were used to assess adequate iodine status (33). Mild-to-moderate iodine deficiency was defined as median UIC 50–149 μg/L (5). UIC was presented as UIC:creatinine ratio (UIC:Cr) (μg/g) in the models to adjust for individual hydration status (34) and, owing to better association with iodine intake from the FFQ, compared with only UIC (**Supplemental Table 1**).

Iodine intake and iodine supplement use.

Iodine intake and use of iodine supplements were self-reported and estimated from a validated electronic iodine-specific FFQ which was developed specifically for this study (35). The FFQ was completed by the participants at GWs 18 and 36, and 3 and 6 mo postpartum. In the FFQ completed in GW 18, the participants were asked to report an estimate of their diet since they became pregnant, whereas the FFQ in GW 36 covered the intake during the last 16 wk (approximately since the last time they completed the FFQ). The FFQs completed 3 and 6 mo postpartum were intended to cover the participants' diet during the past 3 mo. The FFQ consisted of 60 iodine-rich food items (milk and dairy products, fish and other seafood, and eggs) and the use of dietary supplements. Total iodine intake (μg/d) was summarized and estimated from the food items and dietary supplements. More information regarding the FFQ and calculation of iodine intake has been published elsewhere (35).

The use of iodine-containing supplements was reported by the participants at each specific time point. In addition, the use of prepregnancy iodine-containing supplements was reported in the FFQ completed in GW 18. The use of iodine-containing dietary supplements was categorized to a dichotomous variable and defined as >2 times/wk (yes/no). Further, the timing of iodine supplement initiation, from prepregnancy and until GW 18, was merged and categorized into the following categories:

- *None*: no use reported either prepregnancy or GW 0–18;
- *Prepregnancy*: only reported use prepregnancy;
- *GW 0–18*: only reported use GW 0–18;
- *Prepregnancy and GW 0–18*: reported use, both prepregnancy and GW 0–18.

The amount of iodine in the iodine-containing supplements varied from 75 to 225 μg per recommended daily dose according to the product label, with most supplements containing 150–200 μg I/dose.

The recommended intake amount from the WHO of 250 μg/d for pregnant and lactating women was used to assess sufficient iodine intake (4).

Background variables.

Baseline characteristics from the study participants were retrieved from the electronic questionnaires conducted in GW 18. The questionnaires included information regarding pregnancy week, age, education level, prepregnancy weight and height, nicotine use during pregnancy, and use of prescribed medications during the last 6 wk. Prepregnancy BMI (in kg/m^2) was calculated by prepregnancy weight (kg) divided by the square of the height in meters. The ferritin concentration was analyzed in serum samples and collected as described for the aforementioned thyroid function tests. Serum ferritin was analyzed by an immunoturbidimetric method using an Advia Chemistry XPT system (Siemens Medical Solutions Diagnostica). The CV for serum ferritin concentration was 2.5%.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics West (REK 2015/879). The trial complies with the Declaration of Helsinki and written informed consent was obtained from the participants after giving both written and oral information about the study. The participants could withdraw from the study at any time without giving any reason.

Statistics

Variables were tested for normality by visual inspection of Q-Q plots and histograms. Descriptive results are reported as proportions (%) for categorical variables. For continuous variables means ± SDs, medians, or percentiles are reported as appropriate. P values < 0.05 were considered statistically significant.

We measured the associations between the thyroid hormones (TSH, fT3, and fT4) and UIC:Cr, UIC, and iodine intake in generalized estimating equations (GEEs), including data from all time points (GWs 18 and 36, and 3 and 6 mo postpartum). In the GEE analyses, the associations between the variables of the model at different time points were analyzed concurrently, and the interdependence in multiple data from each participant at the different time points was accounted for (36). TSH, fT3, fT4, or thyroid dysfunction (dichotomized) were used as dependent variables, and UIC:Cr, UIC, or iodine intake as either continuous or dichotomous independent variables. In the GEE models, we used an exchangeable correlation matrix, and for the continuous outcome variables (TSH, fT3, and fT4) we used the Gaussian distribution family with identity link functions. In the analyses with dichotomous outcome variables (thyroid dysfunction), we used a binomial distribution with logit link functions. The concentrations of TSH were log2 transformed in the analyses to achieve normality.

Potential covariates in adjusted models were included using "Purposeful selection of covariates" as suggested by Hosmer et al. (37). The following covariates to use were considered based on known associations from the literature: age of the mother, prepregnancy BMI, education level, nicotine use during pregnancy, and ferritin concentration. All potential covariates were assessed in univariate models with the outcome variable and further included if the P value was <0.25. In the multivariable model containing all covariates identified at step 1 ($P < 0.25$), variables that were not significant at the traditional $P < 0.05$ level were excluded stepwise if the coefficient for UIC:Cr, UIC, or iodine intake did not change considerably (>20%). The following covariates (adjustment variables) were included in the GEE models: TSH: no covariates; fT3, fT4, and fT4:fT3 ratio: prepregnancy BMI and ferritin concentrations; and thyroid dysfunction: prepregnancy BMI.

The correlation of thyroid hormones with UIC:Cr, UIC, and iodine intake was assessed using Spearman's rank order correlation coefficient (Spearman's ρ).

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 26 (IBM Corporation).

Results

Figure 1 gives the flow of the study population and data used in this study. A total of 137 pregnant women were enrolled in the

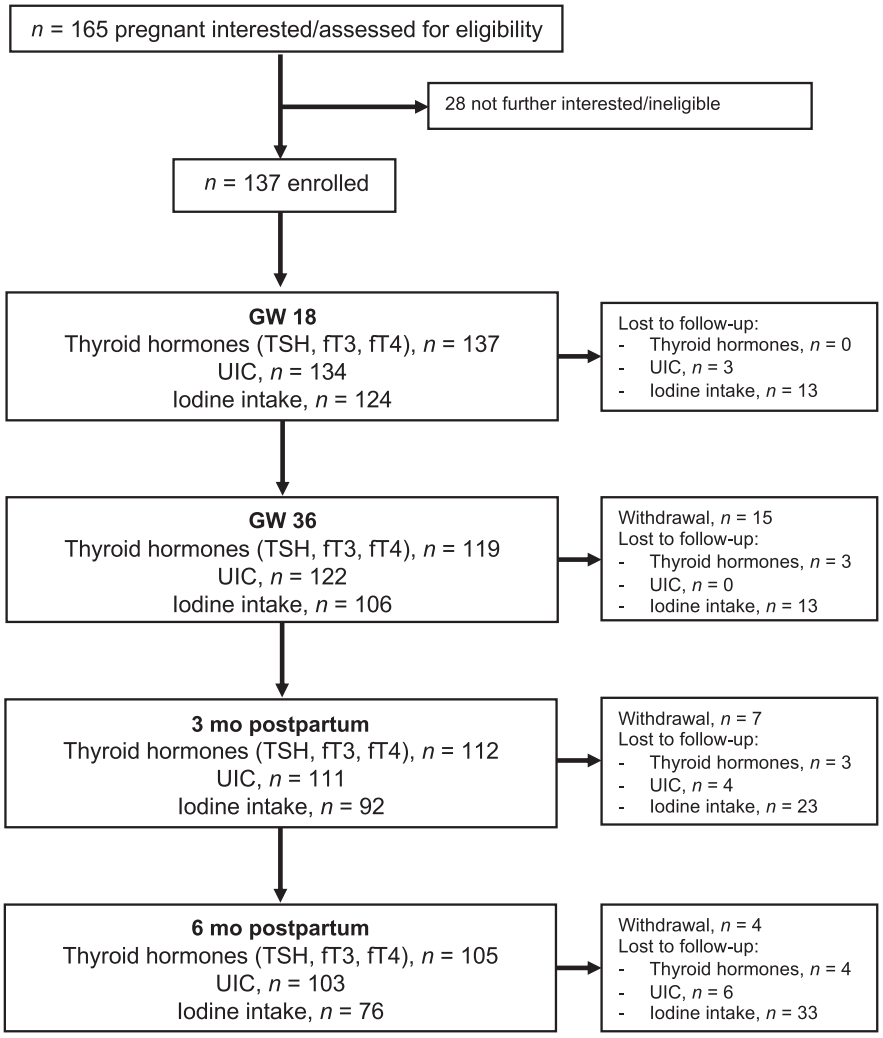

FIGURE 1 Flowchart of the study population and data available at each time point. fT3, free triiodothyronine; fT4, free thyroxine; GW, gestational week; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.

study at GW 18. Table 1 shows baseline characteristics of the study population.

Table 2 shows the thyroid hormones (TSH, fT3, and fT4), UIC, UIC:Cr, and iodine intake during pregnancy (GWs 18 and 36) and postpartum (3 and 6 mo). The median UIC was below the recommended WHO concentrations (150 μg/L during pregnancy and 100 μg/L during lactation) at all time points, with a median UIC of 94, 85, 74, and 84 μg/L at the 4 time points, respectively. Thus, this indicated mild-to-moderate iodine deficiency in this population group. The estimated iodine intake was below the WHO recommended amount of iodine intake during pregnancy and lactation (250 μg/d) at all time points, with a median iodine intake of 202, 153, 143, and 134 μg/d, respectively. In GW 18, 41% of the participants took an iodine-containing supplement. This decreased to 28% in GW 36, and 30% and 17% at 3 and 6 mo postpartum, respectively. A total of 25% of the participants took an iodine-containing supplement prepregnancy.

Table 3 gives the associations of thyroid hormones with UIC:Cr and iodine intake in GEE models. UIC:Cr was negatively associated with fT3 and fT4 concentrations, showing an adjusted coefficient (95% CI) (per 100 μg/L) of −0.191 (−0.331, −0.051) ($P = 0.008$) and −0.756 (−1.372, −0.142) ($P = 0.016$), respectively. These associations were not seen for UIC alone, only when using UIC:Cr (**Supplemental Table 2**). No association was seen between TSH or thyroid dysfunction and UIC:Cr, nor UIC. No association was seen between fT4:fT3 ratio and UIC:Cr, but fT4:fT3 ratio was negatively associated with UIC with an adjusted coefficient (per 100 μg/L) of −0.065 (95% CI: −0.115, −0.015) ($P = 0.011$) (Supplemental Table 2). TSH was positively associated with iodine intake, showing an adjusted coefficient (per 100 μg/d) of 0.099 (95%

TABLE 1 Baseline characteristics of pregnant women (GW 18) enrolled in the Mommy's Food study[1]

Characteristic	*n*	Value
Age, y	135	29.3 ± 3.4
GW	127	19.0 ± 1.3
Prepregnancy BMI, kg/m^2	132	22.2 [20.6–24.3]
Education level	133	
Elementary school		2 (1.5)
High school		17 (13)
≤4 y university/college		33 (25)
>4 y university/college		81 (61)
Nicotine use ≤GW 8[2]	132	
Smoking		1 (0.8)
Snuff		12 (9)

[1]Values are means ± SDs, medians [IQRs], or *n* (%). GW, gestational week.
[2]No participants reported use of nicotine after GW 8.

CI: 0.022, 0.177) ($P = 0.012$). Furthermore, fT3 and fT4 were negatively associated with iodine intake, showing an adjusted coefficient (per 100 μg/d) of −0.084 (95% CI: −0.141, −0.027) ($P = 0.004$) and −0.390 (95% CI: −0.599, −0.182) ($P < 0.001$), respectively. We found no associations of fT4:fT3 ratio or thyroid dysfunction with iodine intake (Table 3).

Figure 2 and **Supplemental Tables 3–6** show concentrations of TSH, fT3, and fT4, and the fT4:fT3 ratio by categories of the timing of iodine supplement initiation (from prepregnancy until GW 18). In total, 15% of the participants reported the use of an iodine-containing supplement both prepregnancy and during the first part of pregnancy (GWs 0–18). Further, 9% reported only use prepregnancy, 23% reported only use during the first part of pregnancy, and 53% reported no use either prepregnancy or during the first part of pregnancy. Compared with no use of an iodine supplement, initiation of an iodine-containing supplement prepregnancy and continuing through pregnancy (GWs 0–18) was in adjusted GEE models associated with lower concentrations of TSH (estimated means: 1.35 compared with 1.68 mIU/L, $P = 0.021$) and higher concentrations of fT3 (4.48 compared with 4.28 pmol/L, $P = 0.035$) and fT4 (15.2 compared with 14.4 pmol/L, $P = 0.024$). This association was not seen for those initiating an iodine-containing supplement after the conception of pregnancy.

Discussion

In this observational study of pregnant and postpartum women with mild-to-moderate iodine deficiency, we found that iodine

TABLE 2 Thyroid hormones (TSH, fT3, and fT4), UIC, and iodine intake in pregnant and postpartum women[1]

	Time point							
	GW 18		GW 36		3 mo postpartum		6 mo postpartum	
Variable	*n*	Value	*n*	Value	*n*	Value	*n*	Value
TSH, mIU/L								
Median [IQR]	137	1.4 [1.0–2.1]	119	1.7 [1.3–2.2]	112	1.3 [0.82–1.6]	105	1.3 [0.75–1.7]
p10–p90		0.84–2.5		0.9–3.0		0.54–2.2		0.49–2.7
p2.5–p97.5		0.26–3.4		0.47–3.9		0.035–2.9		<0.01–6.8
fT3, pmol/L								
Median [IQR]	137	4.3 [3.9–4.6]	119	3.9 [3.6–4.1]	112	4.6 [4.3–4.9]	105	4.7 [4.4–5.0]
p10–p90		3.7–4.8		3.5–4.4		4.1–5.4		4.1–5.4
p2.5–p97.5		3.5–5.3		3.3–4.8		3.8–5.9		3.7–9.5
fT4, pmol/L								
Median [IQR]	137	13.8 [12.9–14.9]	119	13.4 [12.4–14.4]	112	15.3 [14.2–17.1]	105	15.5 [14.4–17.3]
p10–p90		11.9–16.2		11.3–15.3		13.5–18.6		13.4–18.4
p2.5–p97.5		11.3–17.0		9.9–16.6		12.4–22.6		12.5–26.7
Thyroid dysfunction, *n* (%)								
Overt hypothyroidism	137	1 (0.7)	119	2 (1.7)	112	2 (1.8)	105	1 (1.0)
Subclinical hypothyroidism		7 (5.1)		11 (9.2)		0		6 (5.7)
Overt hyperthyroidism		0		0		1 (0.9)		3 (2.9)
Subclinical hyperthyroidism		5 (3.6)		2 (1.7)		4 (3.6)		5 (4.8)
Isolated hypothyroxinemia		0		5 (4.2)		1 (0.9)		0
UIC,[2] μg/L								
Median [IQR]	134	94 [62–130]	122	85 [57–123]	111	74 [42–130]	103	84 [49–120]
Mean ± SD		103 ± 56		98 ± 55		97 ± 79		97 ± 79
UIC:creatinine ratio,[2] μg/g								
Median [IQR]	134	104 [81–144]	122	104 [82–155]	111	69 [40–107]	103	69 [50–96]
Mean ± SD		116 ± 51		124 ± 58		85 ± 64		77 ± 38
Total iodine intake,[3] μg/d								
Median [IQR]	124	202 [106–275]	106	153 [119–253]	92	143 [83–240]	76	134 [79–201]
Mean ± SD		202 ± 108		180 ± 87		166 ± 101		154 ± 95
<250 μg/d, %		61		75		79		80
≥250 μg/d, %		39		25		21		20
Iodine intake from supplements,[4] μg/d								
Mean ± SD (all)	124	69 ± 81	106	42 ± 72	92	50 ± 72	76	30 ± 62
Mean ± SD (only supplement users)		163 ± 24		172 ± 22		158 ± 34		161 ± 30
Supplement user, yes, %		41		28		30		17
Supplement user, no, %		59		72		70		83

[1]fT3, free triiodothyronine; fT4, free thyroxine; GW, gestational week; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.
[2]Pooled sample of 6 spot urine samples from 6 consecutive days in GWs 18 and 36. One spot urine sample at 3 and 6 mo postpartum.
[3]Estimated total iodine intake from foods and supplements from a validated iodine-specific FFQ (35).
[4]Supplement user defined as taking iodine-containing supplements >2 times/wk.

TABLE 3 Associations of thyroid function tests (TSH, fT3, and fT4) and disturbed thyroid function with repeated measurements of UIC:creatinine ratio and iodine intake during pregnancy (GWs 18 and 36) and postpartum (3 and 6 mo) in GEE models[1]

	Independent variables							
	UIC:creatinine ratio[2]				Iodine intake[3]			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Dependent variables	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
TSH[4]	0.041 (−0.159, 0.240)	0.690	0.041 (−0.159, 0.240)	0.690	0.099 (0.022, 0.177)	0.012	0.099 (0.022, 0.177)	0.012
fT3[5]	−0.206 (−0.340, −0.072)	0.003	−0.191 (−0.331, −0.051)	0.008	−0.046 (−0.109, 0.017)	0.156	−0.084 (−0.141, −0.027)	0.004
fT4[5]	−0.791 (−1.365, −0.218)	0.007	−0.756 (−1.372, −0.141)	0.016	−0.325 (−0.537, −0.113)	0.003	−0.390 (−0.599, −0.182)	<0.001
fT4:fT3 ratio[5]	−0.042 (−0.113, 0.029)	0.249	−0.061 (−0.134, 0.013)	0.104	−0.028 (−0.075, 0.020)	0.255	−0.017 (−0.066, 0.032)	0.499
Thyroid dysfunction[6]	1.40 (0.93, 2.12)	0.106	1.36 (0.89, 2.09)	0.158	1.15 (0.83, 1.60)	0.406	1.11 (0.79, 1.58)	0.545

[1]GEE models with exchangeable correlation matrix. TSH, fT3, fT4: normal distribution with identity link function. Thyroid dysfunction: binomial distribution with logit link function. UIC:creatinine coefficient expressed as per 100 μg/g. Iodine intake coefficient expressed as per 100 μg/d. fT3, free triiodothyronine; fT4, free thyroxine; GEE, generalized estimating equation; GW, gestational week; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration.
[2]Pooled sample of 6 spot urine samples from 6 consecutive days in GWs 18 and 36. One spot urine sample at 3 and 6 mo postpartum.
[3]Estimated total iodine intake (from foods and supplements) from a validated iodine-specific FFQ (35).
[4]Log2-transformed values of TSH owing to skewed data. Covariates in adjusted model: none.
[5]Covariates in adjusted model of fT3, fT4, and fT4:fT3 ratio: prepregnancy BMI and ferritin concentration.
[6]Dichotomous variable: 0 = reference category, normal thyroid function; 1 = disturbed thyroid function (TSH and/or fT4 or fT3 outside reference ranges). Coefficient given as OR (95% CI). Covariates in adjusted model: prepregnancy BMI.

nutrition was associated with altered thyroid hormone function. Lower UIC:Cr and iodine intake were associated with higher fT3 and fT4 concentrations, whereas lower iodine intake was associated with lower TSH concentrations. In contrast, the use of an iodine supplement that was initiated before conception and continuing through pregnancy was associated with lower TSH, and higher fT3 and fT4 concentrations.

The women in this study had a median UIC <100 μg/L throughout pregnancy and until 6 mo postpartum, corresponding to mild-to-moderate iodine deficiency (5). In addition, the mean iodine intake was well below the WHO recommendations of 250 μg/d for pregnant and lactating women at all time points. As of today, several countries and health authorities recommend iodine supplementation during pregnancy, owing to frequently observed mild-to-moderate iodine deficiency in this group (21). However, this recommendation is in contrast to the evidence, because there are uncertain data to support the effect of iodine supplementation in this group (21, 24, 38). In this study, we found no effect on thyroid hormone function, either beneficial or harmful, if initiating an iodine-containing supplement after the conception of pregnancy. However, initiation of iodine supplements before conception and continuing through pregnancy was associated with lower concentrations of TSH and higher concentrations of fT4 and fT3, which might suggest improved thyroid function. Thus, iodine supplementation should start before pregnancy, such that intrathyroidal iodine stores are optimized before conception. Initiation of iodine supplementation too late may also be the reason why other studies that examined the effect of iodine supplementation during pregnancy found mostly no effect on thyroid function (39–43). Currently, the largest RCT with iodine supplementation in mildly-to-moderately iodine-deficient pregnant women was conducted in India and Thailand from 2008 to 2011 (39). Supplementing 200 μg I/d had no effect on maternal thyroid function or child neurodevelopment. However, the stratum consisting of Indian pregnant women had a median UIC at 188 μg/L, indicating iodine sufficiency. When restricting the analysis to the participants from Thailand (baseline median UIC of 112 μg/L) (44), iodine supplementation resulted in a small negative effect on maternal thyroxine (T4) concentrations. There was, however, no effect of iodine supplementation on child development in this subgroup.

In contrast to the positive association between the use of iodine supplements preconception and continuing through pregnancy and fT4 concentrations, we found a negative association of UIC:Cr and iodine intake with fT4 concentrations. This was not expected, because based on physiological adaptations one would rather expect a positive association between iodine status and fT4 concentrations (45, 46). Furthermore, we found a positive association between iodine intake and TSH concentrations. Decreased TSH concentrations may occur in populations with mild-to-moderate iodine deficiency because of an increase in thyroid nodularity and autonomy (47). TSH and fT4 concentrations are usually inversely correlated, which we also found (Supplemental Table 1). Consequently, this may explain the inverse association of UIC:Cr and iodine intake with fT4 concentrations. Similar to our results, an inverse association between iodine nutrition and fT4 concentrations, in pregnant women, was also found in birth cohorts from Sweden (13) and Norway (14). In addition, studies have also shown that women who started taking iodine-containing supplements (16, 25, 48) or used iodized salt (49) during pregnancy had higher TSH concentrations, in line with our observation of a positive association between iodine intake

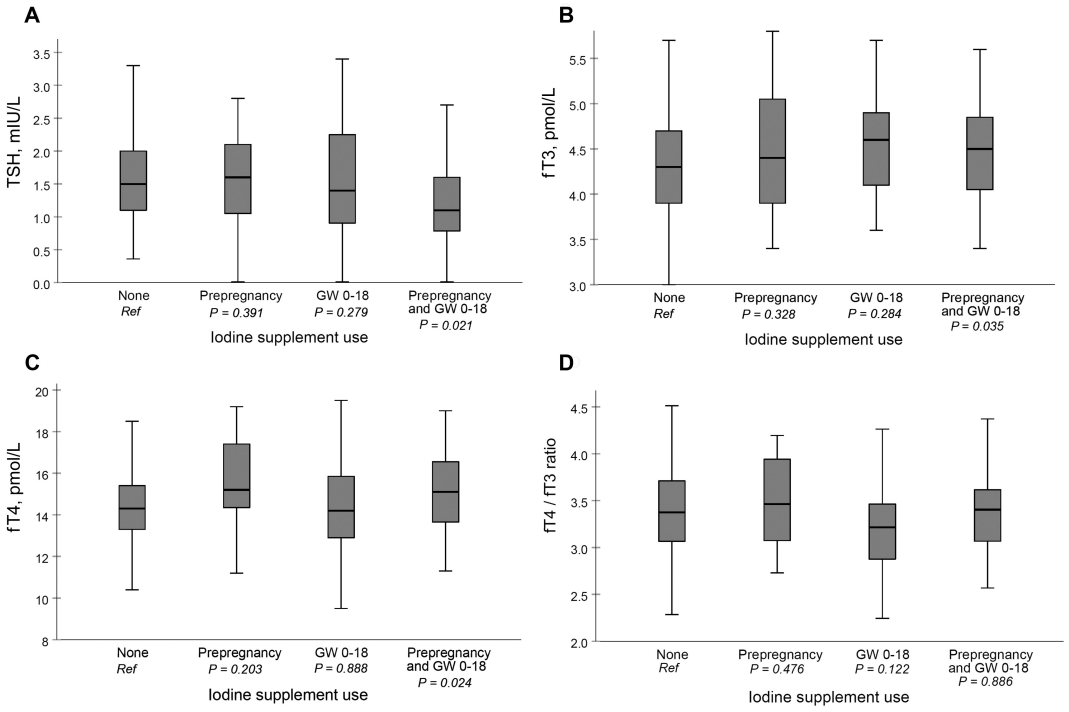

FIGURE 2 Box plot of TSH (A), fT3 (B), fT4 (C), and fT4:fT3 ratio (D) during pregnancy and postpartum by categories of timing of iodine-containing supplement initiation (from prepregnancy until GW 18). *P* values were obtained from adjusted generalized estimating equation models (Supplemental Tables 3–6). Boxes indicate the upper (75th percentile) and lower (25th percentile) quartiles with the thick black line giving the median (50th percentile). The T-bars indicate 1.5 × length of the box (IQR). fT3, free triiodothyronine; fT4, free thyroxine; GW, gestational week; TSH, thyroid-stimulating hormone.

and TSH concentrations. How an increased intake of iodine may affect the thyroid and give an inhibited production of fT4 has been suggested by others (13, 14, 25) to be a result of a "stunning effect" on thyroid hormone production, a similar mechanism to the Wolff–Chaikoff effect (50). The Wolff–Chaikoff effect may occur after acute large doses of iodine and shuts down the thyroid hormone synthesis to prevent an overproduction of thyroid hormones. However, the doses described when the Wolff–Chaikoff effect occurs are much larger than the recommended intake amount of iodine, and at which doses the stunning effect may occur is still uncertain. The stunning effect is proposed to be a result of an abrupt increase in intake; for example, after initiation of an iodine supplement during pregnancy. In this study, we did not have data on prepregnancy UIC or total iodine intake. Thus, we cannot draw any conclusion on how an abrupt increase of iodine intake at the beginning of pregnancy influences thyroid function. Furthermore, the mechanisms of this stunning effect have not been described properly and remain unclear. In addition, several studies also found no effect of an increased iodine intake during pregnancy on thyroid function (39–42). Thus, the evidence of whether an abrupt increase in iodine intake, even within the recommended intake range, during pregnancy can be potentially harmful for thyroid hormone production is still not conclusive.

We observed a negative association of fT4:fT3 ratio with UIC, but not with UIC:Cr and iodine intake; however, the negative coefficients indicated a similar direction of the associations. The negative association with UIC can be explained by the autoregulatory mechanisms when the availability of iodine is low—where the secretion of T3 over T4 is preferred to save 1 iodine atom and to prioritize production of the active hormone (T3) (46). This is also why one typically sees elevated concentrations of fT3 with lower iodine intake (45, 46, 51), which also was confirmed in our study.

There were no clear associations between iodine status and thyroid dysfunction, and the study population had a low prevalence of thyroid dysfunction according to the thyroid function tests (Table 2). This was observed even though the reference range for TSH in pregnancy, derived from the MoBa study to define thyroid dysfunction, was lower than most other reference ranges (32). However, this reference range was the most appropriate, because it is recommended to use population-, trimester-, and assay-specific reference ranges when these are available (52). Also, the effect sizes observed between UIC:Cr and iodine intake with TSH, fT3, and fT4 were relatively low. Thus, the clinical impact of the observed associations between iodine nutrition and thyroid function in this study is not known. However, studies have found that both low and high maternal thyroid function during pregnancy are associated with less child total gray matter and cortex volume (53, 54) and lower child IQ (55). Consequently, the observed associations between maternal iodine nutrition and thyroid function may also have importance for child development, even though the effect sizes were low.

There are some limitations of this study that should be mentioned. The explorative nature of the study limits the assumption of causality. Furthermore, the study comprised a relatively low number of participants, which has implications for its internal validity because of the reduced precision of the effect estimates and reduced statistical power. Low statistical power increases the risk of making type 2 errors. In other words, because of the limited sample size, we could have overlooked clinically meaningful differences. However, despite this, we demonstrated associations between iodine nutrition, supplement use, and thyroid function. Reduced statistical power will generally not result in type 1 errors and we therefore believe that the observed associations were not affected by the relatively small sample size. It is also worth mentioning that each participant had ≤4 repeated measurements of each outcome and exposure, improving the reliability of these measurements. Thus, considering the aforementioned limitations and strengths of the sample size, we believe our data are relevant for similar populations. We did not measure thyroid size, thyroglobulin (Tg), TPOAb, or thyroglobulin antibody (TgAb) which could have added further information regarding thyroid function. Also, breast milk iodine concentration (BMIC) was not included in this study. This is a limitation, because BMIC may be a more accurate marker of iodine status postpartum (56). Thus, the overall UIC status at 3 and 6 mo postpartum should be interpreted with caution. The strengths of this study are the use of 2 markers of iodine nutrition, both UIC and iodine intake. The UIC during pregnancy was derived from spot samples from 6 consecutive days. It has been suggested that ≥10 spot urine samples are needed to reliably estimate individual iodine status (57). Ten samples were not feasible to obtain in this study, but we believe that 6 samples are highly strengthened compared with most other studies, that typically use 1 spot sample, because it reduces the day-to-day variation and further the inter- and intraindividual variability. UIC was also presented as UIC:Cr to adjust for individual hydration status. Because the participants in this study consisted of a rather homogeneous population group—first-time pregnant women with similar age and BMI ranges (Table 1) with a sufficient energy and protein intake—we decided to present the main results as UIC:Cr, which is preferred in a homogeneous population (34). The use of self-reported dietary intake from an FFQ has several limitations, and measurement error may have reduced the power of the reported associations (58). However, the FFQ used in the study was designed specifically to capture iodine intake in this population group, and it has previously been validated (35).

The thyroid can store iodine for ∼3 mo for thyroid hormone production (59), thus the prepregnancy iodine status may be important for coping with the mechanisms of increased demand for thyroid hormone synthesis during pregnancy (60). To date, no RCTs with supplementation starting preconception have been published, and few observational studies have included prepregnancy iodine status. Well-designed RCTs are highly warranted; however, this may not be feasible owing to ethical considerations. Thus, if RCTs are not achievable, well-designed cohort studies with sufficient sample size and including prepregnancy iodine status with appropriate measurements of iodine nutrition (UIC and dietary intake) and thyroid function should be considered.

In conclusion, in an observational study of pregnant and postpartum women with mild-to-moderate iodine deficiency, we found that lower UIC:Cr and iodine intake were associated with higher fT3 and fT4 concentrations, whereas lower iodine intake was associated with lower TSH concentrations. In contrast, the use of an iodine-containing supplement that was initiated before conception and continuing through pregnancy was associated with lower TSH and higher fT3 and fT4 concentrations, which suggest improved thyroid function. Taken together, these findings support the notion that optimization of iodine intake should start before pregnancy.

Acknowledgments

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Data availability

Requests for data collected in the Mommy's Food study (such as deidentified participant data) can be made to the corresponding author, and requests will be considered on an individual basis. Any requests require completion and approval of the application for use of data from the Mommy's Food study. The trial project group will review and, if acceptable and approved by the Regional Committee for Medical and Health Research Ethics West, Norway, provide approval of the request. A signed data-sharing access agreement will be required. The data will be provided as an SPSS data set. Any other format requests might incur costs to the requestor. To facilitate the data access process, please contact MWM at maria.wik.markhus@hi.no and mammasmat@hi.no.

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Online Supplementary Material (OSM)

Supplementary Table 1: Spearman's rho correlation coefficients matrix between TSH, fT3, fT4, UIC and iodine intake

Supplementary Table 2: Associations between thyroid functions tests (TSH, fT3 and fT4) and disturbed thyroid function with repeated measurements of UIC during pregnancy (GW 18 and 36) and post-partum (3 and 6 months) in generalized estimating equations (GEE) models

Supplementary Table 3: TSH (mIU/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

Supplementary Table 4: fT3 (pmol/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

Supplementary Table 5: fT4 (pmol/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

Supplementary Table 6: fT4/fT3 ratio by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

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Supplementary Table 1 Spearman's rho correlation coefficients matrix between TSH, fT3, fT4, UIC and iodine intake

	N	TSH	fT3	fT4	UIC	UIC/ Creatinine [a]	Iodine intake [b]
TSH	473	1.00					
fT3	473	-0.253 (*P* <0.001)	1.00				
fT4	473	-0.299 (*P* <0.001)	0.472 (*P* <0.001)	1.00			
UIC [a]	464	-0.045 (*P*= 0.330)	0.023 (*P*= 0.623)	-0.026 (*P*= 0.579)	1.00		
UIC/Creatinine [a]	464	0.106 (*P*= 0.023)	-0.266 (*P*< 0.001)	-0.234 (*P*< 0.001)	0.567 (*P*< 0.001)	1.00	
Iodine intake [b]	390	0.078 (*P*= 0.123)	-0.098 (*P*= 0.054)	-0.142 (*P*= 0.005)	0.288 (*P* <0.001)	0.418 (*P* <0.001)	1.00

Data from all time points (pregnancy (GW 18 and 36) and post-partum (3 and 6 months)) included.

[a] Pooled sample of six spot urine sample from six consecutive days in gestational week 18 and 36. One spot urine sample 3- and 6-months post-partum.

[b] Estimated total iodine intake (from foods and supplements) from a validated iodine specific food frequency questionnaire (Næss et al. 2019).

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Supplementary Table 2 Associations between thyroid functions tests (TSH, fT3 and fT4) and disturbed thyroid function with repeated measurements of UIC during pregnancy (GW 18 and 36) and post-partum (3 and 6 months) in generalized estimating equations (GEE) models

	Urinary iodine concentration (UIC) [a]			
	Unadjusted		Adjusted	
Variables	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
TSH [b]	-0.010 (-0.189, 0.169)	*0.911*	-0.010 (-0.189, 0.169)	*0.911*
fT3 [c]	0.028 (-0.072, 0.127)	*0.583*	0.029 (-0.084, 0.142)	*0.612*
fT4 [d]	-0.164 (-0.544, 0.216)	*0.397*	-0.168 (-0.591, 0.256)	*0.438*
fT4/fT3 ratio	-0.061 (-0.113, -0.010)	*0.018*	-0.065 (-0.115, -0.015)	*0.011*
Thyroid dysfunction [e]	1.32 (0.96, 1.82)	*0.091*	1.30 (0.92, 1.82)	*0.126*

GEE models with exchangeable correlation matrix. TSH, fT3, fT4: Normal distribution with identity link function. Thyroid dysfunction: Binomial distribution with logit link function. UIC coefficient given in per 100 µg/L.

[a] Pooled sample of six spot urine sample from six consecutive days in GW 18 and 36. One spot urine sample 3- and 6-months post-partum.

[b] Log2 transformed values of TSH due to skewed data. Covariates in adjusted model: None

[c] Covariates in adjusted model: Pre-pregnancy BMI and ferritin concentration

[d] Covariates in adjusted model: Pre-pregnancy BMI and ferritin concentration

[e] Dichotomous variable: 0= Reference category, normal thyroid function. 1= Disturbed thyroid function (TSH and/or fT4 or fT3 outside reference ranges). Coefficient given as odds ratio (OR). Covariates in adjusted model: Pre-pregnancy BMI.

CI, confidence interval; GEE, generalized estimating equations; GW, gestational week; TSH, thyroid stimulating hormone; fT3, free tri-iodothyronine; fT4, free thyroxine; UIC, urinary iodine concentration;

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Supplementary Table 3 TSH (mIU/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

	TSH (mIU/L) [b]		
Use of supplements [a]	β (95% CI)	Estimated means (95% CI)	*P*
None (ref)	-	1.68 (1.55-1.81)	-
Pre-pregnancy	-0.502 (-1.649, 0.644)	1.18 (0.54-2.61)	0.391
GW 0-18	-0.168 (-0.473, 0.136)	1.49 (1.23-1.81)	0.279
Pre-pregnancy and GW 0-18	-0.311 (-0.576, -0.047)	1.35 (1.14-1.59)	0.021

GEE models in exchangeable correlation matrix. TSH is entered with normal distribution with identity link function. Data are only presented as unadjusted models due to no covariates were selected after purposeful selection of covariates.

[a] Supplement user defined as taking an iodine containing supplements >2 times/week

[b] Log2 transformed values of TSH due to skewed data. Estimated means (95% CI) are anti-log2 for interpretation.

GW, gestational week

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Supplementary Table 4 fT3 (pmol/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

	fT3 (pmol/L)					
	Unadjusted			Adjusted [b]		
Use of supplements [a]	β (95% CI)	Estimated means (95% CI)	*P*	β (95% CI)	Estimated means (95% CI)	*P*
None (ref)	-	4.29 (4.20-4.38)	-	-	4.28 (4.17-4.39)	-
Pre-pregnancy	0.220 (-0.115, 0.555)	4.51 (4.19-4.83)	0.198	0.163 (-0.570, 0.249)	4.45 (4.14-4.76)	0.328
GW 0-18	0.393 (0.095, 0.692)	4.68 (4.40-4.97)	0.010	0.135 (-0.112, 0.382)	4.42 (4.22-4.62)	0.284
Pre-pregnancy and GW 0-18	0.251 (0.083, 0.419)	4.54 (4.40-4.68)	0.003	0.199 (0.014, 0.384)	4.48 (4.34-4.63)	0.035

GEE models in exchangeable correlation matrix. fT3 is entered with normal distribution with identity link function.

[a] Supplement user defined as taking an iodine containing supplements >2 times/week

[b] Covariates in adjusted model: Pre-pregnancy BMI and ferritin concentration.

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Supplementary Table 5 fT4 (pmol/L) by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

	fT4 (pmol/L)					
	Unadjusted			Adjusted [b]		
Use of supplements [a]	β (95% CI)	Estimated means (95% CI)	*P*	β (95% CI)	Estimated means (95% CI)	*P*
None (ref)	-	14.5 (14.1-14.9)	-	-	14.4 (14.0-14.8)	-
Pre-pregnancy	1.097 (-0.414, 2.608)	15.6 (14.1-17.1)	0.155	0.988 (-0.534, 2.510)	15.4 (13.9-16.9)	0.203
GW 0-18	0.264 (-0.697, 1.225)	14.8 (13.9-15.7)	0.590	-0.084 (-1.258, 1.090)	14.3 (13.3-15.3)	0.888
Pre-pregnancy and GW 0-18	0.889 (0.213, 1.565)	15.4 (14.8-16.0)	0.010	0.825 (0.107, 1.543)	15.2 (14.7-15.8)	0.024

GEE models in exchangeable correlation matrix. fT4 is entered with normal distribution with identity link function.

[a] Supplement user defined as taking an iodine containing supplements >2 times/week

[b] Covariates in adjusted model: Pre-pregnancy BMI and ferritin concentration.

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Supplementary Table 6 fT4/fT3 ratio by categories of timing of iodine-containing supplement (from pre-pregnancy until GW 18) in GEE models of repeated measurements during pregnancy (GW 18 and 36) and post-partum (3 and 6 months)

	fT4/fT3 ratio					
	Unadjusted			Adjusted [b]		
Use of supplements [a]	β (95% CI)	Estimated means (95% CI)	*P*	β (95% CI)	Estimated means (95% CI)	*P*
None (ref)	-	3.41 (3.24-3.52)	-	-	3.41 (3.30-3.51)	-
Pre-pregnancy	0.068 (-0.161, 0.296)	3.48 (3.28-3.52)	0.562	0.084 (-0.148, 0.316)	3.49 (3.28-3.70)	0.476
GW 0-18	-0.232 (-0.404, -0.060)	3.18 (3.05-3.31)	0.008	-0.143 (-0.324, 0.038)	3.26 (3.12-3.41)	0.122
Pre-pregnancy and GW 0-18	-0.004 (-0.203, 0.196)	3.41 (3.24-3.58)	0.972	0.015 (-0.185, 0.214)	3.42 (3.26-3.59)	0.886

GEE models in exchangeable correlation matrix. fT4/fT3 ratio is entered with normal distribution with identity link function.

[a] Supplement user defined as taking an iodine containing supplements >2 times/week

[b] Covariates in adjusted model: Pre-pregnancy BMI and ferritin concentration

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